Systematic Review and Meta-Analysis

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Prevalence of antibiotic susceptibility and resistance of *Escherichia coli* in acute uncomplicated cystitis in Korea

Systematic review and meta-analysis

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Abstract

Background: The aim of this study is to determine the prevalence of antibiotic susceptibility and resistance of Escherichia coli *Escherichia coli* (*E coli*) in female uncomplicated cystitis in Korea using meta-analysis.

Methods: A cross-search of the literature was performed with MEDLINE for all relevant data published before October 2015 and EMBASE from 1980 to 2015, the Cochrane Library, KoreaMed, RISS, KISS, and DBPia were also searched. Observational or prospective studies that reported the prevalence of antimicrobial susceptibility and resistance of *E coli* were selected for inclusion. No language or time restrictions were applied. We performed a meta-analysis using a random effects model to quantify the prevalence of antimicrobial susceptibility and resistance of *E coli*.

Results: Ten studies were eligible for the meta-analysis, which together included a total of 2305 women with uncomplicated cystitis. The overall resistance rate to antibiotics was 0.28 (95% confidence interval [CI]: 0.25, 0.32). The pooled resistance rates were 0.08 (95% CI: 0.06, 0.11) for cephalosporin, 0.22 (95% CI: 0.18, 0.25) for fluoroquinolone (FQ), and 0.43 (95% CI: 0.35, 0.51) for trimethoprim/sulfamethoxazole (TMP/SMX). Regression analysis showed that resistance to FQ is increasing ($P=0.014$) and resistance to TMP/SMX is decreasing ($P=0.043$) by year. The generation of cephalosporin was not a significant moderator of differences in resistance rate.

Conclusion: The resistance rate of FQ in Korea is over 20% and is gradually increasing. Although the resistance rate of TMP/SMX is over 40%, its tendency is in decreasing state. Antibiotic strategies used for the treatment of uncomplicated cystitis in Korea have to be modified.

Abbreviations: AUC = acute uncomplicated cystitis, FQ = fluoroquinolone, IDSA = Infectious Diseases Society of America, TMP/SMX = trimethoprim/sulfamethoxazole, UTI = urinary tract infection.

Keywords: antibiotic resistance, cystitis, *E coli*, meta-analysis

1. Introduction

Urinary tract infection (UTI) is a common disease in women; more than 50% of women will experience at least 1 episode of UTI sometime in their lives.[1] Acute uncomplicated cystitis (AUC) makes up the greatest percentage of all cases of UTI. A large number of antibiotics can be used to treat community-acquired AUC.[2]

Many countries use fluoroquinolones (FQs) as a primary treatment for UTI. The worldwide resistance of UTI to FQ is known not to exceed 10%.[3] However, recent reports in Korea found a resistance rate to FQ of over 20%.[4,5] The Infectious Diseases Society of America (IDSA) recommends that physicians consider information on local susceptibility and resistance rates of antibiotics and not use antibiotics with local resistance rates greater than 20%.

Considering that treatment of AUC is related to a rise in antimicrobial resistance, the increasing resistance to FQ is a challenge. In Korea, the antimicrobial resistance rate jumped from 15.2% in 2002 to 20.4% in 2008.[4,5] To date, few efforts have been made to document the local and worldwide antimicrobial susceptibility and resistance rates of *Escherichia coli* (*E coli*).[3] Published studies concerning antimicrobial

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resistance of uropathogens in communities or hospitals are scarce, and most of them are single-center studies.[6–8]

When resistance to FQ has increased, there are fewer options for the treatment of UTI caused by *E coli*. Considering the scarcity of observational studies which address the susceptibility and resistance rates to trimethoprim/sulfamethoxazole (TMP/SMX), FQ, fosfomycin, and cephalosporin using well designed community-based methods or multicenter hospital-based methods, an evidence-based review of the studies that does exist is indispensable. In this systematic review and meta-analysis, we present antimicrobial susceptibility and resistance rates over time and also provide information that can be used to establish evidence-based guidelines for antibiotic treatment for cases of acute uncomplicated cystitis (AUC).

2. Methods

This meta-analysis was carried out using the guidelines published by the Cochrane Collaboration and the standard PRISMA protocol. This work was approved by Institutional Review Board of Soonchunhyang University Hospital.

2.1. Types of studies and participants

Clinical trials which were conducted at medical institutions in Korea were included in this meta-analysis. Nonrandomized clinical trials were included. The participants were Korean patients diagnosed with urinary pain, dysuria, increased urinary frequency, and/or urinary urgency caused by urinary infection (cystitis) (Table 1).

2.2. Types of interventions

All of the studies were observational. Several different types of antibiotics were used to treat patients. The subjects received cephalosporin (first generation, Cefazolin; second generation, Cefoxitin and Cefotetam; third generation, Ceftriaxone, Ceftazidime, and Cefotaxime), FQ (Levofloxacin and Ciprofloxacin), TMP/SMX (Trimethoprim/Sulphamethoxazole), aminoglycoside (Amikacin, Gentamicin, Netilmicin, and Tobramycin), or betalactam (Ampicillin, amoxicillin/clavunanic acid, Ticarcillin +Ca, Ticarcillin, Ampicillin/Sulbactam, and Piperacillin/Tazobactam). The target uropathogen was limited to *E coli* (Table 1).

2.3. Types of outcome measures

Primary outcomes included the susceptibility and resistance rates to the antibiotics used. Secondary outcomes were susceptibility and resistance to cephalosporin by generation. We excluded the cases in which there was only 1 instance of treatment with each antibiotic.

