Outcome of Nonadherence to Antimicrobial Treatment Guidelines in Ambulatory Patients with Acute Cystitis: A Nationwide Population-based Study

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Abstract

Objective The recurrence rate after acute cystitis treatment failure with inappropriate antimicrobials remains unclear. The goal of this study was to explore the relationship between cystitis recurrence and nonadherence of antimicrobial prescriptions to national guidelines using a nationwide population-based data set.

Methods This was a retrospective longitudinal observational cohort study that was conducted using the clinical records of the National Health Insurance Research Database in Taiwan from 2006-2007. After excluding patients younger than 18 years of age, with concurrent infections, urinary tract anomaly, and no antimicrobial treatment, the remaining study population included 36,395 patients with acute cystitis. We evaluated the hazard ratio (HR) of cystitis recurrence within 28 days between the adherence and nonadherence groups using Cox proportional hazard regression analysis.

Results Adherence to antimicrobial prescription guidelines was the factor that most strongly influenced acute cystitis recurrence, with a HR of 0.91 (95% confidence interval 0.87-0.95) after adjusting for all variables. The incidence rate of acute cystitis in patients receiving antimicrobials adherent to national guidelines was 59.78 per 10,000 person-days. The results of the likelihood ratio test indicated that age, sex, and guideline nonadherence were significant risk factors for recurrent cystitis. The percentage of first-generation cephalosporin prescription was 31.61%, making it the most frequently prescribed guideline-recommended drug.

Conclusion Acute cystitis patients with or without multiple chronic comorbidities should be treated with antimicrobials that adhere to recommended guidelines to attain a better therapeutic outcome.

Key words: cystitis, guideline, adherence, antimicrobial agents, recurrence, outcome

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Introduction

Urinary tract infections (UTIs) are a common medical condition, accounting for more than 7 million ambulatory visits in the United States annually (1). Cystitis is the most common bacterial UTI that requires antimicrobial therapy in ambulatory patients. Although young, healthy women gener-

ally have anatomically and physiologically normal urinary tracts, recurrent cystitis is common in this population (2). A study estimated that the incidence of cystitis among sexually active young women is 0.5 per person per year (3). Approximately 20% of young women with an initial episode of cystitis have subsequent infections and require empirical antimicrobial therapy (1).

Several studies have demonstrated that recurrence, treat-

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ment failure, and increased pathogen resistance may occur from the inappropriate antimicrobial treatment of many infectious diseases. However, very few studies have discussed the recurrence rate of acute cystitis due to nonadherence of antimicrobial treatment to national guidelines, although it has been shown that recurrent cystitis can travel to other sites and lead to other complications, such as pyelonephritis, urosepsis, and even more severe diseases such as renal scarring (4). Therefore, acute cystitis should be appropriately treated during the first visit.

Inappropriate antimicrobial prescriptions or overuse can result in antimicrobial resistance, a phenomenon that has become an increasingly well-known public health problem worldwide (5, 6). In particular, countries where antibiotics are commonly available without guidelines are more likely to encounter uropathogen resistance patterns (7, 8). The prevalence rates of resistance among *Escherichia coli* and other uropathogens that cause cystitis have significantly increased (9, 10). The cure rate for cystitis varies from 61-82% in women (3). Because the antimicrobial susceptibility profiles of cystitis-causing uropathogens are highly variable, antimicrobial treatment guidelines for lower UTIs have been established in many countries. These guidelines are based on evidence- and consensus-based recommendations, including common etiologic pathogens, knowledge of the antimicrobial susceptibility profile of uropathogens in the community, and agents that have already been marketed in local regions. Therefore, antimicrobial prescriptions that adhere to national guidelines can be defined as appropriate prescriptions.

Several studies have evaluated factors associated with local physicians' adherence to UTI treatment guidelines in many health care settings. However, to the best of our knowledge, no study has explored the relationship between cystitis recurrence and adherence of antimicrobials to regional treatment guidelines. Inappropriate antimicrobial prescriptions may intensify microorganism resistance and result in poor outcomes in patients with acute cystitis. Therefore, considering the varied uropathogen resistance patterns, selecting antibiotics that adhere to guidelines will reduce the burden of cystitis, thereby lowering its consequences and costs. The goal of this study was to explore the relationship between cystitis recurrence and nonadherence of antimicrobial prescriptions to national guidelines using a nationwide population-based dataset.

