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Role of age and sex in determining antibiotic resistance in febrile urinary tract infections

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SUMMARY

Objectives: To identify the age- and sex-specific antimicrobial susceptibility patterns of Gram-negative bacteria (GNB) in outpatient febrile urinary tract infections (UTIs) in Korea.
Methods: A total 2262 consecutive samples collected from patients aged 1–101 years with febrile UTIs, during the period January 2012 to December 2014, were analyzed in this multicentre, retrospective cohort study.
Results: The sensitivities to cefotaxime and cefoxitin were over 85% for females but under 75% for males. Sex played an important role in the susceptibility of GNB to cefotaxime ($p < 0.001$) and cefoxitin ($p < 0.001$). The sensitivity to ciprofloxacin (age >20 years) was under 75% in both sexes, and was not influenced by sex ($p = 0.204$). Age distributions of the incidences of resistance to cefotaxime, cefoxitin, and ciprofloxacin (age >20 years) were similar to the age distribution of the incidence of GNB, which indicates that the resistance patterns to these drugs were not affected by age (Kolmogorov–Smirnov test, female/male: $p = 0.927/p = 0.509$, $p = 0.193/p = 0.911$, and $p = 0.077/p = 0.999$, respectively).
Conclusions: Age is not a considerable factor in determining the antibiotic resistance in febrile UTIs. Ciprofloxacin should be withheld from both sexes until culture results indicate its use. Second- or third-generation cephalosporins such as cefoxitin and cefotaxime can be used empirically only in females.

1. Introduction

The selection of empirical antibiotics is of great importance in the management of febrile urinary tract infections (UTIs). According to international guidelines, fluoroquinolones, second-generation cephalosporins, third-generation cephalosporins, and co-trimoxazole are designated empirical antimicrobials for UTIs,[1,2] unless the resistance rate to community-dwelling *Escherichia coli* is over 20%. Recent guidelines for the treatment of UTIs in Korea are similar to international guidelines.[3] However, recent data from Korea have shown that, currently, only second- and third-generation cephalosporins are appropriate empirical antibiotics for community-acquired UTIs in adult females.[4] Furthermore, clinical susceptibility data are scarce regarding febrile UTIs, including UTIs in males, in Korea. Data ($n = 115$) reported in 2008 showed that the sensitivities of pathogens to second- and third-generation cephalosporins in acute prostatitis were 82.0% and 82.5%, respectively.[5] In addition, susceptibility data are lacking for all age groups, as well as both sexes, for the outpatient setting.

Several studies have reported that age and/or sex could be risk factors for emerging drug resistance in outpatient UTIs.[6,7] Therefore, urine samples should be cultured before the administration of antimicrobials, and clinicians should consider treating high-risk groups (specific age or sex groups) empirically with the

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relevant antimicrobials. Furthermore, awareness of sensitivities in the outpatient setting would facilitate the appropriate selection of empirical agents for the treatment of UTIs.[8] Hence, antimicrobial susceptibility data from an outpatient setting, with consideration of age and sex, are presented herein. Furthermore, it was determined whether age and/or sex could impact the emergence of drug resistance.

2. Materials and methods

2.1. Data collection

The present study was first approved by a central ethics committee (Catholic Medical Centre, The Catholic University of Korea College of Medicine, Seoul, Korea; No. XC12RIMI0018 V, XC14RIMI0109 V) and then approved by the respective local ethics committees. This was a multicentre, retrospective cohort study. UTIs were identified by positive specimens in a microbiology laboratory, and a chart review was performed to differentiate febrile UTIs. The data were collected from three teaching hospitals with 600–1300 beds in the capital region of Korea (Seoul and Gyeonggi) and three other teaching hospitals with 300–1000 beds located in metropolitan areas (Daejeon, Busan, and Incheon), using a web-based electronic system in which the data could be shared among all of the institutes. A central office managed all of the electronically recorded data.

2.2. Study population and design

Any UTI patient, regardless of age or sex, with a clinical and microbiological diagnosis of a UTI from January 2012 to December 2014, was eligible for the study. All patients with UTIs who were included in the study presented the following characteristics: (1) evidence of bacteriuria ($\geq 10^4$ CFU/ml) in the midstream urine; (2) fever (tympanic membrane temperature >37.8 °C);[9] (3) ≥5 white blood cells per high-power field in the urine; and (4) one or more of the following symptoms/signs: dysuria, urgency, frequency, suprapubic pain, perineal pain, tenderness of prostate during digital rectal examination, or costovertebral angle tenderness upon percussion. Only cases in which a urine specimen had been cultured before antimicrobials were administered were included. Furthermore, only outpatient UTIs were included; inpatient UTIs were excluded. For the present study, an outpatient UTI was defined as a case in which the patient had visited an outpatient clinic due to a UTI, or symptoms and signs of a UTI were detected within 48 h of hospitalization. Successive cultures from the same patient were excluded to avoid data duplication during the treatment period, and recurrent UTIs were excluded because they could negatively or positively influence the susceptibility data. Thus, individual patients were not included in the study multiple times. Finally, patients who had bladder augmented with intestine, intestinal neobladder, or any urinary-intestinal fistulas were also excluded.

Only patients who had had indwelling urethral catheters for more than 7 days were defined as having catheter-associated UTIs. The administration of antimicrobials within the previous 3 months was classified as exposure to antibiotics.

The sensitive automatic MicroScan identification system (MicroScan; Baxter Diagnostics, Inc., West Sacramento, CA, USA) was used to identify the subject bacteria, and minimal inhibitory concentrations (MICs) were measured using the broth microdilution method. MICs were obtained for the following antibiotics: amikacin, ampicillin, amoxicillin/clavulanic acid, cefoxitin, cefotaxime, ceftazidime, ciprofloxacin, imipenem, piperacillin/tazobactam, and cotrimoxazole. A sensitive/intermediate/resistant (SIR) interpretation similar to that used in previous studies was used for the data report, to obtain a simple description and for easy comparison;[10–13] however, reporting the MICs would have improved the monitoring of dynamic and subtle changes in the antimicrobial susceptibilities. The standard Clinical and Laboratory Standards Institute (CLSI) guidelines were applied to set the MIC breakpoints.