2.4. Search methods used to identify studies

A cross-search of the literature was performed with MEDLINE for all relevant data published before October 2015 and an optimally sensitive Cochrane Collaboration search using specific MeSH headings, including urinary infection, cystitis, antibiotics, and anti-infective agents, with all subheadings including "Bacterial/drug effects" or "Drug Resistance, Bacterial" or "Bacterial/isolation and purification." EMBASE from 1980 to 2015, the Cochrane Library, KoreaMed, RISS, KISS, and DBPia were also searched. The reference lists of potentially relevant manuscripts and review articles were manually searched for suitable studies. There were no language restrictions.

Studies were included if they met the following criteria: reported outcome measurements in Korea, interventions included administration of antibiotics, and participants were diagnosed with AUC.

2.5. Data collection and analysis

The initial screening of electronic databases for the selection of studies was based on information in titles and abstracts. The screening was performed by 2 independent authors (SRS and JHK). Complete study reports were reviewed for selection by both authors. In cases of insufficient data, the authors reviewed the full text of the article for further information and clarification. Final selection was made using GRADE Working Group guidelines. References and data for each study were carefully cross-checked to ensure that no overlapping data were present and to maintain the integrity of the meta-analysis.

2.6. Assessment of risk of bias

All studies used in this analysis were independently assessed for quality by 2 reviewers (SRS and JHK). Downs and Black, which is an appropriate quality assessment tool for nonrandomized studies, was used to evaluate the risk of bias. Downs and Black consists of 10 questions for overall reporting, 3 for external validity, 7 for internal validity bias, 6 for internal validity confounding (selection bias), and 1 for power.[9] There were some limitations for direct application of the Downs and Black assessment tool to evaluate the specific characteristics of each study. Thus, we set up the 1 criterion for quality assessment whether the study design conducted clinical trials or not. As a result, 10 items for overall reporting were ranked as high value because all of the studies were clinical trials. However, 6 items for internal validity confounding were ranked as low value because all of the studies did not conduct randomization and blind method.

We graded each parameter as Excellent/Good=20 to 28, Fair=15 to 19, and Poor=<14. The quality of the evidence related to the estimation of benefits and disadvantages in the population followed the suggestions of the GRADE Working Group.

2.7. Meta-analysis of findings and statistical analysis

All variables that had the same measurement units and outcomes were recorded as proportional data. Meta-analysis was performed using the metaprop command in STATA version 11.2 (StataCorp LP, College Station, TX),[10] and pooled estimates of the susceptibility and resistance rates to antibiotics along with 95% confidence intervals (CIs) were calculated. Meta-analyses were performed using the random-effects model developed by DerSimonian and Laird to obtain pooled overall effect sizes and 95% CIs.[11]

Meta-regression analysis was conducted in order to identify potential moderators of the resistance rate. We analyzed the variability in effect sizes due to differences between the moderators (e.g., study duration for FQ and TMP/SMX and generation for cephalosporin) with a restricted maximum likelihood estimator of the variance of the true effects.

Table 1

Characteristics of included clinical studies.

Study & publish year	Study duration		No. of subjects for analysis for *E coli* in women	Determination of antibiotic susceptibility	Subject description
	Susceptibility	Resistance	Susceptibility/resistance		
Lee 2008	2007 (Oct. 2007–Jan. 2008)	–	54/–	CLSI guideline	Male and female. Age 18–65 y with more than one symptoms at least dysuria, frequency, urgency, suprapubic pain, and confirmed pathogenic bacteria Single center prospective observational study
Kim 2012	2008 (Jan. 2008–Dec. 2008)	2008 (Jan. 2008–Dec. 2008)	115/115	N/A	Male and female. Age ≥ 15 y with acute uncomplicated cystitis Multicenter retrospective case control study (acute pyelonephritis vs acute uncomplicated Cystitis)
Son 2006	2004 (Oct. 2004–Jun. 2006)	2004 (Oct. 2004–Jun. 2006)	102/102	NCCLS guideline and used cation-adjusted Mueller–Hinton broth	Female with acute uncomplicated cystitis Single-center prospective observational study
Lee 2004	2002 (May 2002–Oct. 2002)	2002 (May 2002–Oct. 2002)	191/191	GPS-429, 430 and GNS-433, 434 cards and the Vitek (bioMérieux, MO) instrument	Female. Age 18–65 y with acute uncomplicated cystitis Multicenter prospective observational study
Lee 2011	2008 (Jan. 2008–Jun. 2009)	2008 (Jan. 2008–Jun. 2009)	1071/1071	CLSI guideline and used cation-adjusted Mueller–Hinton broth	Male and female with acute uncomplicated cystitis Multicenter prospective observational study
Kim 2000	1996 (Jun. 1996–Jun. 1999)	–	75/–	Kirby–Bauer method on Mueller–Hinton agar or automatic measurement using Microscan Walkaway-96 (USA)	Male and female with acute uncomplicated cystitis with or without fever, frequency, urgency, dysuria, and lower abdominal pain Single-center prospective observational study
Huh 2003	–	1998	–/27		Male and female with uncomplicated cystitis with or without fever (>37.2 °C), urgency, dysuria, and lower abdominal pain frequency, and confirmed pyuria in urine analysis
		2000	–/38	NCCLS guideline	Single-center prospective observational study
		2001	–/67		
		2002	–/50		
Kim 2008	2002	2002	191/191	NCCLS guideline and used the Vitek (bioMérieux, MO,) instrument	Female. Age 18–65 y with acute uncomplicated cystitis
	2006	2006	214/214		Multicenter prospective observational study
Lee 2010 (a)	–	2006 (May 2006–Oct. 2006)	–/225	Agar dilution method on Mueller–Hinton agar	Female. Age 18–65 y with acute uncomplicated cystitis and with urinary pain, urgency, and frequency Multicenter prospective observational study
Kim 2008 (a)	2006 (Jun. 2006–Dec. 2007)	2006 (Jun. 2006–Dec. 2007)	–/61	NCCLS guideline and used disk dilution method	Female with acute uncomplicated cystitis Single-center retrospective observational study

CLSI = Clinical and Laboratory Standards Institute, NCCLS = National Committee for Clinical Standards.

