Review

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National Trends of Antimicrobial Resistance in Uncomplicated Cystitis

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Acute uncomplicated cystitis is a common bacterial infection of the urinary bladder in women. Antibiotic resistance against *Escherichia coli* is increasing nationwide in Korea; therefore, we reviewed the local available data regarding acute cystitis. The recently determined susceptibilities of *E. coli* to gentamicin, fluoroquinolone, 3rd generation cephalosporin, and amikacin are 75%, 85-95%, 95%, and 97%, respectively. The resistance rates of *E. coli* to trimethoprim/sulfamethoxazole, fluoroquinolone, and even 3rd generation cephalosporin are higher in Korea compared with other countries, however, the studies that determined those resistance rates included data collected at tertiary referral hospitals, which may have been overestimated. Continuous monitoring of antibiotic resistance and opportune establishment and revision of treatment guidelines are required for the optimal management of acute cystitis.

Keywords: Cystitis; Antibiotic resistance; Community-acquired infections

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INTRODUCTION

Urinary tract infection (UTI) is the most frequent infectious disease in the clinical field and is very common in women [1]. More than 50% of women have at least one episode of UTI during their lifetime [2]. As many as 15% of women develop UTIs every year, and at least 25% have one or more recurrences [3,4]. Acute uncomplicated UTI is defined as acute cystitis or pyelonephritis in women with no urinary tract abnormality, who are not pregnant and are healthy. Diagnosis is based on typical symptoms and laboratory findings. Typical symptoms of acute cystitis include dysuria, frequent urination, and urination urgency. The laboratory finding of leukocyturia (>5-10 leukocytes/high-power field) in symptomatic patients or a positive urine culture ($>10^4$ CFU/ml from midstream urine specimen) is used in diagnosis of acute cystitis. Recently, more patients with uncomplicated UTIs have not been cured in primary clinics. Therefore, the major causative organisms of acute cystitis and the changes in the antibiotic susceptibility pattern of those organisms in South Korea should be examined.

CAUSATIVE ORGANISM

Escherichia coli is the most frequent causative organism of acute cystitis, which includes South Korea. The causative microorganisms of UTIs recorded in Korea since 1995 are listed in Table 1 [5-10]. The trend of an increasing incidence of UTIs is more obvious for cases that are community-acquired and uncomplicated.

ANTIMICROBIAL SUSCEPTIBILITY OF COMMUNITY-ACQUIRED UTIs IN SOUTH KOREA

The antibiotic susceptibilities of uropathogens (*E. coli*)

Table 1. Causative organisms of community-acquired urinary tract infections in Korea

Causative organisms	Lee et al. [5] (2009)		Shin et al. [6] (2008)	Lee et al. [7] (2002)	Wie et al. [8] (2001)	Kim et al. [9] (1996-1999)		Min [10] (1995-1997)
	APN	Cystitis	APN	Cystitis	APN	APN	Cystitis	APN
Escherichia coli	153 (76.1)	1,071 (72.7)	661 (91.9)	191 (79.9)	120 (92.3)	34 (70.8)	41 (64.1)	191 (88.0)
Klebsiella pneumoniae	9 (4.4)	52 (3.5)	15 (2.1)	6 (2.5)	6 (4.3)	2 (4.2)	2 (3.1)	8 (3.7)
Proteus species			1 (0.1)	7 (2.8)	2 (1.5)	1 (2.1)		
Enterococcus species	13 (6.5)	158 (10.7)	11 (1.6)	9 (3.8)		5 (10.4)	6 (9.3)	7 (3.2)
Streptococcus species		44 (3.0)	7 (1)	1 (0.4)			9 (14.1)	
Others	26 (13.0)	149 (10.1)	24 (3.3)	25 (10.5)	2 (1.5)	6 (12.5)	6 (9.4)	11 (5.1)
Total number	201	1,474	719	239	130	48	64	217

Values are presented as number (%).
APN: acute pyelonephritis.

Table 2. Antimicrobial susceptibility of uropathogens (*Escherichia coli*) of uncomplicated urinary tract infection cases

Susceptibility (%)	Lee et al. [5] (2009)		Shin et al. [6] (2008)	Lee et al. [7] (2002)	Wie et al. [8] (2001)	Kim et al. [9] (1996-1999)		Min [10] (1995-1997)
	APN	Cystitis	APN	Cystitis	APN	APN	Cystitis	APN
Amikacin	99.3	99.5	99.5	99	99.2	100	95.5	97.5
Gentamicin	75.8	76.6	74.4	81.7	81.5	75.7	81.8	68.5
Ampicillin	31.4	38.5	37	37.2	-	64.9	54.1	17.2
Cefuroxime	86.9	86.1	-	-	98.5	-	-	95.5
Ciprofloxacin	81.7	74.6	84.1	84.8	93.1	83.8	86.4	86.5
Ceftriaxone	88.2	94.7	95.4	99.5	99.2	-	-	98.1
TMP/SMX	64.7	67.3	67.2	61.3	63.8	67.6	47.7	34.7
Isolate no.	153	1,071	660	191	130	37	44	191