Materials and Methods

Database

This was a retrospective cohort study that used the clinical records of the National Health Insurance Research Database (NHIRD) in Taiwan from 2006 to 2007. The database was obtained from the Longitudinal Health Insurance Database 2005 (LHID 2005) of the National Health Insurance (NHI) Research Database. The study population comprised 1,073,891 patients (4.7%) randomly sampled from the

22,717,053 people enrolled in the NHI program. There were 22,770,383 residents in Taiwan in 2005, and the NHI program covered the medical care of 99.8% of these citizens. The claims dataset is one of the largest and most comprehensive nationwide population-based datasets available worldwide and includes diagnostic codes of individual diseases, pharmaceutical prescriptions, and medical expenditures on outpatient and inpatient care since 1995. The database was created by the Taiwan National Health Research Institute (NHRI) using a systematic sampling method to randomly select a representative sample of all enrollees. There were no statistically significant differences in demographic characteristics, including age, gender, and distribution between the sample and original populations (11). Because the LHID 2005 dataset consisted of de-identified and secondary data released to the public for research, the study was exempted from full review by the Institutional Review Board of Taipei Medical University.

Study sample/case identification

Our study sample included all ambulatory patients who obtained treatment for cystitis in this dataset, with the principal diagnosis of these patients being International Classification of Diseases, Ninth Revision (ICD-9-CM) codes 595.0 or 595.9. The study period was from January 1, 2006 to December 31, 2007 (n=82,940). We restricted the study population to adult patients over 18 years of age. To exclude patients with recurrent cystitis, we excluded patients who were diagnosed with the same ICD-9-CM codes within 3 months prior to the date of their ambulatory care visit. Patients with urinary tract anomalies (ICD-9-CM codes 591-594), such as cystocele, were excluded because they were at risk for recurrent cystitis. We only included the first visit for cystitis treatment if a patient had more than one visit during the study period. Patients with acute cystitis and no antimicrobial treatment were also excluded because they did not receive the studied treatment. Additionally, ambulatory patients who visited for concurrent infectious diseases were excluded from our study due to the possibility of concurrent antimicrobial prescriptions (12). In total, our study population included 36,395 patients. We defined cystitis recurrence as ICD-9-CM code 595.0 or 595.9; other sites of UTI as ICD-9-CM codes 590.3, 590.9, 597.8, or 599.0; pyelonephritis as ICD-9-CM codes 590.0, 590.1, 590.2, or 590.8; and urosepsis as ICD-9-CM code 038.9. Poor outcome was defined as patients who experienced illness recurrence within 28 days of their first visit with acute cystitis (inpatient care and outpatient claims data) (13). Antimicrobial prescriptions adherent to guidelines were defined according to the antimicrobial treatment guidelines of acute cystitis established by the Infectious Diseases Society of Taiwan (IDST) (14). This guideline was announced and bulletined on the Department of Health (DOH) website (15). If patients received more than two antimicrobials for acute cystitis or disobeyed the guidelines, we defined it as "nonadherence to guidelines of antimicrobial treatment."

Figure 1. Flowchart of the study subjects recruited from the National Health Insurance Research Database.

Statistical analysis

The SAS 9.1 statistical package (SAS Institute Inc., Cary, USA) was used for all analyses in this study. Student *t*-tests and χ^2 tests were conducted to compare continuous variables and the association of variables, including age, sex, and potential confounders. These included diabetes, chronic obstructive pulmonary disease (COPD), renal disease, other cardiovascular diseases (e.g., hypertension, coronary heart disease, congestive heart disease), diagnosis of the first UTI at less than 15 years of age, urinary incontinence, and contraceptive usage between guideline-recommended drugs and non-guideline-recommended drugs during the follow-up period. Cox proportional hazard regressions were performed to estimate the hazard ratio (HR) of acute cystitis recurrence after adjusting for co-morbidities. Due to the possible collinearity of those comorbidities, we inspected these comorbidities by the multicollinearity method using variance inflation factors. We used the likelihood ratio test to determine the significant risk of a particular variable in the presence of recurrent cystitis and to determine the interaction between variables. In addition, we calculated the 28-day recurrence rate and evaluated the differences in recurrence risk between the two groups by the log-rank test. *p* values less than 0.05 were considered statistically significant.

