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Original Article

Risk factors of ciprofloxacin resistance in urinary *Escherichia coli* isolates

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Background and Purpose: Increasing rates of fluoroquinolone resistance among *Escherichia coli* have been reported in Taiwan and worldwide. We aimed to identify the risk factors of ciprofloxacin resistance in urinary *E. coli* isolates.

Methods: Patients with positive urine culture result for *E. coli* and resistance to ciprofloxacin between September 1, 1999 and December 31, 1999 were prospectively identified as cases, and compared with ciprofloxacin-susceptible *E. coli* isolates (controls). The case:control ratio was 1:2. Data were collected with standardized case record forms.

Results: Sixty one cases and 122 controls were compared. Multivariate analysis indicated that urinary tract catheterization (odds ratio [OR] = 2.631, 95% confidence interval [CI] = 1.058-6.544; p=0.037) and prior exposure to quinolones (OR = 13.072, 95% CI = 3.367-50.75; p<0.001) were independent risk factors for ciprofloxacin resistance in urinary *E. coli* isolates. Compared with ciprofloxacin-susceptible *E. coli* isolates, ciprofloxacin-resistant *E. coli* isolates from urine specimens had a significantly higher rate of resistance to all other tested antimicrobial agents, except amikacin and imipenem.

Conclusion: In patients with urinary tract infection, urinary catheterization and prior quinolone exposure are associated with a high risk of ciprofloxacin-resistant *E. coli* which may cause treatment failure.

Key words: Ciprofloxacin; Drug resistance, bacterial; *Escherichia coli*; Risk factors; Urinary tract

Introduction

In Taiwan, the trimethoprim-sulfamethoxazole (TMP/SMX) resistance rate in *Escherichia coli* of community-acquired urinary tract infection (UTI) was more than 50% [1]. Because treatment with TMP/SMX for uncomplicated UTI caused by TMP/SMX-resistant *E. coli* resulted in microbiologic and clinical failure, Raz et al recommended that fluoroquinolones (FQs) should be considered in areas where the rate of *E. coli* resistance to TMP/SMX was more than 10% to 20% [2]. Furthermore, according to a cost analysis study conducted in the United States, when the rate of *E. coli* resistance to TMP/SMX is more than 22% in a community, empirical FQ therapy becomes less costly than TMP/SMX therapy. Therefore Le et al suggested that in a community with >20% resistant rate to TMP/SMX among *E. coli*, an FQ should be used [3]. The Infectious Diseases Society of America guidelines do not recommend FQs as initial empirical treatment for uncomplicated UTIs, except in communities with 10% to 20% resistance to TMP/SMX among uropathogens [4].

The guidelines for antimicrobial therapy of UTIs in Taiwan published in 2000 also recommended FQs as one of the drugs of choice when acute bacterial cystitis, chronic bacterial prostatitis and nosocomial/catheter-related UTIs are suspected [5]. Because of high resistance rates of community-acquired urinary *E. coli* isolates to cephalothin, gentamicin and ampicillin [1], quinolones are usually considered as an option, especially in the outpatient setting, because of the availability of oral formulations. In Taiwan, the rate of

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ciprofloxacin resistance of *E. coli* ranged from 11% to 33% among different hospitals in 2000 [6], which may jeopardize quinolone treatment for UTI. We aimed to identify the risk factors for ciprofloxacin resistance in urinary *E. coli* isolates in order to avoid inappropriate quinolone.