2.3. Statistical analysis

The Kolmogorov–Smirnov test was used to assess the differences in age distribution of the incidence of UTIs according to the age distribution. The Chi-square test or Fisher's exact test was used for the univariate analysis to assess the potential risk factors for resistance to each antimicrobial agent. Variables with a significant p-value ($p < 0.05$) were selected for inclusion in the multivariate analysis. The logistic regression test was used for the multivariate analysis (non-selection). Each statistical method is also summarized in brief in the footnotes to the corresponding table.

3. Results

E. coli was the most frequently isolated bacterium in both sexes; however, *E. coli* was present in only 46.1% of male outpatient febrile UTIs, but was present in 73.5% of female outpatient febrile UTIs. *Klebsiella pneumoniae*, the second most frequently isolated Gram-negative bacterium, was present in 5.3% of female febrile UTIs and 7.7% of male febrile UTIs. Among Gram-negative bacteria, *E. coli* was present in 85.2% of female outpatient febrile UTIs, whereas 58.8% of outpatient febrile UTIs in males were associated with *E. coli*. Meanwhile, Gram-negative bacteria explained 86.3% of female febrile UTIs and 78.5% of male febrile UTIs, which was more representative of outpatient febrile UTIs than *E. coli* by itself (Table 1). The antimicrobial susceptibilities of Gram-negative bacteria as well as *E. coli* are presented in Figure 1 and Tables 2 and 3; the antimicrobial susceptibilities of Gram-negative bacteria were sub-analyzed for three different age groups.

The susceptibility of Gram-negative bacteria to the vast majority of antibiotics was greater in females (over 80%) than

Table 1
Patient baseline characteristics and microorganisms isolated from 2262 UTIs[a]

	Total(N = 2262)	Female (n = 1538)	Male (n = 724)
Age (years)	48.59 ± 26.63	53.13 ± 22.41	38.93 ± 31.82
Diabetes mellitus (%)	336 (14.9)	213 (13.8)	123 (17.0)
Urinary catheter (%)	67 (3.0)	16 (1.0)	51 (7.0)
Exposure to antibiotics (%)	654 (28.9)	464 (30.2)	190 (26.2)
Escherichia coli	1465 (64.8)	1131 (73.5)	334 (46.1)
Klebsiella pneumoniae	138 (6.1)	82 (5.3)	56 (7.7)
Pseudomonas aeruginosa	63 (2.8)	9 (0.6)	54 (7.5)
Proteus mirabilis	71 (3.1)	37 (2.4)	34 (5.0)
Enterobacter aerogenes	46 (2.0)	18 (1.2)	28 (3.9)
Enterobacter cloacae	32 (1.4)	14 (0.9)	18 (2.5)
Citrobacter freundii	20 (0.9)	14 (0.9)	6 (0.8)
Other Gram-negative bacteria	61 (2.7)	23 (1.5)	38 (5.2)
Total Gram-negative bacteria	1896 (83.8)	1328 (86.3)	568 (78.5)
Enterococcus faecalis	145 (6.4)	70 (4.6)	75 (10.4)
Enterococcus faecium	50 (2.2)	25 (1.6)	25 (3.5)
Streptococcus agalactiae	33 (1.5)	31 (2.0)	2 (0.3)
Staphylococcus aureus	43 (1.9)	29 (1.9)	14 (1.9)
Other Gram-positive bacteria	79 (3.5)	41 (2.7)	38 (5.2)
Total Gram-positive bacteria	350 (15.5)	196 (12.7)	154 (21.3)
Fungal infection	16 (0.7)	14 (0.9)	2 (0.3)

UTI, urinary tract infection.
[a] Age is presented as the mean ± standard deviation value; other data are presented as the number and frequency (%).