APN: acute pyelonephritis, TMP/SMX: trimethoprim/sulfamethoxazole.

of uncomplicated UTI cases since 1995 are shown in Table 2, and the contents of Table 2 are schematized in Fig. 1 [5-10]. The threshold of 20% as the resistance prevalence at which the agent is no longer recommended for the empirical treatment of acute cystitis was determined based on an expert opinion derived from clinical, in vitro, and mathematical modeling studies [11]. The resistance of *E. coli* to ampicillin is above 50%, thus it cannot be used as an empirical antibiotic for the treatment of UTI, and the resistance of *E. coli* to trimethoprim/sulfamethoxazole (TMP/SMX) is more than 40%, and its resistance to 1st generation cephalosporin is more than 30%. Therefore, those agents also cannot be used as empirical antibiotics for the treatment of UTI. The susceptibilities of *E. coli* to gentamicin, fluoroquinolone, 3rd generation cephalosporin, and amikacin are 75%, 85-95%, 95%, and 97%, respectively. However, the studies that determined those resistance rates included data collected from tertiary referral hospitals and most of the included patients had acute uncomplicated pyelonephritis. Therefore, these resistance rates may have been overestimated.

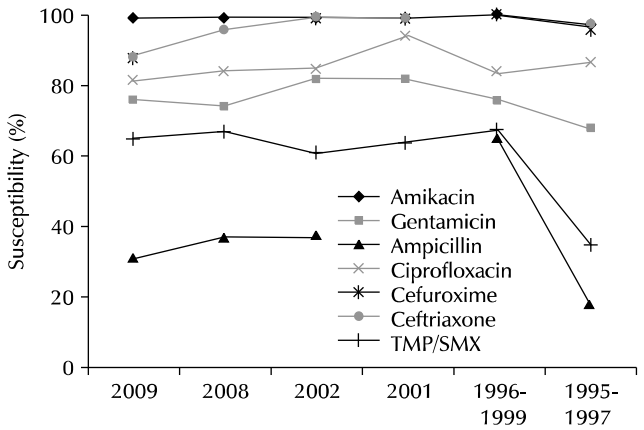

Fig. 1. Schematization of Table 2. TMP/SMX: trimethoprim/sulfamethoxazole.

In 2009, Lee et al. [5] reported antimicrobial resistance in community-acquired UTIs using data from a nationwide network that included 27 general hospitals and 7 private clinics. In that study uncomplicated UTI was classified by exclusion of male gender, urinary catheter, diabetes, renal transplantation, reflux disease, and urinary stone disease. In addition, the researchers tried to include as many

community-acquired uncomplicated UTI cases as possible. As a result, the susceptibilities of *E. coli* to ciprofloxacin and TMP/SMX were 74.6% and 67.3%, respectively. In comparison of the data of the study by Lee et al. [7] study with data obtained in 2002, the resistance of *E. coli* to TMP/SMX decreased, and its resistance to ciprofloxacin showed a steady increase.

The resistance rate of ciprofloxacin was not so high compared with a study by Kim et al. [12] (2006), who reported that ciprofloxacin resistance was 23.4% in acute uncomplicated cystitis. In general, compared with the late 1990s and early 2000s, the increase in the resistance rate of TMP/SMX and ciprofloxacin was not significant, rather, the prevalence of extended-spectrum β-lactamase (ESBL) producing bacteria increased (in 2006, 11.8% [12/102] [12], in 2009 7.6% [30/397] [6]). Production of ESBLs carries tremendous clinical significance. ESBLs are frequently plasmid-encoded [13], plasmids responsible for ESBL production frequently carry genes that provide resistance to other drug classes. Therefore, antibiotic options for the treatment of ESBL-producing organisms are extremely limited. In 2009, 69 of 649 *E. coli* (10.6%) isolates were resistant to both ciprofloxacin and TMP/SMX, and 4.3% (16/397) were resistant to ciprofloxacin, TMP/SMX, and extended-spectrum cephalosporins (e.g., cefotaxime, ceftazidime, aztreonam, etc.) [6].