2.8. Assessment of heterogeneity

Statistical heterogeneity was evaluated using Cochran Q test and the I^2 statistic. Either a Cochran Q value $P < 0.1$ or an I^2 value >50% indicated the existence of significant heterogeneity between studies. A nonsignificant chi-square test result ($P \geq 0.1$) or I^2 statistic (≤50%) indicated a lack of evidence for heterogeneity, but did not necessarily imply homogeneity because there may have been insufficient statistical power to detect heterogeneity.

2.9. Management of outliers

We eliminated outlying data from each study in order to obtain a more valid effect size. First, presumed effect size of extreme data was examined to conclude whether or not certain data points were outliers; then, we judged whether to include or exclude those points during combined analysis of the data.[12]

2.10. Assessment of reporting bias

This meta-analysis assessed small-study effects using Begg and Mazumdar rank correlation test and Egger linear regression method test for publication biases. The *P* values of the 2 statistical tests were calculated for all antibiotic types separately. The funnel plot analysis of publication bias is not reported as the plots are not visually interpretable.

3. Results

3.1. Inclusion of studies

The initial search identified a total of 326 articles from the electronic databases and manual searches (PubMed, 129; Cochrane, 82; Embase, 57; KoreaMed, 30; RISS, 27; and DBpia, 1). After eliminating 50 studies that contained overlapping data or that appeared in more than 1 database, and after screening the titles and abstracts, 188 studies were determined to be eligible for intensive screening. Of these, 175 studies were further eliminated as they did not include Korean population or hospital data (150), were not clinical studies (19), or were case series or abstracts only (6). A total of 13 studies met the selection criteria. However, 3 of them did not include the susceptibility or resistance rates to antibiotics or address recurrent cystitis. Finally, 10 studies that met all inclusion criteria were used. The 10 studies included a total of 2048 subjects for susceptibility and 2305 subjects for resistance. A detailed flowchart showing the selection process is given in Fig. 1. The 10 studies had detailed descriptions of the duration of research and of subjects' characteristics (Table 1). The studies were done from 1996 to 2009.

3.2. Quality assessment and reporting bias

Table 2 shows the quality assessment of the studies used. All of the studies were clinical trials. Two studies[13,14] were rated as poor, 4 studies[15–18] were rated as fair, and 4 studies[19–22] were rated as good using the Downs and Black assessment tool. Table 3 shows the small-study effects and the publication biases of resistance rates for all types of antibiotics. TMP/SMX ($P = 0.029$) on the Begg test and cephalosporin ($P = 0.011$) and aminoglycoside ($P = 0.001$) on the Egger test were found to have publication biases. Thus, there was generally no evidence of publication bias in this meta-analysis.

3.3. Outcomes and findings

Detailed findings on susceptibility are described in Figs. 2 and 3 and those on resistance are given in Figs. 4 and 5.

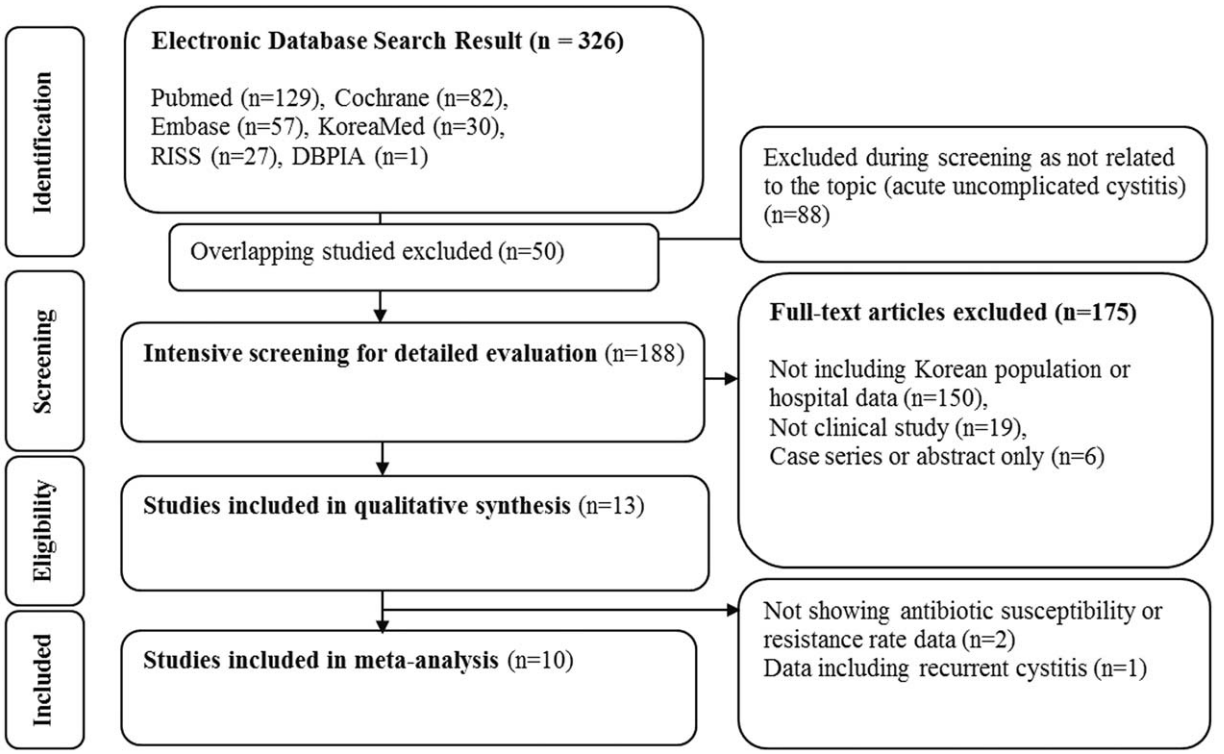

Figure 1. Flowchart of the study selection process.