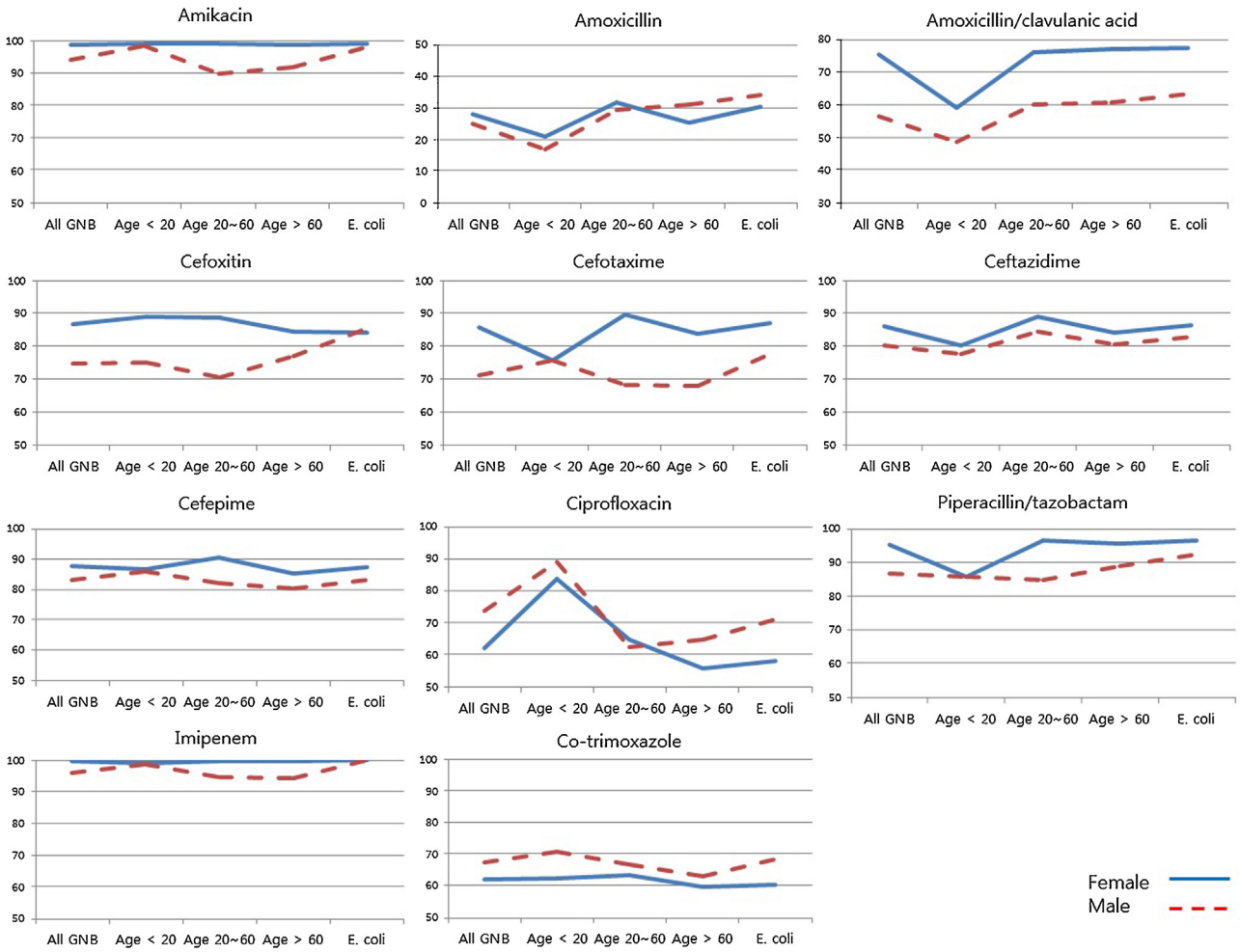

Figure 1. Antimicrobial susceptibility patterns for the drugs tested in the present study. The name of each antibiotic is given at the top of each graph. The *y*-axis shows the sensitivity (%) to the relevant antibiotic. The sensitivity of Gram-negative bacteria was sub-analyzed for three different age groups. The sensitivity of *E. coli* is provided at the end of the *x*-axis.

males, with the exception of ciprofloxacin and co-trimoxazole. In females, the sensitivity of Gram-negative bacteria was >85% to third-generation cephalosporin (group 3a cephalosporin: cefotaxime) and second-generation cephalosporin (cephamycin: cefoxitin), regardless of the patient's underlying condition, whereas susceptibility was < 80% in males . The sensitivity of Gram-negative bacteria was >80% for amikacin and restricted antibiotics such as cefepime, piperacillin/tazobactam, and imipenem in both sexes (Figure 1, Tables 2 and 3).

The mean patient age for the total study population was 48.59 ± 26.63 years (Table 1). However, the mean age of patients with UTIs was of no clinical importance considering the whole age distribution, because the incidence of UTIs showed a bimodal age distribution (Figure 2). The percentage of diabetes mellitus, indwelling

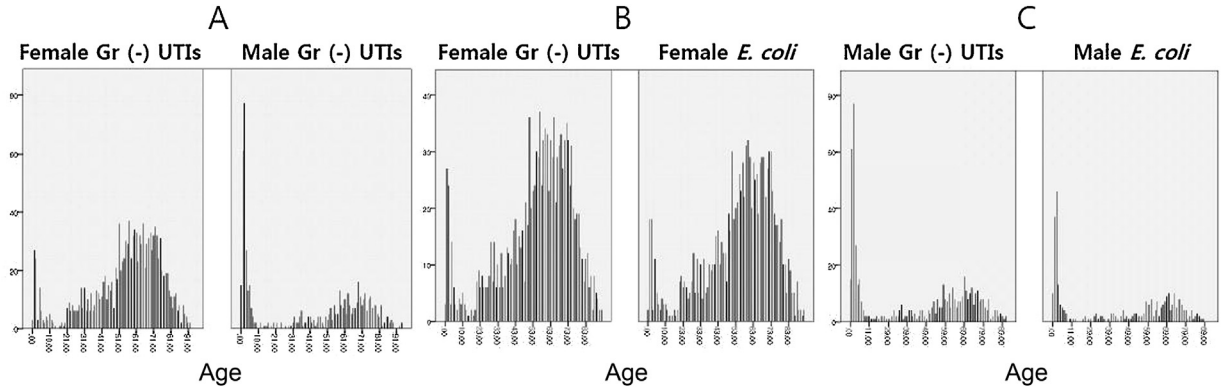

Figure 2. Age-specific distributions of incidences for Gram-negative febrile UTI in outpatients of both sexes. Each *y*-axis represents the incidence. (A) Age distributions of the incidence of total Gram-negative UTIs in the two sexes were different (left graph: female; right graph: male); Kolmogorov–Smirnov $Z = 6.583$, $p < 0.001$. (B) Age distributions of the incidences of Gram-negative UTIs and *E. coli* were not different in females (left graph: total UTI population; right graph: *E. coli* population); Kolmogorov–Smirnov $Z = 0.656$, $p = 0.783$. (C) Age distributions of the incidences of Gram-negative UTIs and *E. coli* were not different in males (left graph: total UTI population; right graph: *E. coli* population); Kolmogorov–Smirnov $Z = 0.556$, $p = 0.916$.

Table 2
Antimicrobial susceptibilities of 1328 Gram-negative bacteria in female febrile UTI outpatients[a]