Methods

Data collection

A case-control study was conducted at the Kaohsiung Medical University Chung-Ho Memorial Hospital (KMUH), a 1200-bed tertiary care teaching hospital. We prospectively searched the cases by screening the computer database day by day to find all consecutive *E. coli* urinary isolates during a 4-month period between September 1, 1999 and December 31, 1999. All polymicrobial specimens were ignored. Colonized *E. coli* isolates which did not cause fever (>38°C), urgency, frequency, dysuria, or suprapubic tenderness were excluded by medical records review and patient interviews. Isolates were classified as either resistant or susceptible to ciprofloxacin by disk diffusion method according to the Clinical and Laboratory Standards Institute (CLSI; formerly National Committee for Clinical Laboratory Standards [NCCLS]) criteria [7]. Antimicrobial susceptibility testing for ampicillin, ampicillin-sulbactam, amoxicillin-clavulanate, piperacillin, ticarcillin-clavulanate, cefmetazole, ceftazidime, ceftriaxone, aztreonam, imipenem, gentamicin, netilmicin, amikacin, TMP/SMX, minocycline, and chloramphenicol were also undertaken by disk diffusion method according to the CLSI criteria.

Association between susceptibilities of the *E. coli* isolates to ciprofloxacin and to other antibiotics was analyzed. Disk diffusion results for other antimicrobial agents mentioned above were categorized into resistant (including intermediately susceptible isolates) and susceptible.

Patients

Patients with ciprofloxacin-resistant *E. coli* (CREC) urinary isolates were assigned consecutively as the case group. When a CREC was isolated, two patients with ciprofloxacin-susceptible *E. coli* (CSEC) isolated within 2 days before or after this CREC case were randomly selected as the controls.

Variables that were explored by medical records review and patient interviews as possible predictors of CREC urinary isolates included: age; gender; patient source (outpatient or inpatient); Acute Physiology and Chronic Health Evaluation II score on the day of urine specimen collection; nosocomial (health care-associated) versus community-acquired; previous hospitalization for more than 48 h within 90 days before urine specimen collection; underlying diseases; urologic procedures within 2 weeks before urine specimen collection; antimicrobial agent administration (intravenous or oral) for more than 48 h within 2 weeks before urine specimen collection (categorized into three groups: quinolones, beta-lactams, or TMP/SMX); and medical devices on the day of urine specimen collection.

Underlying diseases were recorded according to patients' charts. Connective tissue disease included systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis and Behçet's disease. Malignancy included solid and hematologic malignancy. Cardiac diseases included arrhythmia, congestive heart failure and ischemic heart disease. Gastrointestinal diseases included peptic ulcer disease, gastrointestinal tract bleeding and ileus. Nephrologic diseases included chronic kidney diseases, proteinuria and microscopic hematuria. Proteinuria was defined as urinary protein appearing ≥1+ (30 mg/dL) by dipstick test and the same criterion was used for urinary occult blood as for microscopic hematuria. Neurological diseases included cerebral vascular accidents, dementia and Parkinsonism. Urinary tract catheterization included Foley catheterization (urethral catheterization), cystostomy creation and ureteral catheterization. Intravascular catheterization included central venous catheterization, pulmonary artery catheterization and hemodialysis catheter (peripheral intravascular catheters were excluded).

Respiratory catheterization included endotracheal tube intubation and tracheostomy tube placement. Gastrointestinal tract catheterization included nasogastric tube placement and nasoduodenal tube placement.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows (Version 13.0; SPSS, Chicago, IL, USA) software package. Odds ratio (OR) and 95% confidence interval (CI) was calculated for binomial variables; p values were calculated by the chi-squared test for discrete variables and by the Student's t test for continuous variables. Variables with a p value ≤0.05 in the univariate analysis were included in a logistic regression model

for multivariate analysis. All tests were two-tailed, and $p \leq 0.05$ was considered significant.

Results

Sixty one cases and 122 controls were enrolled during the study period. 124 patients (67.8%) were females and 59 (32.2%) were males. The mean age was 52.9 years (range, 1-96 years). Among the 183 *E. coli* isolates, 53 (29.0%) were recognized as nosocomial and 130 (71.0%) were community-acquired. There was no evidence of clustering in time or location for ciprofloxacin resistance.