Table 2

Quality assessment of the included studies, using the Downs and Black method.

Study & publish year	Reporting score (10 items)	External validity (3 items)	Internal validity bias (7 items)	Internal validity confounding (selection bias) (6 items)	Power (1 item)	Total
Lee 2008	8	3	4	2	3	20
Kim 2012	8	0	3	3	3	17
Son 2006	6	0	3	1	2	12
Lee 2004	7	2	5	2	4	20
Lee 2011	8	2	5	2	4	21
Kim 2000	6	1	4	1	4	16
Huh 2003	6	1	4	1	3	15
Kim 2008	7	2	5	2	4	20
Lee 2010 (a)	7	2	4	1	4	18
Kim 2008 (a)	6	0	3	1	3	13

Answers were given scores of 0 or 1, except for 1 item (#5) in the reporting subscale, which was scored 0 to 2, and 1 item (#27) on power, which was scored 0 to 5. Separate scores are given for each section (reporting, internal validity, external validity), and the overall total score. Papers were rated as "excellent/good", "fair", or "poor" depending on the numerical score assigned to the paper (excellent/good = 20–28; fair = 15–19; poor $\leq$ 14).

Table 3

Publication bias of the resistance rates given small-study effects.

Antibiotics	*k*	Begg		Egger	
		z	*P*	*t*	*P*
Cephalosporin	14	0.88	0.381	2.99	0.011
Quinolone	12	0.34	0.732	−0.55	0.596
TMP/SMX	9	2.19	0.029	2.32	0.053
Aminoglycoside	20	0.29	0.77	4.1	0.001
Penicillin	20	0.68	0.496	0.41	0.69

Test of H0: no small-study effects. TMP/SMX = trimethoprim/sulfamethoxazole.
Continuity corrected with Kendall tau. *k*, number of effect sizes; Begg, Begg and Mazumdar rank correlation test; Egger, Egger linear regression method test.

3.4. Susceptibility

The pooled overall antibiotic susceptibility rate was 0.75 (95% CI: 0.72, 0.79). The heterogeneity Cochrane Q statistic was $P <$ 0.001 and the Higgins' I^2 value was 98.97%. We conducted subgroup analysis to evaluate susceptibility to the different classes of antibiotics. The pooled susceptibility rates were 0.92 (95% CI: 0.87, 0.96) for cephalosporin, 0.78 (95% CI: 0.74, 0.82) for FQ, 0.62 (95% CI: 0.55, 0.68) for TMP/SMX, 0.86 (95% CI: 0.83, 0.89) for aminoglycoside, 0.39 (95% CI: 0.36, 0.41) for penicillin, and 0.77 (95% CI: 0.69, 0.86) for betalactam (Fig. 2).

In subgroup analysis of cephalosporin generations, we found susceptibility rates of 0.88 (95% CI: 0.84, 0.93) for cefazolin (first generation) and 0.97 (95% CI: 0.93, 1.00) for ceftriaxone (third generation) (Fig. 3).

3.5. Resistance

The pooled overall antibiotic resistance rate was 0.28 (95% CI: 0.25, 0.32). The heterogeneity Cochrane Q statistic was $P <$ 0.001 and the Higgins' I^2 value was 98.91%. We conducted subgroup analysis to evaluate resistance to the different classes of antibiotics. The pooled resistance rates were 0.08 (95% CI: 0.06, 0.11) for cephalosporin, 0.22 (95% CI: 0.18, 0.25) for FQ, 0.43 (95% CI: 0.35, 0.51) for TMP/SMX, 0.12 (95% CI: 0.08, 0.16) for aminoglycoside, and 0.54 (95% CI: 0.42, 0.67) for penicillin (Figs. 4 and 5).

In subgroup analysis of cephalosporin generations, we found resistance rates of 0.13 (95% CI: 0.09, 0.18) for cefazolin and cephalothin (first generation), 0.05 (95% CI: 0.00, 0.09) for cefoxitin (second generation), and 0.03 (95% CI: −0.01, 0.06) for ceftriaxone (third generation) (Fig. 6).

3.6. Quinolone and TMP/SMX resistance rates by year

Figure 7 shows the trend in the rates of antibiotic resistance to FQ and TMP/SMX by year. On the whole, the quinolone resistance rate gradually increased; it was 0.11 (95% CI: 0.04, 0.28) in 1998 and 0.25 (95% CI: 0.22, 0.27) in 2008. By contrast, the TMP/SMX resistance rate rapidly decreased from 0.75 (95% CI: 0.59, 0.86) in 2000 to 0.32 (95% CI: 0.30, 0.35) in 2008. These results were supported by the moderator analysis through which we analyzed the resistance rates to quinolone and TMP/SMX by year and cephalosporin by generation (Fig. 8). Study year was a significant moderator of FQ (P=0.014) and TMP/SMX (P= 0.043) resistance. However, the generation of cephalosporin was not a significant moderator of differences in resistance rate.