E. coli %	1131/1328 (85.2)	81/106 (76.4)	530/607 (87.3)	520/615 (84.6)	1131/1131 (100.0)
Age	GNB, all ages	Young (<20 years)	Middle (20–60 years)	Old (>60 years)	*E. coli*, all ages
AMK	S 1294/1308 (98.9)	S 105/106 (99.1)	S 594/590 (99.0)	S 605/612 (98.9)	S 1120/1131 (99.0)
	I 9/1308	I 1/106	I 4/590	I 4/612	I 8/1131
	R 5/1308	R 0/106	R 2/590	R 3/612	R 3/1131
AMX	S 361/1282 (28.2)	S 20/95 (21.1)	S 186/585 (31.8)	S 155/612 (25.3)	S 339/1118 (30.3)
	I 11/1282	I 1/95	I 3/585	I 7/612	I 9/1118
	R 910/1282	R 74/95	R 396/585	R 440/612	R 770/1118
AUG	S 830/1101 (75.4)	S 42/71 (59.2)	S 385/506 (76.1)	S 403/524 (76.9)	S 743/960 (77.4)
	I 167/1101	I 12/71	I 79/506	I 76/524	I 156/960
	R 104/1101	R 17/71	R 42/506	R 45/524	R 61/960
CFX	S 958/1104 (86.8)	S 64/72 (88.9)	S 450/507 (88.8)	S 444/525 (84.6)	S 809/961 (84.1)
	I 63/1104	I 2/72	I 20/507	I 41/525	I 105/961
	R 83/1104	R 6/72	R 37/507	R 40/525	R 47/961
CTX	S 1130/1315 (85.9)	S 75/99 (75.8)	S 542/604 (89.7)	S 513/612 (83.8)	S 976/1120 (87.1)
	I 8/1315	I 4/99	I 1/604	I 3/612	I 2/1120
	R 177/1315	R 20/99	R 61/604	R 96/612	R 142/1120
CTZ	S 1122/1304 (86.0)	S 85/106 (80.2)	S 524/588 (89.1)	S 513/610 (84.1)	S 974/1128 (86.3)
	I 10/1304	I 1/106	I 5/588	I 4/610	I 6/1128
	R 172/1304	R 20/106	R 59/588	R 93/610	R 145/1128
CFP	S 1147/1308 (87.7)	S 92/106 (86.7)	S 534/591 (90.4)	S 521/611 (85.3)	S 983/1128 (87.1)
	I 0/1308	I 0/106	I 0/591	I 0/611	I 0/1128
	R 161/1308	R 14/106	R 57/591	R 90/611	R 142/1128
CP	S 803/1298 (61.9)	S 81/97 (83.5)	S 380/588 (64.6)	S 342/613 (55.8)	S 650/1123 (57.9)
	I 39/1298	I 1/97	I 12/588	I 26/613	I 32/1123
	R 456/1298	R 15/97	R 196/588	R 245/613	R 433/1123
PT	S 1239/1302 (95.2)	S 90/105 (85.7)	S 567/588 (96.4)	S 582/609 (95.6)	S 1087/1128 (96.4)
	I 24/1302	I 4/105	I 8/588	I 12/609	I 17/1128
	R 39/1302	R 11/105	R 13/588	R 15/609	R 24/1128
IMP	S 1305/1309 (99.7)	S 105/106 (99.1)	S 590/591 (99.8)	S 610/612 (99.7)	S 1131/1131 (100.0)
	I 0/1309	I 0/106	I 0/591	I 0/612	I 0/1131
	R 4/1309	R 1/106	R 1/591	R 2/612	R 0/1131
CTMZ	S 811/1307 (62.1)	S 66/106 (62.3)	S 375/591 (63.5)	S 365/610 (59.8)	S 682/1129 (60.4)
	I 0/1307	I 0/106	I 0/591	I 0/610	I 0/1129
	R 496/1307	R 40/106	R 216/591	R 240/610	R 447/1129

UTI, urinary tract infection; GNB, Gram-negative bacteria; S, susceptible; I, intermediate; R, resistant; AMK, amikacin; AMX, amoxicillin; AUG, amoxicillin/clavulanic acid; CFX, cefoxitin; CTX, cefotaxime; CTZ, ceftazidime; CFP, cefepime; CP, ciprofloxacin; PT, piperacillin/tazobactam; IMP, imipenem; CTMZ, co-trimoxazole.
[a] For the reader's convenience, percentages are presented in parenthesis only for the susceptible category.

catheter, and previous exposure to antibiotics was 14.9%, 3.0%, and 28.9%, respectively, in total febrile UTIs.

The age distribution of the incidence of total febrile Gram-negative UTIs exhibited a bimodal peak for both sexes; however, the age distributions of total outpatient febrile Gram-negative UTIs differed by sex (Figure 2). Most febrile Gram-negative UTIs were observed in the middle-age and older age groups in females, whereas over one-third of male febrile Gram-negative UTIs were found in the younger age group (Figure 2, Table 3). The age distribution of *E. coli* was similar to that of the Gram-negative bacteria for each sex (Figure 2).

When age was classified as young, middle, and old, susceptibilities of Gram-negative UTIs to amoxicillin/clavulanic acid, cefotaxime, and ciprofloxacin were seen to differ according to the age distribution (Figure 1), but on statistical analysis, it was found that only susceptibility to ciprofloxacin differed over the entire age distribution (Figures 3 and 4) .

Susceptibility to ciprofloxacin was higher in the younger age group than in the middle or old age group for both sexes (Table 2 and 3, and Figure 4) . However, for patients aged >20 years, the age distribution of the incidence of resistance to ciprofloxacin was similar to the age distribution of the incidence of total Gram-negative UTIs in both sexes (for age >20 years: Kolmogorov–Smirnov $Z = 0.370$, $p = 0.999$ in males; Kolmogorov–Smirnov $Z = 1.277$, $p = 0.077$ in females), which indicated that the resistance pattern for ciprofloxacin was not affected by age in adult febrile Gram-negative UTIs. Antimicrobial resistance for cefoxitin, cefotaxime, and amoxicillin/clavulanic acid also showed no association with age (Figure 3 and 4) .

A sub-analysis of potential risk factors for ciprofloxacin resistance was performed for those aged < 20 years. Tables 4 and 5 show the risk factors for resistance to cefoxitin, cefotaxime, and ciprofloxacin . Regarding fluoroquinolones (age >20 years), only exposure to antibiotics was a risk factor for selecting resistance, whereas sex, the presence of an indwelling catheter (only significantly associated with cefotaxime), and exposure to antibiotics were predisposing factors for emerging resistance of Gram-negative bacteria with the use of second- and third-generation cephalosporins.

Among Gram-negative febrile UTIs, catheter-associated UTIs were more frequently observed in males than in females, were more closely related to exposure to antibiotics, and exhibited a higher occurrence of infection caused by an atypical organism such as *Citrobacter* species, *Proteus mirabilis*, *Morganella morganii*, *Enterobacter* species, and *Pseudomonas aeruginosa* rather than *E. coli* (Table 6).