Results

The LHID2005 database had complete information about cystitis and thus offered a unique opportunity to evaluate antimicrobial treatment and the cystitis recurrence rate. A total of 28,600,400 ambulatory visits for acute cystitis were found in 2006-2007 in the NHI database, and 36,395 pa-

Table 1. Demographic Characteristics of Patients with or without Antimicrobial Adherence to Guidelines in 2006-2007 (n=36,395)

Variables	Adherence to Guidelines (n=24,636)		Nonadherence to guidelines (n=11,759)		p value
	n	%	n	%	
Mean age (SD) (year)	47.03	(18.18)	47.62	(18.05)	0.01
Gender (male)	3,826	15.53	2,302	19.58	<0.001
Diabetes	2,034	8.26	1,013	8.61	0.25
COPD ^a	25	0.10	10	0.09	0.63
Renal disease	347	1.41	155	1.32	0.49
Urinary incontinence	1,180	4.79	504	4.29	0.03
Other cardiovascular diseases	4,660	18.92	2,327	19.79	0.04
Having a first UTI ≤ 15 years-old	48	0.19	24	0.20	0.85
Contraceptive usage	420	1.70	217	1.85	0.34
Recurrent cystitis	3743	15.19	1988	16.91	<0.001

^aCOPD: chronic obstructive pulmonary disease

Student *t*-test for comparison of age; χ^2 tests were conducted to compare the other categorized variables between two groups.

tients remained after excluding patients younger than 18 years age, with concurrent infections, with urinary tract anomalies, and those not receiving antimicrobial treatment (Fig. 1). Table 1 shows the significant differences found in the recurrence rate between patients with antimicrobials adherent to guidelines compared to those with nonadherent antimicrobials. In addition, gender and rates of concurrent comorbidities, such as cardiovascular diseases and urinary incontinence, were significantly different between these two groups. However, there were no significant differences with regard to the other comorbidities (Table 1).

The incidence rate per 10,000 person-days and multivariate adjusted HRs during the 28-day follow-up for acute cystitis recurrence are shown in Table 2. The incidence rate of acute cystitis in patients receiving antimicrobials adherent to national guidelines was 59.78 per 10,000 person-days. However, its adjusted HR was 0.89 [95% confidence interval (CI) 0.85-0.95] compared to the nonadherent group. The adjusted HR showed that women and elderly patients had a higher incidence of recurrence than male patients and younger patients (*p*<0.01). All of the comorbidities had non-collinearity and variance inflation factors. The results of the likelihood ratio test indicated significant associations of recurrent cystitis with the following variables: age, sex, and guideline nonadherence. Antimicrobial prescriptions that adhered to the guidelines resulted in significantly lower recurrence rates than nonadherent prescriptions, even after adjusting for age, gender, other comorbidities, and contraceptive usage. In addition to age and sex, adherence of antimicrobial treatment to the guidelines was also one of the important influencing factors in acute cystitis recurrence after adjusting for all variables.