4. Discussion

Although antimicrobial treatment has been effective in controlling AUC for the last few decades, assessment of the resistance rate by urine culture are becoming more important because AUC makes up a large percentage of cases of community-acquired UTI. The aim of this study was to perform a systematic review and meta-analysis to shed light on the time-dependent antimicrobial susceptibility and resistance rates considering the tendency toward increasing FQ resistance. To our knowledge, this is the first systematic review and meta-analysis of antimicrobial susceptibility and resistance in the English literature.

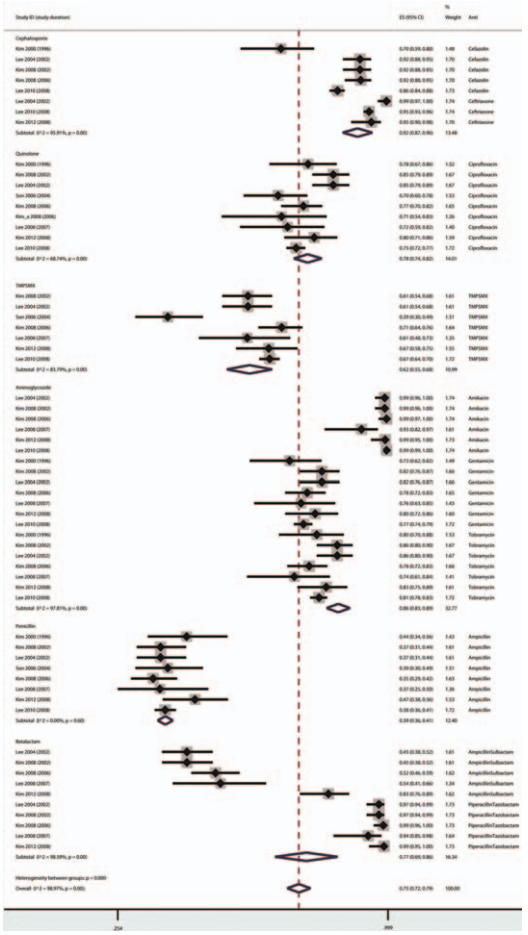

Figure 2. The pooled overall susceptibility rate to antibiotics.

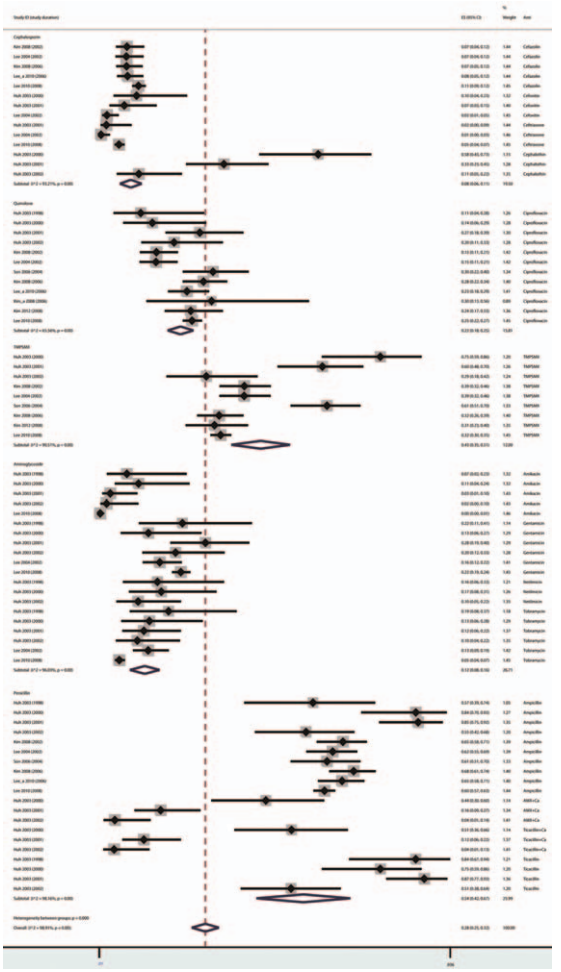

Figure 4. The pooled overall resistance rate to antibiotics.

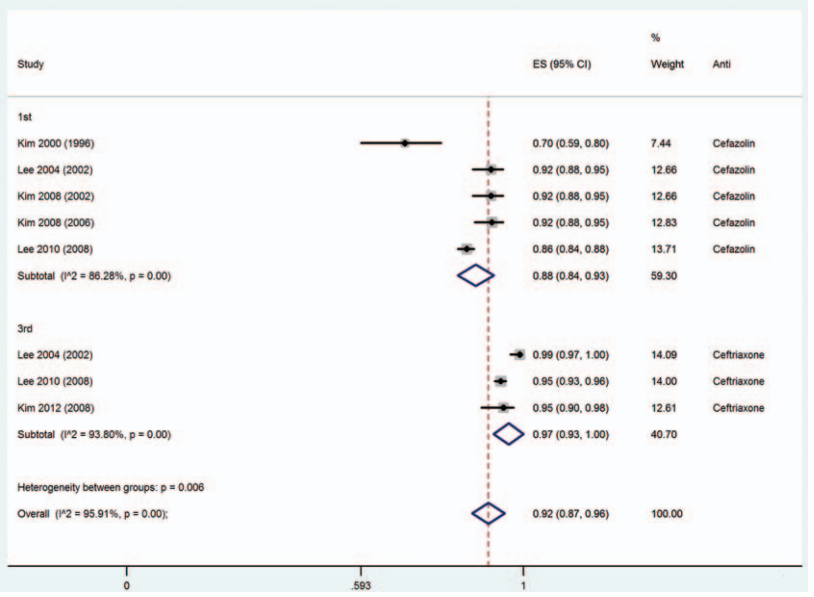

Figure 3. The pooled susceptibility rate by cephalosporin generation.