4. Discussion

Interestingly, no differences in the age distribution between Gram-negative febrile UTIs and febrile UTIs caused by second- and third-generation cephalosporin-resistant organisms were found for either sex, despite a difference in the age distribution between the sexes. These findings suggest that age does not exert any influence on the acquisition of resistance to second- and third-generation cephalosporins .

Most Gram-negative UTIs were observed in the middle and older age groups in females, whereas one-third of Gram-negative

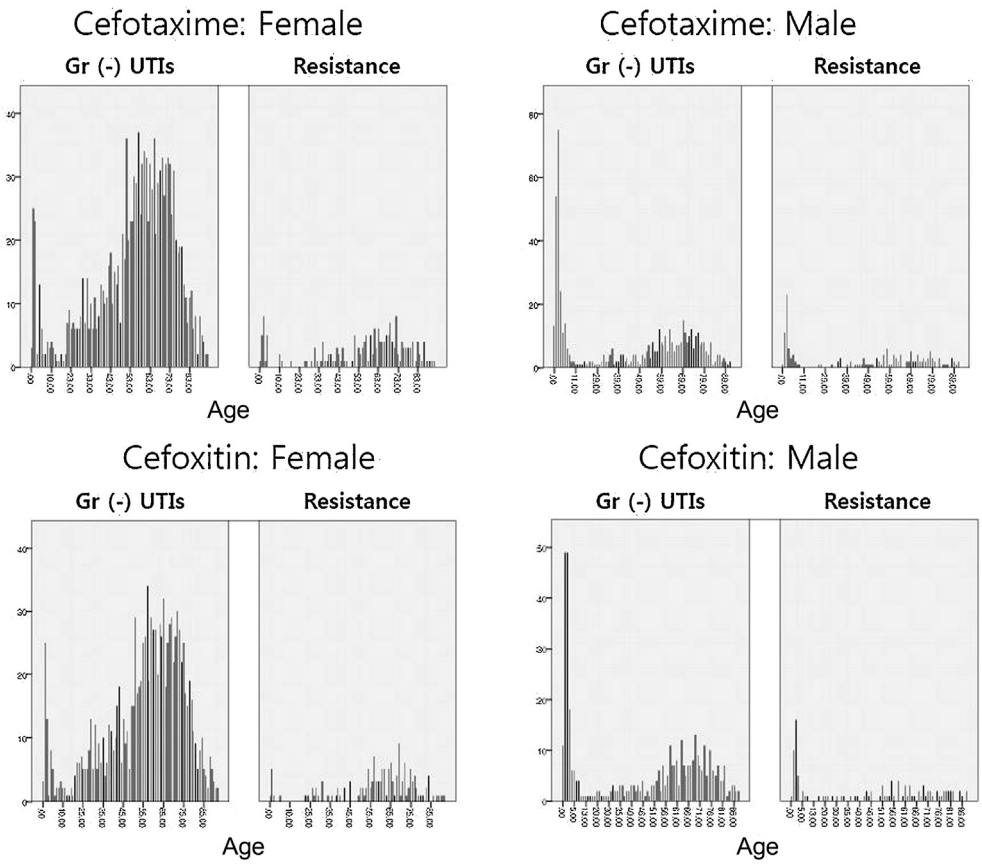

Figure 3. Age distributions of the incidences of resistance to second- and third-generation cephalosporins. Each *y*-axis represents the incidence. The incidence of resistance to second-generation cephalosporins (cefoxitin) was similar to the incidence of total Gram-negative UTIs across the different ages, which indicates that the resistance pattern to cefoxitin was not affected by age (for females, Kolmogorov–Smirnov $Z = 1.081$, $p = 0.193$; for males, Kolmogorov–Smirnov $Z = 0.561$, $p = 0.911$). The incidence of resistance to third-generation cephalosporins (cefotaxime) was similar to the incidence of total Gram-negative UTIs across the different ages, which indicates that the resistance pattern to cefotaxime was not affected by age (for females, Kolmogorov–Smirnov $Z = 0.546$, $p = 0.927$; for males, Kolmogorov–Smirnov $Z = 0.822$, $p = 0.509$).

UTIs were found in the young age group in males (Figure 2, and Table 2 and 3). These features are very important when considering the sensitivities of fluoroquinolones in an entire age group. Because fluoroquinolones are relatively contra-indicated in the younger age group,[14] which results in the susceptibility to fluoroquinolones being preserved in this group compared to the middle and older age groups (Figure 1 and 4, and Table 2 and 3), the subsequent result is more indicative of the sensitivity to fluoroquinolones of Gram-negative UTIs in males than of Gram-negative UTIs in females. Thus, it appears that Gram-negative bacteria were more susceptible to fluoroquinolones in male febrile UTIs than in female febrile UTIs. Therefore, the conclusion that antimicrobial susceptibility could be affected by age may not be accurate. If we consider the age group >20 years (potential users of these drugs), the susceptibilities to fluoroquinolones were not affected by age (Figure 4) or influenced by sex (Table 5). Therefore, it is concluded that age alone might not be a risk factor for fluoroquinolone resistance, as it was not a risk factor for cephalosporin resistance. Adam et al. summarized antibiotic susceptibility regardless of the site of infection and found that the susceptibility of *E. coli* to ciprofloxacin was relatively higher in the younger age group than in the middle and older age groups. These results are similar to those presented herein, although they did not discuss any reason for this phenomenon.[15]

The next step should be to identify whether exposure to antibiotics, sex, and/or other possible conditions such as diabetes mellitus and catheterization, affect the sensitivities of Gram-negative febrile UTIs to antibiotics. In the present study, despite considering other possible conditions, exposure to antibiotics was the most important risk factor for selecting resistance to cefoxitin, cefotaxime, and ciprofloxacin in outpatient febrile Gram-negative UTIs (Table 4 and 5). Considering that these drugs are currently recommended empirical antibiotics and are the most frequently prescribed treatments in Korea,[16] a national strategy to reduce exposure to these antibiotics should be developed.