Demographic and clinical data for the two groups are listed in Table 1. In univariate analysis, cases were more likely than controls to be inpatients, to be nosocomial, and to have previous hospitalization within 90 days, cardiac disease, neurological disease, urinary tract catheterization, intravascular catheterization, respiratory tract catheterization, gastrointestinal tract catheterization, and exposure to any quinolone within 2 weeks before urine specimen collection. In contrast, exposure to beta-lactams and TMP/SMX was not associated with the isolation of CREC. None of the other tested variables was significantly associated with the detection of CREC or reached the entry criteria for the multivariate model.

Results of the logistic regression model that included the significant variables of the univariate analysis are shown in Table 2. The independent risk factors for the emergence of CREC included urinary tract catheterization on the day of urine specimen collection (adjusted OR = 2.631, 95% CI = 1.058-6.544; p=0.037) and any quinolone administration within 2 weeks before urine specimen collection (adjusted OR = 13.072, 95% CI = 3.367-50.75; p<0.001).

Table 1. Univariate analysis of risk factors for the detection of ciprofloxacin-resistant *Escherichia coli* in clinical specimens

Variable	Cases (n = 61) No. (%)	Controls (n = 122) No. (%)	Odds ratio (95% CI)	p^a
Demographic characteristics				
Female gender	37 (60.7)	87 (71.3)	0.620 (0.325-1.184)	0.146
Inpatient source	43 (70.5)	56 (45.9)	2.815 (1.462-5.422)	0.002
Nosocomial	30 (49.2)	23 (18.9)	4.165 (2.117-8.194)	<0.001
Previous hospitalization within 90 days	11 (18.0)	5 (4.1)	5.148 (1.700-15.59)	0.002
Age (years; mean) [SD]	62.4 (22.1)	48.2 (28.2)		0.001
APACHE II score (mean) [SD]	9.8 (8.2)	6.2 (6.6)		0.002
Underlying disease				
Connective tissue disease	1 (1.6)	6 (4.9)	0.322 (0.038-2.738)	0.276
Malignancy	18 (29.5)	21 (17.2)	2.013 (0.976-4.151)	0.056
Diabetes mellitus	18 (29.5)	33 (27.0)	1.129 (0.572-2.228)	0.727
Cardiac disease	29 (47.5)	38 (31.1)	2.003 (1.065-3.769)	0.030
Chronic obstructive pulmonary disease	3 (4.9)	9 (7.4)	0.649 (0.169-2.491)	0.526
Gastrointestinal disease	12 (19.7)	14 (11.5)	1.889 (0.814-4.384)	0.134
Nephrologic disease	25 (41.0)	35 (28.7)	1.726 (0.907-3.286)	0.095
ESRD with hemodialysis	3 (4.9)	1 (0.8)	6.259 (0.637-61.48)	0.074
Neurologic disease	23 (37.7)	23 (18.9)	2.605 (1.309-5.186)	0.006
Urologic procedures[b]	2 (3.3)	4 (3.3)	1.000 (0.178-5.618)	1.000
Medical devices				
Urinary tract catheterization	38 (62.3)	25 (20.5)	6.410 (3.250-12.64)	<0.001
Intravascular catheterization	16 (26.2)	7 (5.7)	5.841 (2.253-15.15)	<0.001
Respiratory tract catheterization	12 (19.7)	5 (4.1)	5.731 (1.917-17.14)	0.001
Gastrointestinal tract catheterization	18 (29.5)	10 (8.2)	4.688 (2.005-10.96)	<0.001
Antibiotics administration within 2 weeks before *Escherichia coli* isolation				
Quinolones	13 (21.3)	4 (3.3)	7.990 (2.480-25.74)	<0.001
beta-Lactams	8 (13.1)	10 (8.2)	1.691 (0.631-4.529)	0.292
TMP/SMX	2 (3.3)	4 (3.3)	1.000 (0.178-5.618)	1.000

Abbreviations: CI = confidence interval; SD = standard deviation; APACHE = Acute Physiology and Chronic Health Evaluation; ESRD = end-stage renal disease; TMP/SMX = trimethoprim-sulfamethoxazole

[a]Two-tailed chi-squared test or Student's *t* test, as appropriate.