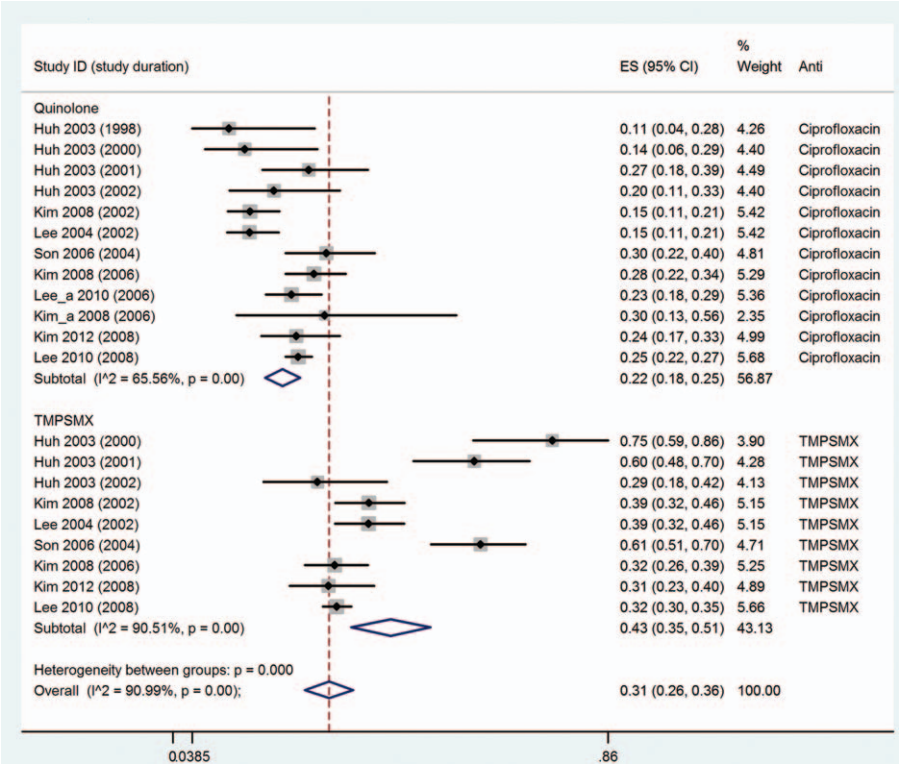

Figure 5. The pooled overall resistance rate to fluoroquinolone and trimethoprim/sulfamethoxazole.

The most important findings of our study are the increasing resistance to FQ and decreasing resistance to TMP/SMX (Figs. 5 and 7). Our results support the opinion that physicians should use FQ sparingly in both community and hospital settings because doing so is part of responsible antimicrobial stewardship in that it will prevent a further increase in FQ resistance.[23,24]

Through the worldwide lessons taken from changes in TMP/SMX resistance in the last few decades, the importance of urine culture, including antibiotic susceptibility tests, is reinforced. Such tests will help physicians decide on the optimal antimicrobial treatment for each individual case of AUC.[25] It is clear that the chance of treatment failure or relapse of UTI is increasing in cases in which nonsusceptible antimicrobial agents are prescribed.

Since the IDSA has suggested various treatment strategies for AUC that include 3 days of TMP/SMX, 3 days of FQ, 5 days of nitrofurantoin, 1 day of fosfomycin, and 3 to 7 days of pivmecrillinam, TMP/SMX and FQ have played a major role in treatment. However, the IDSA persistently recommended that antimicrobial agents with resistance rates over 20% not be used as first-line therapies.[3]

Considering that the resistance rate to FQ is increasing in Korea,[5,15] the treatment strategy for AUC has to be changed. The most recent report about hospital-based UTI found that the resistance rate to FQ in AUC is 20.4%, and it is 15.9% in acute pyelonephritis.[1] Although the current resistance to FQ in community-acquired infection is reported to be just 8.8% to 15.3%, our study confirmed that resistance to FQ is increasing rapidly.

It is important to monitor FQ resistance not only because FQ should continue to be a viable treatment option in the future but also because FQ resistance could yield colonization of methicillin-resistant *Staphylococcus aureus* (MRSA) or *Clostridium difficile*.[26,27]

Unlike in Korea, the prevalence of resistance to FQ is not very high in other countries, but still, increasing resistance to FQ is a worldwide phenomenon. In France, the FQ resistance rate increased from 14.8 % in 2007 to 17.8 % in 2012 (www.ecdc.europa.eu/en/healthtopics/antimicrobial resistance/database/Pages/database.aspx), which was confirmed in another French report.[28]

In Japan, Hayami et al[29] reported that FQ susceptibility was at least 87% in *E coli* isolates in 2009 to 2010. In Germany, Savaria et al[30] reported that resistance to TMP/SMX was 28% and resistance to FQ was 16% in 2010. Resistance to nitrofurantoin and fosfomycin were low (3.6% and 0.7%, respectively). In the United States, Hames and Rice[31] reported that the resistance rate to TMP/SMX was 23%, whereas resistance to FQ and nitrofurantoin were both <1%. In Brazil, Araujo et al[32] reported that gentamicin had the lowest overall resistance rate, 3.5%, followed by ceftriaxon at 5%, and then by FQ at 7.5%.