Carson et al. demonstrated that the vast majority of men with a UTI had underlying factors that impede bacteriological eradication.[17] However, can it be said that the male sex alone is a risk factor for selecting resistance? In the present study, considering the total amount of Gram-negative bacteria, male sex was a risk factor for selecting antimicrobial resistance with regard to second- and third-generation cephalosporins; however, the proportion of *E. coli* was different in the two sexes (Tables 1–3). McGregor et al. collected data from primary care clinics in the USA and concluded that differences in antimicrobial susceptibilities between sexes were not of clinical significance because the differences were generally less than 5% in most of the tested antibiotics.[18] In the present study, Gram-negative bacteria exhibited lower sensitivity in males than in females for the majority of the tested antibiotics, except ciprofloxacin and co-trimoxazole; however, for *E. coli*-related UTIs, the susceptibilities to most antibiotics exhibited a difference within 5% between the sexes, except for cefotaxime, which is a reason to consider other atypical Gram-negative bacteria during the management of febrile UTIs, especially in

Table 3
Antimicrobial susceptibilities of 568 Gram-negative bacteria in male febrile UTI outpatients[a]

E. coli %	334/568 (58.8)	129/233 (55.4)	73/127 (57.5)	132/208 (63.5)	334/334 (100.0)
Age	GNB, all ages	Young (<20 years)	Middle (20–60 years)	Old (>60 years)	*E. coli*, all ages
AMK	S 534/568 (94.0)	S 229/233 (98.3)	S 114/127 (89.8)	S 191/208 (91.8)	S 328/334 (98.2)
	I 20/568	I 3/233	I 9/127	I 8/208	I 4/334
	R 14/568	R 1/233	R 4/127	R 9/208	R 2/334
AMX	S 122/490 (24.9)	S 34/201 (16.9)	S 32/109 (29.4)	S 56/180 (31.1)	S 110/324 (34.0)
	I 126/490	I 4/201	I 46/109	I 76/180	I 70/324
	R 242/490	R 163/201	R 31/109	R 48/180	R 144/324
AUG	S 252/447 (56.4)	S 76/156 (48.7)	S 66/110 (60.0)	S 110/181 (60.8)	S 185/292 (63.4)
	I 85/447	I 25/156	I 26/110	I 34/181	I 48/292
	R 110/447	R 55/156	R 18/110	R 37/181	R 59/292
CFX	S 325/435 (74.7)	S 64/156 (75.0)	S 74/105 (70.5)	S 134/174 (77.0)	S 249/292 (85.3)
	I 39/435	I 7/156	I 16/105	I 16/174	I 13/292
	R 71/435	R 32/156	R 15/105	R 24/174	R 30/292
CTX	S 388/546 (71.1)	S 162/214 (75.7)	S 86/126 (68.3)	S 140/206 (68.0)	S 251/324 (77.5)
	I 75/546	I 8/214	I 26/126	I 41/206	I 31/324
	R 83/546	R 44/214	R 14/126	R 25/206	R 42/324
CTZ	S 454/566 (80.2)	S 180/232 (77.6)	S 107/127 (84.3)	S 167/207 (80.7)	S 275/332 (82.8)
	I 35/566	I 8/232	I 9/127	I 18/207	I 14/332
	R 77/566	R 44/232	R 11/127	R 22/207	R 43/332
CFP	S 469/566 (82.9)	S 199/232 (85.8)	S 104/127 (81.9)	S 166/207 (80.2)	S 276/332 (83.1)
	I 31/566	I 2/232	I 9/127	I 20/207	I 13/332
	R 66/566	R 31/232	R 14/127	R 21/207	R 43/332
CP	S 403/546 (73.8)	S 190/214 (88.8)	S 78/125 (62.4)	S 134/207 (64.7)	S 231/325 (71.1)
	I 65/546	I 4/214	I 26/125	I 35/207	I 38/325
	R 78/546	R 20/214	R 21/125	R 37/207	R 56/325
PT	S 491/566 (86.7)	S 200/233 (85.8)	S 107/126 (84.9)	S 184/207 (88.9)	S 308/334 (92.2)
	I 20/566	I 4/233	I 7/126	I 9/207	I 4/334
	R 55/566	R 29/233	R 12/126	R 14/207	R 21/334
IMP	S 546/568 (96.1)	S 230/233 (98.7)	S 120/127 (94.5)	S 196/208 (94.2)	S 334/334 (100.0)
	I 11/568	I 3/233	I 3/127	I 5/208	I 0/334
	R 11/568	R 0/233	R 4/127	R 7/208	R 0/334
CTMZ	S 376/557 (67.5)	S 162/229 (70.7)	S 82/123 (66.7)	S 129/205 (62.9)	S 228/334 (68.3)
	I 60/557	I 0/229	I 20/123	I 40/205	I 31/334
	R 121/557	R 67/229	R 21/123	R 33/205	R 75/334

UTI, urinary tract infection; GNB, Gram-negative bacteria; S, susceptible; I, intermediate; R, resistant; AMK, amikacin; AMX, amoxicillin; AUG, amoxicillin/clavulanic acid; CFX, cefoxitin; CTX, cefotaxime; CTZ, ceftazidime; CFP, cefepime; CP, ciprofloxacin; PT, piperacillin/tazobactam; IMP, imipenem; CTMZ, co-trimoxazole.
[a] For the reader's convenience, percentages are presented in parenthesis only for the susceptible category.

Table 4
Potential risk factors for cefoxitin and cefotaxime resistance in Gram-negative UTIs

	Resistance to cefoxitin for all ages		*p*-Value[a] OR, 95% CI	*p*-Value[b] OR, 95% CI	Resistance to cefotaxime for all ages		*p*-Value[a] OR, 95% CI	*p*-Value[b] OR, 95% CI
Sex	Male	Female	<0.001	<0.001	Male	Female	<0.001	<0.001
	110/435	146/1104	2.221, 1.683–2.931	2.239, 1.676–2.992	158/546	185/1315	2.487, 1.953–3.167	2.593, 1.998–3.364
Diabetes mellitus	Yes	No	0.225	–	Yes	No	0.001	0.131
	47/244	209/1295	1.240, 0.873–1.761		76/295	267/1566	1.688, 1.260–2.262	1.276, 0.930–1.751
Catheter	Yes	No	<0.001	0.061	Yes	No	<0.001	0.003
	18/46	238/1493	3.390, 1.845–6.227	1.850, 0.972–3.520	29/56	314/1805	5.100, 2.978–8.735	2.406, 1.336–4.331
Exposure to antibiotics	Yes	No	<0.001	<0.001	Yes	No	<0.001	<0.001
	100/395	156/1144	2.364, 1.783–3.133	2.412, 1.803–3.227	169/507	174/1354	3.391, 2.657–4.327	3.745, 2.897–3.364

UTI, urinary tract infection; OR, odds ratio; CI, confidence interval.
[a] *p*-Value measured using the Chi-square test.
[b] *p*-Value measured using the logistic regression test (non-selection).