[b]Within 2 weeks before urine specimen collection.

Table 2. Multivariate analysis (logistic regression) of risk factors for the emergence of ciprofloxacin-resistant *Escherichia coli* in clinical specimens

Variable	Adjusted odds ratio (95% CI)	*p*
Demographic characteristics		
Inpatient	1.832 (0.696-4.819)	0.220
Nosocomial	1.011 (0.346-2.957)	0.983
Previous hospitalization within 90 days	3.783 (0.954-14.99)	0.058
Underlying disease		
Cardiac disease	1.022 (0.452-2.309)	0.959
Neurological disease	1.531 (0.616-3.806)	0.360
Medical devices		
Urinary tract catheterization	2.631 (1.058-6.544)	0.037
Intravascular catheterization	2.805 (0.601-13.08)	0.189
Respiratory tract catheterization	0.763 (0.118-4.914)	0.776
Gastrointestinal tract catheterization	1.358 (0.331-5.562)	0.671
Antibiotics administration within 2 weeks before *Escherichia coli* isolation		
Quinolones	13.072 (3.367-50.75)	<0.001

Abbreviation: CI = confidence interval

The results of susceptibility testing of case and control isolates are shown in Table 3. CREC isolates from urine specimens were frequently resistant to multiple antimicrobial agents, including drugs commonly prescribed in the outpatient setting, such as ampicillin (95.1% of isolates), ampicillin-sulbactam (68.9%), amoxicillin-clavulanate (57.4%), TMP/SMX (91.8%), minocycline (67.2%), and chloramphenicol (86.9%).

Sixty CREC isolates (98.4%) were concurrently resistant to at least one of eight antimicrobial classes other than ciprofloxacin, including penicillins, cephalosporins, monobactams, carbapenems, aminoglycosides, TMP/SMX, minocycline, and chloramphenicol. Among these isolates, one (1.6%) was concurrently resistant to another one class of antibiotics, three (4.9%) were resistant to two classes, five (8.2%) were resistant to

Table 3. Resistance to other antimicrobial agents among ciprofloxacin-resistant and ciprofloxacin-sensitive *Escherichia coli*

Antimicrobial agent	Number of resistant isolates (%)		Odds ratio (95% CI)	p^a
	Cases (n = 61)	Controls (n = 122)		
Penicillins				
Ampicillin[b]	58 (95.1)	101 (82.8)	4.020 (1.149-14.06)	0.020
Ampicillin-sulbactam[b]	42 (68.9)	30 (24.6)	6.779 (3.432-13.39)	<0.001
Amoxicillin-clavulanate[b]	35 (57.4)	28 (23.0)	4.519 (2.336-8.744)	<0.001
Piperacillin	27 (44.3)	27 (22.1)	2.794 (1.442-5.416)	0.002
Ticarcillin-clavulanate	22 (36.1)	13 (10.7)	4.730 (2.175-10.29)	<0.001
Cephalosporins				
Cefmetazole	15 (24.6)	9 (7.4)	4.094 (1.673-10.02)	0.001
Ceftazidime	7 (11.5)	4 (3.3)	3.824 (1.074-13.62)	0.028
Ceftriaxone	18 (29.5)	7 (5.7)	6.877 (2.684-17.62)	<0.001
Aztreonam	5 (8.2)	2 (1.6)	5.357 (1.008-28.46)	0.029
Imipenem	2 (3.3)	0 (0.0)	-	-
Aminoglycosides				
Gentamicin	41 (67.2)	32 (26.2)	5.766 (2.951-11.26)	<0.001
Netilmicin	10 (16.4)	7 (5.7)	3.221 (1.161-8.939)	0.019
Amikacin	3 (4.9)	2 (1.6)	3.103 (0.505-19.09)	0.200
TMP/SMX[b]	56 (91.8)	83 (68.0)	5.263 (1.954-14.17)	<0.001
Minocycline[b]	41 (67.2)	58 (47.5)	2.262 (1.191-4.298)	0.012
Chloramphenicol[b]	53 (86. 9)	67 (54.9)	5.438 (2.384-12.40)	<0.001

Abbreviations: CI = confidence interval; TMP/SMX = trimethoprim-sulfamethoxazole

[a]Two-tailed chi-squared test.

