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ORIGINAL ARTICLE

Risk factors and clinical impact of levofloxacin or cefazolin nonsusceptibility or ESBL production among uropathogens in adults with community-onset urinary tract infections

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Background: Gram-negative bacilli causing community-onset urinary tract infections (CoUTIs) are getting increasingly resistant to antimicrobial agents. Clinical significance and risk factors of the acquisition of antimicrobial-nonsusceptible pathogens are still under investigation.
Methods: A prospective study was performed in the medical wards of two hospitals in southern Taiwan between August 2009 and January 2012. Patients were enrolled if they were aged >18, admitted through the emergency department, and had CoUTI due to *Enterobacteriaceae* isolates.
Results: Overall 136 adults with CoUTI were enrolled. Their mean age was 67 years and females were predominant (68.4%). Comorbidities, such as diabetes mellitus (30.1%) and hypertension (54.4%), were common. *Escherichia coli* (111, 81.6%) was the predominant species, followed by *Klebsiella pneumoniae* (11, 8.1%), and *Proteus mirabilis* (7, 5.1%). Nine (8.0%) of *E. coli* isolates and 5 (45%) of *K. pneumoniae* isolates had extended-spectrum β-lactamase (ESBL) production. Out of 122 non-ESBL producing isolates, 35 (28.7%) and 31 (25.4%) were nonsusceptible to levofloxacin and cefazolin, respectively. In the multivariate analysis, several clinical characters were

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found to be independently associated with CoUTIs due to levofloxacin-nonsusceptible (i.e. males, recent hospitalization, underlying old stroke, diabetes mellitus, and altered consciousness, or absence of chills, pyuria, or tachycardia), cefazolin-nonsusceptible (i.e. males, recent hospitalization, underlying old stroke, absence of fever or chills), or ESBL-producing isolates (i.e. recent hospitalization or antimicrobial therapy). All patients survived and discharged. However, the patients with CoUTIs due to levofloxacin-nonsusceptible (16.1 vs. 7.5 days, $p < 0.01$), cefazolin-nonsusceptible (15.4 vs. 8.4 days, $p < 0.01$) or ESBL-producing (16.7 vs. 9.6 days; $p < 0.01$) pathogens had a longer hospitalization stay than those due to their susceptible comparators.
Conclusion: Several host factors were recognized to be independently associated with the acquisition of UTIs due to levofloxacin- or cefazolin- nonsusceptible, or ESBL-producing Gram-negative bacilli. The clinical impact of UTIs due to nonsusceptible uropathogens is that they result in the prolongation of hospital stays.

Introduction

Urinary tract infection (UTI) is the most common bacterial infection encountered in the ambulatory care settling in the United States, and is associated with significant morbidity and mortality.[1,2] The global surveillance study called SMART revealed, that among *Enterobacteriaceae* isolates from complicated UTIs, there was significant antimicrobial resistance to levofloxacin/ciprofloxacin (33%) and extended spectrum cephalosporins (>30%) in the Asia-Pacific region.[2] In addition, high prevalence rate of extended-spectrum β-lactamase (ESBL) production among uropathogenic *Escherichia coli* isolates was seen. Increasing fluoroquinolone resistance is another critical issue since fluoroquinolones (FQs) have been recommended as the drugs of choice for empirical treatment of uncomplicated and complicated UTIs caused by trimethoprim-sulfamethoxazole-resistant uropathogens.[3]

The resistance issue among uropathogens has become a global problem, necessitating consensus on revising the guidelines of empirical treatment of UTIs.[4,5] There are many articles discussing the risk factors of fluoroquinolone resistance among *E. coli* isolates from UTI.[6,7] In this study, we conducted a prospective study to identify host-related risk factors for community-onset UTI (CoUTI) due to levofloxacin- or cefazolin-nonsusceptible isolates or uropathogens with ESBL production in adults admitted to medical wards. Also clinical impact of UTIs due to antimicrobial-nonsusceptible pathogens was investigated.

Materials and methods

A prospective study was conducted at medical wards of National Cheng-Kung University Hospital, Douliu branch of NCKUH, and Tainan Hospital, Department of Health, Executive Yuan, at southern Taiwan between August 2009 and January 2012. Hospitalized patients were enrolled if they met the following criteria: they were older than 18 years, admitted through the emergency department and diagnosed as having CoUTI due to one species of *Enterobacteriaceae*. There were 164 cases enrolled into the study, and 28 were excluded because of polymicrobial infections or no available causative isolates for antibiotic susceptibility tests. Clinical information including age, gender, residence in nursing home, recent hospitalization within 6 months, recent antibiotic exposure within 60 days, underlying diseases (including end-stage renal disease, old stroke, diabetes mellitus, hypertension, chronic kidney disease, renal stone, or chronic hepatitis), and the use of indwelling urinary catheter, were retrieved from chart reviews or electronic databases, or by interviewing with their care-givers. The primary end-point for clinical impact was the duration of hospitalization, since there were no fatalities until discharge.