The log-rank test showed that patients with cystitis who were prescribed guideline-adherent antibiotics had significantly lower recurrence rates during the 28-day follow-up period than those who received nonadherent prescriptions (*p*<0.001) (Fig. 2). Among the total number of antibiotic pre-

Table 2. Incidence Rate and Multivariate Adjusted Hazard Ratios (HRs) during the 28-day Follow-up for Recurrence of Acute Cystitis in 2006-2007

Recurrence of cystitis	n	Cases	Person-days	Incidence rate ^a	LR test ^b	Crude HR (95%CI)	Adjusted LR test ^c	Adjusted HR (95%CI)
Adherence to Guidelines					<0.001		<0.001	
No	11,759	1,988	295,612	67.25		1.00		1.00
Yes	24,636	3,743	626,079	59.78		0.89 (0.85 - 0.94)***		0.89 (0.85 - 0.95)***
Sex					<0.001		<0.001	
Male	6,128	913	152,300	59.95		1.00		1.00
Female	30,267	4,818	769,391	62.62		1.21 (1.13 - 1.29)***		1.18 (1.10 - 1.26)***
Age (years)					<0.001		<0.001	
18-29	7,496	1,072	191,638	55.94		1.00		1.00
30-39	13,505	2,120	342,036	61.98		1.11 (1.03 - 1.19)***		1.09 (1.01 - 1.17)*
50-64	7,991	1,306	201,175	64.92		1.16 (1.07 - 1.25)***		1.14 (1.05 - 1.25)***
≥65	7,403	1,233	186,842	65.99		1.17 (1.08 - 1.27)***		1.14 (1.02 - 1.27)**
Diabetes					0.12		0.76	
No	33,348	5,221	844,943	61.79		1.00		1.00
Yes	3,047	510	76,748	66.45		1.07 (0.98 - 1.17)		1.01 (0.92 - 1.12)
COPD					0.50		0.64	
No	36,360	5,724	920,821	62.16		1.00		1.00
Yes	35	7	870	80.46		1.27 (0.60 - 2.66)		1.17 (0.56 - 2.46)
Renal Diseases					0.81		0.80	
No	35,893	5,650	908,964	62.16		1.00		1.00
Yes	502	81	12,727	63.64		1.03 (0.82 - 1.28)		0.97 (0.78 - 1.21)
Urinary incontinence					0.03		0.08	
No	34,711	5,433	879,490	61.77		1.00		1.00
Yes	1,684	298	42,201	70.61		1.14 (1.01 - 1.28)*		1.11 (0.99 - 1.25)
Other Cardiovascular diseases					0.17		0.31	
No	29,408	4,593	745,169	61.64		1.00		1.00
Yes	6,987	1,138	176,522	64.47		1.04 (0.98 - 1.11)		0.96 (0.89 - 1.04)
Having a first UTI ≤ 15 years-old					0.66		0.88	
No	36,323	5,721	919,837	62.20		1.00		1.00
Yes	72	10	1,854	53.94		0.87 (0.47 - 1.62)		0.95 (0.51 - 1.76)
Contraceptive usage					0.30		0.41	
No	35,758	5,640	905,362	62.30		1.00		1.00
Yes	637	91	16,329	55.73		0.90 (0.49 - 1.67)		0.92 (0.74 - 1.13)

a: Incidence rate: per 10,000 person-days

LR test^b: the likelihood ratio test for models with and without the specified covariateAdjusted LR test^c: adjusted for all variables

*p<0.05, **p<0.01, ***p<0.001

Adjusted HR: adjusted for all variables

Figure 2. Comparison of cystitis recurrence rates of cystitis for adherence and nonadherence to antimicrobial prescription guidelines by log-rank test. The solid and dashed lines indicate the nonadherence and adherence groups, respectively.

scriptions, 67.69% were guideline-recommended drugs that were prescribed during the patient's first visit for cystitis treatment. The frequencies of antibiotic prescriptions for patients with cystitis and their recurrence rate in Taiwan between 2006 and 2007 are listed in Table 3. The percentages of first-generation cephalosporin, fluoroquinolone, and trimethoprim prescribed were 31.61%, 15.32%, and 7.04%, respectively, and those were the most frequently prescribed drugs in the guideline-recommended group. On the other hand, using more than two antimicrobials for acute cystitis (13.56%) was the most common inappropriate drug therapy.