[b]Oral form was available in Taiwan.

three classes, fourteen (23%) were resistant to four classes, and thirty seven (60.7%) were resistant to more than four classes. Two CREC isolates (3.3%) were resistant to imipenem. Just one CREC isolate (1.6%) was resistant only to ciprofloxacin. The rates of resistance to other drugs were consistently lower among ciprofloxacin-susceptible isolates (Table 3). These differences (in proportions) were statistically significant for almost all antimicrobial agents tested except amikacin and imipenem.

Discussion

The increasing prevalence of infections caused by antibiotic-resistant bacteria makes empirical treatment of these patients difficult [8]. Understanding the local antimicrobial susceptibility patterns of urinary isolates and the risk factors for isolation of resistant strains would be helpful when prescribing appropriate antibiotics. However, to our knowledge, there has been no risk factor analysis for CREC urinary isolates in Taiwan. After adjusting for univariate risk factors, quinolone administration within 2 weeks before CREC isolation and urinary tract catheterization remained independent risk factors.

In Spain, Ena et al found that prior quinolone use, presence of urinary catheter, and urinary tract disorder were independent risk factors of CREC UTIs [9]. In the United States, Killgore et al concluded that prior exposure to FQs within 4 weeks before UTI symptoms and recurrent UTI were independent risk factors [10]. Arslan et al also reported that ciprofloxacin use and complicated UTI were independent risk factors [8]. Compared with these retrospective studies [8-10], our prospectively collected data are less likely to be influenced by recall memory bias, especially with regard to the drug used. Nevertheless, all of these studies have found prior quinolone use to be an independent risk factor of CREC. Additionally, as with the study of Arslan et al [8], we found receipt of an antimicrobial agent other than a quinolone was unrelated to ciprofloxacin resistance.

FQ is a reasonable empirical agent for treatment of acute bacterial cystitis, chronic bacterial prostatitis, and nosocomial/catheter-related UTIs according to the Guidelines for Antimicrobial Therapy of UTIs in Taiwan, an area where the rate of TMP/SMX resistance among *E. coli* is over 50% [1,5,8]. FQ is also an alternative choice for acute complicated pyelonephritis and acute bacterial prostatitis. However, our study suggests that clinicians review patients' drug exposure history explicitly before prescribing antibiotics empirically.

Peña et al found that, in addition to prior isolation of *E. coli* in urine, previous FQ use was also an independent risk factor of CREC bacteremia [11]. Previous FQ use is also a major risk factor for the emergence of quinolone-resistant *E. coli* in the gastrointestinal flora of hospitalized patients [12].

As reported by Karlowsky et al in North America [13], our study found that CREC urinary isolates were frequently multidrug-resistant. Among CREC isolates, rates of resistance to other tested antimicrobial agents were all >36%, except for the second-generation cephalosporins, third-generation cephalosporins, aztreonam and imipenem. While CLSI criteria have stipulated use of confirmatory tests for identification of extended-spectrum beta-lactamase-producing *E. coli* since 2000, we found that 29.5% of CREC urinary isolates were resistant to any third-generation cephalosporin. Our results showed that CREC isolates may also be resistant to other antimicrobial agents. Therefore, although Killgore et al recommended that cephalosporins may be a better choice in patients with prior exposure to FQs and recurrent UTI [10], clinicians in Taiwan should be aware of local antimicrobial resistance data and prescribe or adjust antibiotics according to susceptibility testing results.