Table 5
Potential risk factors for ciprofloxacin resistance in Gram-negative UTIs

	Resistance to ciprofloxacin for all ages		*p*-Value[a] OR, 95% CI	*p*-Value[b] OR, 95% CI	Resistance to ciprofloxacin for age >20 years		*p*-Value[a] OR, 95% CI
Sex	Male	Female	<0.001	<0.001	Male	Female	0.204
	143/546	495/1298	0.576, 0.461–0.718	0.547, 0.432–0.693	119/332	479/1201	0.842, 0.654–1.084
Diabetes mellitus	Yes	No	0.003	0.135	Yes	No	0.233
	125/297	513/1547	1.465, 1.137–1.887	1.230, 0.938–1.614	125/297	473/1236	1.172, 0.906–1.516
Catheter	Yes	No	0.064	–	Yes	No	0.265
	26/56	612/1788	1.665, 0.976–2.841		26/56	572/1477	1.371, 0.803–2.342
Exposure to antibiotics	Yes	No	<0.001	<0.001	Yes	No	<0.001
	283/496	355/1348	3.716, 2.997–4.609	3.601, 2.891–4.487	274/459	324/1074	3.428, 2.731–4.304

UTI, urinary tract infection; OR, odds ratio; CI, confidence interval.
[a] *p*-Value measured using the Chi-square test.
[b] *p*-Value measured using the logistic regression test (non-selection).

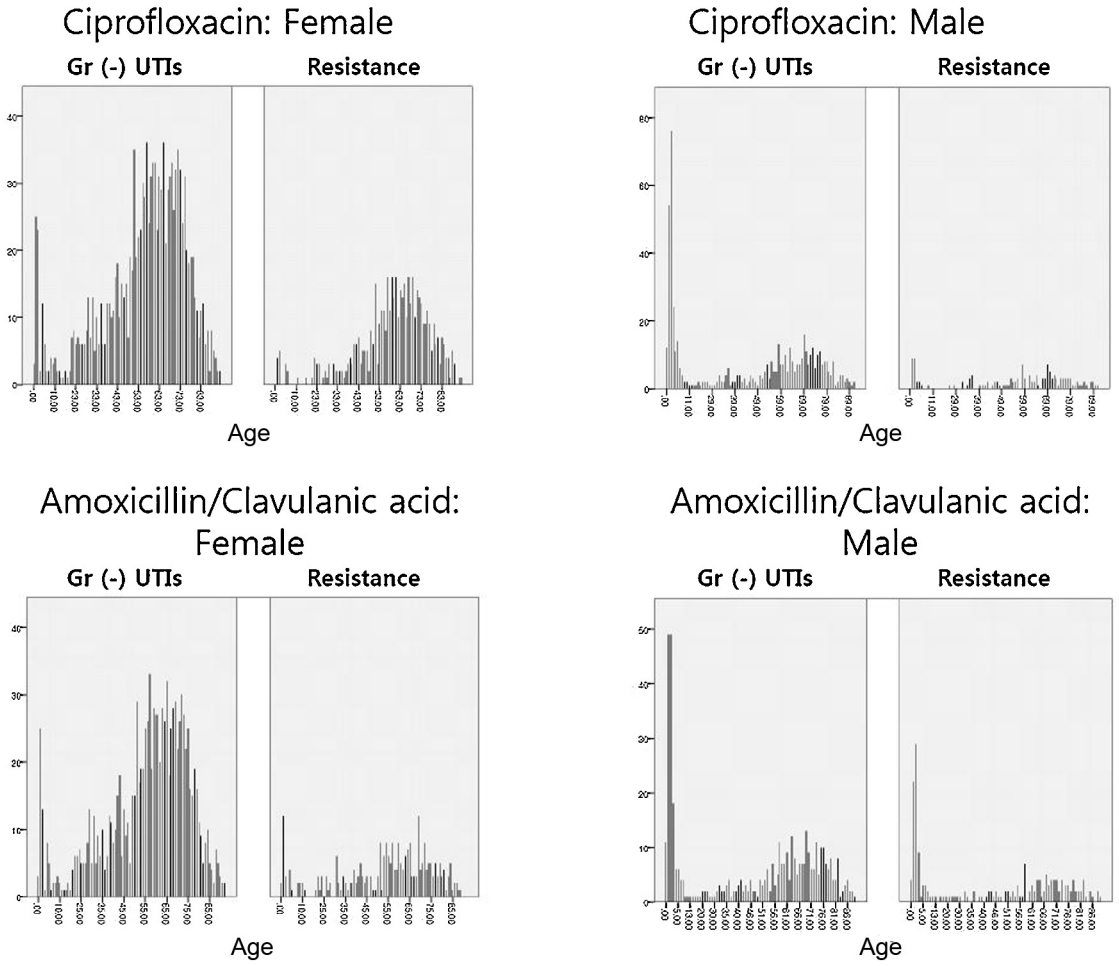

Figure 4. Age distributions of the incidences of resistance to amoxicillin/clavulanic acid and fluoroquinolones in Gram-negative bacteria. Each *y*-axis represents the incidence. The age distribution of the incidence of resistance to fluoroquinolones (ciprofloxacin) was different from the age distribution of the incidence of total Gram-negative UTIs, which indicates that the resistance pattern to ciprofloxacin was affected by age (for females, Kolmogorov–Smirnov $Z = 1.540$, $p = 0.017$; for males, Kolmogorov–Smirnov $Z = 2.405$, $p < 0.001$). Note that for patients >20 years of age, the age distribution of Gram-negative bacteria was not different from that of fluoroquinolone resistance for either sex (Kolmogorov–Smirnov $Z = 0.370$, $p = 0.999$ in males; Kolmogorov–Smirnov $Z = 1.277$, $p = 0.077$ in females). The age distribution of the incidence of resistance to amoxicillin/clavulanic acid was similar to the age distribution of the incidence of total Gram-negative UTIs across the different ages, which indicates that the resistance pattern to amoxicillin/clavulanic was not affected by age (for females, Kolmogorov–Smirnov $Z = 0.881$, $p = 0.420$; for males, Kolmogorov–Smirnov $Z = 0.907$, $p = 0.383$).

males. Consequently, male sex has a minor effect on lowering the susceptibility of *E. coli* but has a great effect on lowering the susceptibility of Gram-negative bacteria by producing an increased chance of atypical bacterial infection.