Discussion

To the best of our knowledge, this is the first nationwide population-based follow-up study to examine the risk of recurrence among acute cystitis patients given inappropriate antimicrobial treatment. Our results indicated that patients with acute cystitis who received antimicrobials that were nonadherent to national guidelines (over- or underuse) had a significantly higher risk of recurrence than patients using ad-

Table 3. Frequency Analysis of Antibiotics Prescribed for Patients with Cystitis and Their Recurrence Rate in Taiwan in 2006-2007 (n=36,395)

Drugs	n	%	Recurrent cases	Person-days	Incidence (95% CI) ^a
Guideline-recommended drugs	24,636	67.69	3,743	626,079	59.78 (44.63 - 74.93)
1st G cephalosporin	11,504	31.61	1,716	292,869	58.59 (43.59 - 73.59)
Quinolone	5,575	15.32	902	140,620	64.14 (48.44 - 79.84)
Trimethoprim	2,562	7.04	373	65,401	57.03 (42.23 - 71.83)
Other drugs	2,538	6.97	408	64,152	63.60 (47.97 - 79.23)
Aminopenicillin	2,439	6.70	340	62,609	54.31 (39.87 - 68.75)
Trimethoprim/Sulfamethol	18	0.05	4	428	93.46 (74.51 - 112.41)
Non-guideline-recommended drugs	11,759	32.31	1,988	295,612	67.25 (51.18 - 83.32)
More than two antimicrobials	4,936	13.56	857	123,945	69.14 (52.84 - 85.44)
Sulfamethol	3,868	10.63	616	97,741	63.02 (47.46 - 78.58)
Other drug	1,450	3.98	284	35,611	79.75 (62.25 - 97.25)
Lincomycin	894	2.46	139	22,770	61.05 (45.74 - 76.36)
Chloramphenicol	541	1.49	74	13,864	53.38 (39.06 - 67.70)
Aminoglycoside	70	0.19	18	1,681	107.08 (86.80 - 127.36)

a: Incidence rate: per 10,000 person-days

herent antimicrobials, even after adjusting for multiple chronic underlying diseases. Overall, first-generation cephalosporins were the most commonly prescribed antibiotics among guideline-recommended drugs, and sulfamethoxazole was the most frequently prescribed single antimicrobial among the non-guideline-recommended drugs.

UTIs, especially acute cystitis, are one of the most frequent diseases requiring antimicrobial treatment in ambulatory patients. Acute cystitis is mainly observed in women, and most of the patients in this study were women (83%). The recurrence rate of cystitis is relatively high. Lawrenson et al. demonstrated that 14% of 75,045 newly treated patients required a second antibiotic therapy within 28 days of cystitis treatment for cystitis (15). These data are compatible with the results of our study; we found an overall 15.7% recurrence rate in 36,395 newly diagnosed patients, and patients prescribed non-guideline-recommended antimicrobials had a significantly higher risk of recurrence (16.91%).

The high rate of acute cystitis recurrence after antimicrobial therapy was mostly due to the high resistance rates of uropathogens (16). The therapeutic management of lower UTIs has been hampered worldwide by the increasing resistance of uropathogens to commonly used antibiotics. The most common pathogens of cystitis are similar around the world; 80-90% of cases are caused by *Escherichia coli* (*E. coli*), and less frequent pathogens are *Klebsiella pneumoniae* and *Proteus mirabilis* (17). The Latin American SENTRY Program reported that the extended spectrum beta-lactamase (ESBL)-producing rates of *E. coli* and *Klebsiella spp.* have increased to 48.4% and 60.4%, respectively (9). Nevertheless, carbapenemase-producing *K. pneumoniae* significantly increased in 2010 with clonal expansion in Latin American hospitals (18). Increased resistance has also been noted in Taiwan; the Taiwan Surveillance of Antimicrobial Resistance (TSAR) found that 124 (52.8%) cases of ESBL-producing