Two CREC isolates were concurrently resistant to imipenem. The first imipenem-resistant *E. coli* at the KMUH was isolated in 1995, 4 years before this study. We confirmed the susceptibility testing results by the disk diffusion method with repeated testing, instead of minimal inhibitory concentration confirmation. Both isolates were hospital-acquired and cultured from two male patients. They were both inpatients and had Foley catheterization. One of them had 10-day imipenem exposure 66 days before urine specimen collection, while the other did not receive carbapenem during the present hospitalization. Although Hong et al reported a documented case in which carbapenem-resistant *E. coli* emerged during therapy with imipenem and meropenem [14], the risk factors of imipenem resistance in *E. coli* isolates necessitated further investigation.

Similar to CREC, another study from Taiwan identified use of an indwelling urinary catheter as a risk factor of *E. coli* resistance to both cephalothin and gentamicin [1]. While no proven effective strategies exist for prevention of catheter-associated UTI in persons who are chronically catheterized [15], our finding that indwelling urinary catheter is a risk factor for CREC

emphasizes a basic rule, i.e., early removal of an unnecessary catheter is beneficial [16]. Effective methods to educate health care workers to avoid the routine use of indwelling catheters may be also helpful [17].

Because microorganisms may form a biofilm which is adherent to an indwelling urinary catheter, it is difficult to eradicate these microorganisms by use of antibiotics [18,19]. On the other hand, inappropriate and excessive use of antimicrobial agents may encourage high resistant rates [20-22]. Antibiotic selective pressure may contribute to the emergence of FQ resistance in *E. coli* [23]. Therefore, clinicians should not treat a catheterized patient with asymptomatic bacteriuria while the catheter remains in situ [24].

In conclusion, previous quinolone use and urinary tract catheterization are two important risk factors for urinary CREC. Because of the high rate of associated resistance to other classes of antibiotics in CREC, urine culture and antimicrobial susceptibility testing are essential in the treatment patients with UTIs and risk factors of CREC.