Outpatient data in Italy showed that 55.0% of UTIs and 62.6% of Gram-negative UTIs in males were caused by *E. coli*, whereas *E. coli* was found in 71.0% of UTIs and 77.5% of Gram-negative UTIs in females.[19] In the present study, only 46.1% of UTIs and 58.8% of Gram-negative UTIs in males were caused by *E. coli*, whereas *E. coli* was detected in 73.5% of UTIs and 85.2% of Gram-negative UTIs in females. Therefore, whether *E. coli* can accurately represent antimicrobial susceptibility, especially in males, is difficult to assess. Physicians should be aware of regional Gram-negative susceptibility data, as well as risk factors for antibiotic resistance, prior to selecting the appropriate empirical antibiotics for outpatient febrile UTIs in males, because the selection of an appropriate drug can improve the prognosis, especially in critically ill patients.[20] Therefore, primary care physicians should select empirical antibiotics carefully for males after determining whether they have been exposed to antibiotics previously or have a history of a recent urinary catheter. If this information is not confirmed in critically ill male outpatients with febrile UTIs, physicians should not hesitate to use amikacin as a combination regimen or use restricted antibiotics such as cefepime, piperacillin/tazobactam, or carbapenems as empirical antibiotics, at least until the culture report indicates the use of other antibiotics such as fluoroquinolones or cephalosporins.

Clinicians should also take into account catheter-associated UTIs. Although only 56 outpatients with catheter-related febrile UTIs were included among the 1896 outpatient Gram-negative febrile UTIs, the results conveyed an important message. In this cohort, catheter-associated UTIs were seven times more common in males than in females and were negatively associated with *E. coli* infection (Table 6). A wide variety of infectious organisms may be

Table 6
Features of catheter-associated UTIs in the Gram-negative UTIs

	Catheterized	Non-catheterized	*p*-Value[a] OR, 95% CI
Sex Male/female	42/14	526/1314	<0.001 7.494, 4.059–13.838
E. coli infection Yes/no	26/30	1439/401	<0.001 0.242, 0.141–0.413
Exposure to antibiotics Yes/no	32/24	476/1364	<0.001 3.821, 2.228–6.553

UTI, urinary tract infection; OR, odds ratio; CI, confidence interval.
[a] *p*-Values measured using the Chi-square test.

isolated from catheter-associated UTIs.[21] In long-term indwelling catheter patients, *E. coli* was isolated in only 18–35% of cases. Instead, atypical Gram-negative bacteria were found in these patients. In addition, increased antimicrobial resistance was found in catheter-associated UTIs,[22] which could be due in part to the frequent exposure to antibiotics.

Research conducted in the Asia-Pacific region showed the variation in extended-spectrum beta-lactamase (ESBL)-producing *E. coli* among countries; however, it was not clear whether the isolates originated from inpatient or outpatient UTIs.[23] Furthermore, although the study was multinational, the results were not reported according to age, sex, or other underlying risk conditions; therefore the results could not be applied directly to any country within the Asia-Pacific area. In that study, the general sensitivities of Gram-negative bacteria to ciprofloxacin, cefoxitin, and cefotaxime were 51.4%, 74.2%, and 50.3%, respectively.[23]

Other studies have been conducted on outpatient UTIs. In India, *E. coli* isolates from outpatient UTIs showed very high resistance rates to second- and third-generation cephalosporins (55–85%), and ESBL was detected in 34.4% of *E. coli* isolates.[24] Although the authors collected specimens from both sexes for all age groups (0–80 years) and presented susceptibility data according to the pathogen, they did not show the data by age or sex .[24]

The present authors have previously presented susceptibility data for organisms causing UTIs in adult females in Korea .[16] These previous data were focused on *E. coli* in UTIs in adult females and on comparing inpatient data with outpatient data; UTIs in males were not discussed, and the age distribution was limited to a range of 25 to 65 years. Although the age was different and the underlying complicating factors such as catheterization and previous exposure to antibiotics were not the same in the present study and previous studies, the antimicrobial susceptibilities of UTIs in female outpatients exhibited little decline in the present study (2012–2014) compared to the previous data (2010–2011).

The present study describes the antimicrobial susceptibility pattern of Gram-negative bacteria with respect to age and sex in Korea. For the populations in which fluoroquinolones were applicable (age >20 years), neither age nor sex was found to be a risk factor for emerging resistance in Gram-negative bacteria. Instead, exposure to antibiotics was a confirmed risk factor for fluoroquinolone resistance; however, the susceptibility of Gram-negative bacteria to these drugs was noticeably lower than 70% in this outpatient setting for both sexes, and physicians should not consider the use of these drugs as empirical antibiotics in Korea . With regard to cephalosporins, age was not a risk factor for lowering antimicrobial susceptibility in Gram-negative febrile UTIs; however, male sex and other factors such as exposure to antibiotics and an indwelling urinary catheter were revealed to be risk factors for the selection of antimicrobial resistance.

The important messages from the present study include the following: (1) physicians should carefully choose an empirical antibiotic agent(s) after considering hospital-related patient histories including medication and catheterization, especially for acute febrile UTIs in males; (2) age itself is not a considerable factor for physicians when determining the antibiotics to use in febrile UTIs; and (3) extensive efforts should be made to reduce the misuse and abuse of antibiotics, and the unnecessary use of a urinary catheter.

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