K. pneumoniae were resistant to ciprofloxacin in the TSAR-III program (10). Considering the patterns of high resistance, appropriately chosen antibiotics will reduce the recurrence rate of UTIs, thereby lowering the associated complications and costs. Thus, many countries and regions have established their own antimicrobial guidelines for acute cystitis therapy, including the European Association of Urology (EAU) guidelines and the Netherlands Huisartsen Genootschap (NHG)-Standard Urine Infection in the Netherlands (2, 19). An antibiotic treatment profile of acute cystitis in Taiwan (14) was established in 2000 and posted on the website of Department of Health as a reference to all practicing physicians in Taiwan. The guidelines demonstrated antimicrobial choices for uncomplicated and complicated UTIs depending upon the various characteristics of these patients. The influencing factors included age, infection site, and pregnancy status. Several studies have evaluated the contributing factors associated with local physicians' adherence to UTI treatment guidelines in many health care settings. The risk factors include age and gender of both the patients and physicians, and level and location of the hospitals (20). To date, no study has addressed the relationship between acute cystitis recurrence and antimicrobial treatments that do not adhere to national guidelines.

Although some previous studies have investigated women receiving norfloxacin treatment, diabetic patients have a significantly higher recurrence rate than nondiabetic controls (16.1 vs. 12.2%, $p=0.003$) (21). However, our study revealed that diabetes and other comorbidities were not significant risk factors for acute cystitis recurrence after multivariate adjustments. These findings support our hypothesis that adherence to the recommended guidelines can reduce the acute cystitis recurrence rate, regardless of whether patients have comorbidities.

According to the EAU classification system, sex and old

age are possible risk factors taken into consideration (22). Similarly, a female sex and old age were significant factors for a poor clinical outcome in our study. Sex is already addressed in Taiwan's guidelines; however, age should also be added to these guidelines.

In general, the combination of sulfamethoxazole and trimethoprim (folic acid-synthesis blockers) is considered appropriate for the treatment or prophylaxis of UTI (15, 23). The clinical efficacy of trimethoprim alone for three days (90%) is similar to the cotrimoxazole (trimethoprim-sulfamethoxazole) regimen for three days (93%) (24), but the prescription of sulfamethoxazole as the sole therapeutic antibiotic may be inappropriate. No previous study has used sulfamethoxazole as the only antibiotic treatment for a UTI. In our findings, sulfamethoxazole was the most frequently drug used in the nonadherent treatment group, but the failure rate of patients treated with sulfamethoxazole alone was 15.93%, which was higher than the overall failure rate in the adherence to guideline treatment group (15.19%). Thus, the spectrum of treatment efficiencies between cotrimoxazole and sulfamethoxazole alone needs further clarification.

One study observed that 12-16% of young women with UTIs return for further treatment within 28 days, irrespective of the initial antibiotic prescribed (18). However, the recurrence rate was significantly higher in patients receiving guideline-adherent antimicrobials (15.19% vs. 16.91%). This indicates that patients would have a good clinical outcome and low recurrence rate if physicians would adhere to guidelines and prescribe appropriate antimicrobials for acute cystitis. The results of our study can help policy-makers understand the variable prescribing behavior patterns among physicians, which could decrease the frequency of inappropriate antibiotic prescriptions and the cystitis recurrence rate. In addition, these findings may provide useful reasons to implement strategies that increase adherence to antimicrobial stewardship.

The longitudinal database and large population size for obtaining newly diagnosed cases with acute cystitis are the main strengths of this study. However, this study had several limitations. First, because the LHID 2005 is a secondary database of claims data for healthy patients with insurance, we could not obtain urine culture reports, including bacteria identification and antimicrobial resistance tests, to demonstrate the relationship between bacterial resistance patterns and antimicrobial treatment recurrence. Second, the risk behaviors for acute cystitis development in the two patient groups were also unavailable with regard to the frequencies of sexual activity, sexual intercourse, and cranberry consumption. Third, other risk factors concerning hospital factors, physician factors, and patient socioeconomic status could not be obtained from the databank.

In conclusion, physicians who adhered to the recommended guidelines for the treatment of bacterial infections achieved better therapeutic outcomes in their patients with acute cystitis, regardless of whether they had multiple chronic comorbidities. Thus, intensive implementation by

physicians in all health care disciplines that treat patients with lower UTIs is necessary to ensure a discreet antibiotic policy that will decrease recurrence rates and improve patient care.

The authors state that they have no Conflict of Interest (COI).

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