References

1. Lau SM, Peng MY, Chang FY. Resistance rates to commonly used antimicrobials among pathogens of both bacteremic and non-bacteremic community-acquired urinary tract infection. J Microbiol Immunol Infect. 2004;37:185-91.
2. Raz R, Chazan B, Kennes Y, Colodner R, Rottensterich E, Dan M, et al; Israeli Urinary Tract Infection Group. Empiric use of trimethoprim-sulfamethoxazole (TMP-SMX) in the treatment of women with uncomplicated urinary tract infections, in a geographical area with a high prevalence of TMP-SMX-resistant uropathogens. Clin Infect Dis. 2002;34: 1165-9.
3. Le TP, Miller LG. Empirical therapy for uncomplicated urinary tract infections in an era of increasing antimicrobial resistance: a decision and cost analysis. Clin Infect Dis. 2001; 33:615-21.
4. Warren JW, Abrutyn E, Hebel JR, Johnson JR, Schaeffer AJ, Stamm WE. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Infectious Diseases Society of America (IDSA). Clin Infect Dis. 1999;29:745-58.
5. Infectious Diseases Society of the Republic of China; Medical Foundation in Memory of Dr. Deh-Lin Cheng; Foundation of Professor Wei-Chuan Hsieh for Infectious Diseases Research and Education; Lee CY's Research Foundation for Pediatric Infectious Diseases and Vaccine. Guidelines for antimicrobial therapy of urinary tract infections in Taiwan. J Microbiol Immunol Infect. 2000;33:271-2.
6. Hsueh PR, Liu CY, Luh KT. Current status of antimicrobial resistance in Taiwan. Emerg Infect Dis. 2002;8:132-7.
7. National Committee for Clinical Laboratory Standards. Performance standards for antimicrobial susceptibility testing. 9th informational supplement. NCCLS document M100-S9. Wayne, PA: National Committee for Clinical Laboratory Standards; 1999.
8. Arslan H, Azap OK, Ergönül O, Timurkaynak F; Urinary Tract Infection Study Group. Risk factors for ciprofloxacin resistance among *Escherichia coli* strains isolated from community-acquired urinary tract infections in Turkey. J Antimicrob Chemother. 2005;56:914-8.
9. Ena J, Amador C, Martinez C, Ortiz de la Tabla V. Risk factors for acquisition of urinary tract infections caused by ciprofloxacin resistant *Escherichia coli*. J Urol. 1995;153: 117-20.
10. Killgore KM, March KL, Guglielmo BJ. Risk factors for community-acquired ciprofloxacin-resistant *Escherichia coli* urinary tract infection. Ann Pharmacother. 2004;38: 1148-52.
11. Peña C, Albareda JM, Pallares R, Pujol M, Tubau F, Ariza J. Relationship between quinolone use and emergence of ciprofloxacin-resistant *Escherichia coli* in bloodstream infections. Antimicrob Agents Chemother. 1995;39:520-4.
12. Richard P, Delangle MH, Raffi F, Espaze E, Richet H. Impact of fluoroquinolone administration on the emergence of fluoroquinolone-resistant gram-negative bacilli from gastrointestinal flora. Clin Infect Dis. 2001;32:162-6.
13. Karlowsky JA, Hoban DJ, Decorby MR, Laing NM, Zhanel GG. Fluoroquinolone-resistant urinary isolates of *Escherichia coli* from outpatients are frequently multidrug resistant: results from the North American Urinary Tract Infection Collaborative Alliance-Quinolone Resistance study. Antimicrob Agents Chemother. 2006;50:2251-4.
14. Hong T, Moland ES, Abdalhamid B, Hanson ND, Wang J, Sloan C, et al. *Escherichia coli*: development of carbapenem resistance during therapy. Clin Infect Dis. 2005;40:e84-6.
15. Trautner BW, Darouiche RO. Role of biofilm in catheter-associated urinary tract infection. Am J Infect Control. 2004; 32:177-83.
16. Trautner BW, Hull RA, Darouiche RO. Prevention of catheter-associated urinary tract infection. Curr Opin Infect Dis. 2005;18:37-41.
17. Kunin CM. Urinary-catheter-associated infections in the elderly. Int J Antimicrob Agents. 2006;28(Suppl 1):S78-81.
18. Costerton JW, Stewart PS, Greenberg EP. Bacterial biofilms: a common cause of persistent infections. Science. 1999; 284:1318-22.
19. Stewart PS, Costerton JW. Antibiotic resistance of bacteria in biofilms. Lancet. 2001;358:135-8.

20. Hsueh PR, Chen WH, Luh KT. Relationships between antimicrobial use and antimicrobial resistance in Gram-negative bacteria causing nosocomial infections from 1991-2003 at a university hospital in Taiwan. Int J Antimicrob Agents. 2005;26:463-72.
21. Lepelletier D, Caroff N, Reynaud A, Richet H. *Escherichia coli*: epidemiology and analysis of risk factors for infections caused by resistant strains. Clin Infect Dis. 1999;29:548-52.
22. Kunin CM. Nosocomial urinary tract infections and the indwelling catheter: what is new and what is true? Chest. 2001;120:10-2.
23. McDonald LC, Chen FJ, Lo HJ, Yin HC, Lu PL, Huang CH, et al. Emergence of reduced susceptibility and resistance to fluoroquinolones in *Escherichia coli* in Taiwan and contributions of distinct selective pressures. Antimicrob Agents Chemother. 2001;45:3084-91.
24. Nicolle LE, Bradley S, Colgan R, Rice JC, Schaeffer A, Hooton TM; Infectious Diseases Society of America; American Society of Nephrology; American Geriatric Society. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. Clin Infect Dis. 2005;40:643-54.