Considering the relatively high resistance to FQ in Korea, the associated factors should be investigated and antibiotic treatment plans should be modified accordingly. As National Health Insurance Database showing increasing use of FQ for AUC overtime was not available, direct correlation between FQ resistance and FQ overuse could not be established. However, considering the current treatment patterns in practice, as well as most guidelines recommendation of FQ as the initial empiric treatment since 1997, overuse of FQ could be the leading cause of this phenomenon. Matsumoto et al[33] reported that the major risk factor for infection with FQ-resistant *E coli* was a history of

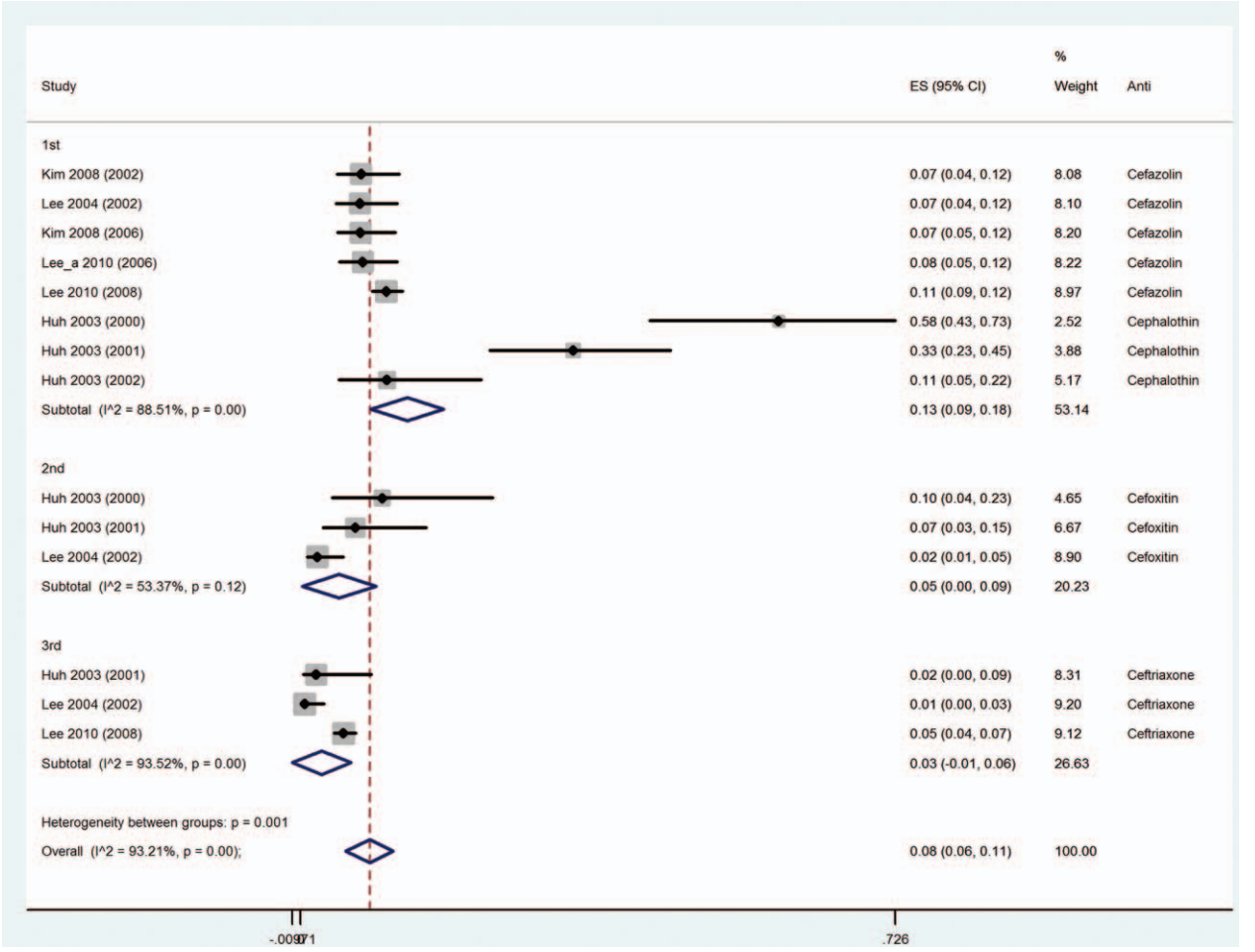

Figure 6. The pooled resistance rate by cephalosporin generation.

prior FQ administration. Other causes include the absence of infection control strategies in both communities and hospitals.[34]

One way to reduce FQ resistance is to perform urine culture with susceptibility tests for each patient. Primary care physicians are not well informed about the importance of urine culture and susceptibility testing. The national health insurance agency does not always pay for urine culture with susceptibility tests for AUC, especially when done in private clinics. If urine culture is done in