TREND OF FLUOROQUINOLONE RESISTANCE

Many studies conducted in diverse countries have reported an increase in fluoroquinolone resistance [14-16]. In community-acquired UTIs, increasing resistance of *E. coli* to extended-spectrum cephalosporins has become a global phenomenon [17]. Many enterobacteriaceae now carry broad-spectrum β-lactamases, such as CTX-M, with particular genotypes associated with different geographical regions. The spread of these enzymes has compromised the clinical utility of a number of β-lactam classes, and with the spread of genes, such as bla_{KPC}, the efficacy of carbapenems may be increasingly compromised in the future. High-level fluoroquinolone resistance (mainly caused by *gyr*A mutations) has also shown association with CTX-M and CMY-type enzymes, commonly due to co-carriage of conjugative plasmids of the gene encoding the aminoglycoside-inactivating enzyme AAC-6^{1}-Ib-cr and *qnr* genes (which confer low-level resistance), allowing easy selection of *gyr*A mutants by the host strain [17].

TREATMENT OF COMMUNITY-ACQUIRED UTIs IN SOUTH KOREA

Although UTI, particularly acute cystitis, is discounted as a minor illness, its repetition rate is relatively high. Therefore, the emergence of resistant bacteria due to antibiotic abuse and treatment failure (social medical cost) due to antibiotic conservation should be considered. Curing urinary infection is dependent on antimicrobial concentrations in the urine rather than in the serum and tests of antimicrobial sensitivity based on urinary levels should be available in clinical practice [18]. Even when a laboratory report indicates resistance to certain antibiotics, treatment efficacy should be verified by measuring the urinary-concentration of antibiotics. For example, in treatment of bacteria resistant to TMP/SMX, results of clinical and microbiological determination of treatment failure rates were different. Clinical success is possible in cases of microbiological failure [19,20]. In a previous study of ciprofloxacin, a mean of 25% of the drug was excreted in the urine over a 12-hour dosing interval, and the concentrations of ciprofloxacin in the urine at a dosage of 500 mg every 12 hours ranged from 100 to 300 μg/ml, well above the MIC (4 mg/L) for the enteric pathogens isolated [21]. Therefore, the treatment success rate of ciprofloxacin in UTI cases with ciprofloxacin-resistant bacteria as the infectious agent should be assessed.

The new cystitis guidelines released by the Infectious Diseases Society of America (IDSA) recommend nitrofurantoin, TMP/SMX, or fosfomycin as first line agents for the empiric treatment of cystitis in adult patients [11]. Fosfomycin does not undergo hepatic metabolism and is primarily eliminated in its original form by the kidneys through glomerular filtration. Thus, it has been regarded as an ideal antibiotic for uncomplicated UTIs. In 1983, Lee et al. [22] reported that fosfomycin showed clinical efficacy of 88.9% for uncomplicated UTI. However, in 2008, Kim et al. [23] reported a relatively high resistance rate of fosfomycin, 28.2% in community-acquired UTI. In 2014, in a nationwide multicenter surveillance study by Seo et al., 346 community-acquired *E. coli* isolates were collected

from patients with UTI from April 2010 to March 2011, and the susceptibility rate of fosfomycin was 100% (346/346).

Nitrofurantoin, another recommended antibiotic for the treatment of cystitis, is not available in Korea. However, Ryu et al. [24] reported that the susceptibility of *E. coli* isolates from community-acquired cystitis cases to nitrofurantoin was 93.3%. Pivmecillinam, a synthetic penicillin for oral use, is absorbed readily from the gastrointestinal tract and is highly concentrated in the urine.

Pivmecillinam is particularly effective against gram-negative bacteria and has beta-lactamase stability, including stability in the presence of CTX-M-type ESBLs. Pivmecillinam is not currently available in Korea. The only study on the use of this drug for the treatment of UTI in Korea was by Lee and Chang [25] in 1982, who reported 95% efficacy in acute cystitis (19/20).

The guidelines for the treatment of acute uncomplicated cystitis in Korea are as follows [26]:

① 3-day regimen of oral fluoroquinolone is recommended for acute cystitis.

② Fosfomycin, nitrofurantoin, and β-lactams (cefpodoxime proxetil, cefixime, amoxicillin/clavulanate) can be used as alternative agents.

CONCLUSIONS

Uncomplicated cystitis is a minor infectious disease, with a high incidence. Therefore, attention should be paid to emerging antibiotic resistance due to the frequent use of agents or to failure of treatment due to reluctant usage of agents, which also increases medical costs. In Korea, the antibiotic resistance pattern of acute cystitis is characterized by higher resistance rates to TMP/SMX, fluoroquinolone, and even 3rd generation cephalosporin compared with advanced countries, causing difficulty in selection of optimal empirical antibiotics. The studies that determined those resistance rates included data collected from tertiary referral hospitals, which may have been overestimated. Therefore, for the optimal management of acute cystitis, continuous monitoring of antibiotic resistance and opportune establishment and revision of treatment guidelines are necessary.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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