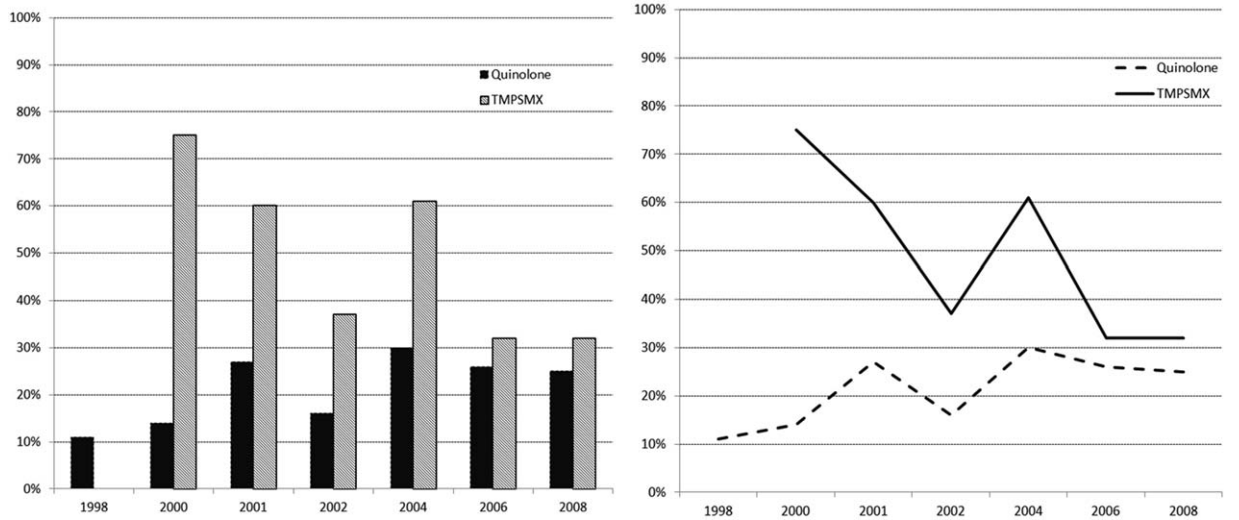

Figure 7. Trend of resistance to fluoroquinolone and trimethoprim/sulfamethoxazole by year.

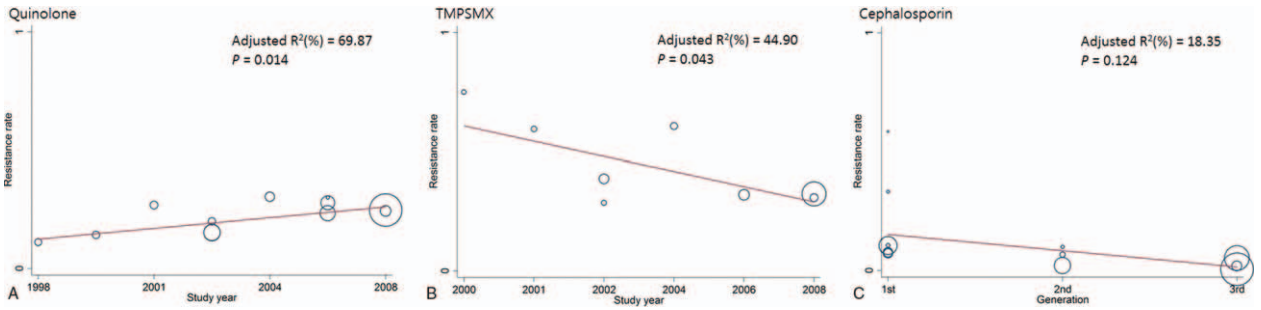

Figure 8. Meta-regression analysis of resistance to fluoroquinolone (A), trimethoprim/sulfamethoxazole (B), and cephalosporin (C) by study year.

AUC, new treatment strategies are possible, including confirmation of community-acquired infection and course of treatment with specific antibiotics. Moreover, practitioners could select an effective antibiotic other than FQ.

Another attractive solution is to consider other antibiotic agents such as TMP/SMX, nitrofurantoin, and fosfomycin. Our study shows lower resistance rates for nitrofurantoin and fosfomycin. Resistance to TMP/SMX is decreasing in Korea (Fig. 7). Today, it is close to 30%, which is attributable to decreased use of TMP/SMX during the last decade.[4,21,35–37]

A recent report from Grigoryan et al[38] supports our suggestion. Although those authors did not recommend routine urine culture for AUC, their recommendation for antibiotics for first-line treatment of AUR include TMP/SMX (160/800 mg twice daily for 3 days), nitrofurantoin (100 mg twice daily for 5–7 days), and fosfomycin (3 g in a single dose). They also suggested that FQ should be reserved for more complicated cases of UTI, even though FQ is quite efficacious in controlling AUC.

In Western countries, several studies done since the early 2000s have attempted to investigate and reduce resistance to TMP/SMX. Gupta et al[25] reported that identifying risk factors for TMP/SMX resistance and knowing the rate of resistance to TMP/SMX in the community are important factors in choosing better antibiotic agents and reducing antibacterial resistance.

Although this is the first systematic review and meta-analysis of the prevalence of antibiotic susceptibility and resistance, there are some limitations to our study. First of all, the resistance rates differ between communities.[39] Differences in resistance rates between hospitals in the same area have been reported.[40] The major reasons for this disparity include differences in patient comorbidities in different communities and hospitals. Comorbidities include history of UTI, previous UTI treatment, neurogenic disorders, postmenopausal status, and underlying bladder disorders.

Second, we did not take into account any uropathogens besides *E coli*. We focused on *E coli* because it is the leading cause of community-acquired UTI. Last, although we have tried to provide specific evidence-based guidelines for the treatment of AUC, we could not provide specific information regarding adverse effects, cost-effectiveness, and means of selecting susceptible strains. This could be accomplished after analyzing the data on antibiotic prescriptions for AUC in the National Health Insurance Database and after large-scale community-based studies.

In summary, resistance to FQ is increasing rapidly, more so in Korea than in other countries. To reduce the overall and antibiotic-specific resistance rates of *E coli* in AUC, routine urine culture is needed and careful prescription of FQ is warranted. Moreover, other antibiotics including fosfomycin, nitrofurantoin, and pivmecrillinam, which are recommended by the IDSA as first-line treatments, could be used to treat AUC in place of FQ. However, before the implementation of this strategy, large-scale community-based studies addressing susceptibility to those antibiotics are necessary.

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