Recurrent UTI was defined if the individual had at least one episode of UTI within 1 year. Complicated UTI was defined as the occurrence of UTI in individuals with functional or structural abnormalities of the genitourinary tract. Concurrent bacteremia was defined as the presence of the identical uropathogen with the same antibiogram in blood cultures. Abnormal liver function was defined as elevated serum levels of aspartate transaminase (>39 U/L) or alanine aminotransferase (>54 U/L). Acute kidney injury was referred to if there at least was a 2-fold increase in serum creatinine level.

This study was supported by the National Cheng Kung University Hospital Research Committee and approved by the institutional review board of National Cheng Kung University Hospital and Tainan hospital, Department of Health, Executive Yuan. Informed consents were obtained from participating patients.

Bacterial cultures and antimicrobial susceptibility tests

Fresh urine samples were delivered to the laboratory and were processed as per standard procedure. Blood cultures were processed using the automated blood culture system (VITEK 2 complete ID/AST Automation system; bioMérieux, Mercy l'Etoile, France). Urine samples were plated on the eosin methylene blue agar and the isolated microorganisms were categorized by Gram staining. Antibiotic susceptibility testing was determined using the disk diffusion method in accordance with the criteria from the Clinical and Laboratory Standards Institute, M100-S21.[8] Drug disks tested for the

isolated Gram-negative bacilli included ampicillin, ampicillin/sulbactam, gentamicin, amikacin, cefazolin, cefuroxime, ceftriaxone, and levofloxacin. In the present study, nonsusceptibility arbitrarily refers to the category of intermediate and resistant results, obtained using the disc diffusion method. A difference of at least 5 mm between the zone diameters of either cefotaxime or ceftazidime disks and their respective cephalosporin/clavulanate disks was taken to be the phenotypic confirmation of ESBL production.

Statistical methods

Descriptive statistics, including means, standard deviations, and ranges, were used to analyze continuous variables, whereas percentages and confidence intervals were used to analyze categorical variables. Independent t test was used for continuous variables. A Chi-square test or Fisher's exact test was used for categorical variables. The variables in bivariate analyses with a $p \leq 0.1$ were included in a multivariate analysis, which was performed using a logistic regression model to identify factors that independently and significantly affected the outcome. A p-value <0.05 was considered to be statistically significant. All statistical analyses were done using SPSS 15 (SPSS Inc., Chicago, IL, USA) for Windows.

Results

A total of 136 adults with microbiologically documented CoUTIs were enrolled during the study period; there were seven patients from Tainan Hospital, 11 from the Douliu Branch, NCKUH, and 118 from NCKUH. Basic characters of the 136 patients are shown in Table 1. There were 93 (68.4%) female patients. The mean age was 67 years with an age range of 19 to 91 years. A recent history of hospitalization within 6 months was noted in 54 (39.7%) patients and recent antibiotic exposure within 60 days in 24 (17.6%) patients. About 20% (27 patients, 19.9%) had recurrent UTI. Structural and functional abnormalities were present in 30 (22.4%) and 20 (14.9%) patients, respectively. Indwelling urinary catheter was present *in situ* in 12 (9.0%) patients. Common comorbidities were hypertension (54.4%) and diabetes mellitus (30.1%).

Usual symptoms or signs at presentation included pyuria (94%), fever (74.1%), and hematuria (57.9%). The episode of UTI in 60 (44.1%) patients was considered to be complicated, of which 61.7% (37 patients) had concurrent bacteremia. Out of all patients with UTI, 75 (55.1%) patients had bacteremia (Table 1). Of the *Enterobacteriaceae* pathogens isolated, *E. coli* (111, 82%) was the predominant species, followed by *Klebsiella pneumoniae* (11, 8%) and *Proteus* spp. (8, 6%). Out of 136 patients, there were 75 (55.1%) patients with bacteremia due to *E. coli* (62 patients, 83%), *K. pneumoniae* (9, 12%), *Proteus* spp. (3, 4%), and *Klebsiella oxytoca* (1, 1%) (Fig. 1).

There were 14 (10.3%) ESBL-producing *Enterobacteriaceae* isolates, of which all but one (13, 92.9%) were resistant to levofloxacin. Of 122 non-ESBL producing clinical isolates, 35 (28.7%), 31 (25.4%), and 16 (13.1%) were nonsusceptible to levofloxacin, cefazolin, and ceftriaxone, respectively. Among 111 *E. coli* isolates, which was the predominant species, 38 (34%) isolates were nonsusceptible to levofloxacin, 28 (25%) to cefazolin, 22 (20%) to cefuroxime, and 20 (18%) to ceftriaxone.

Table 1 Clinical characteristics of 136 adults with community-onset urinary tract infection (UTI) caused by *Enterobacteriaceae*

Characteristics	Number (%)
Recurrent UTI	27 (19.9)
Hospitalization within 6 mo	54 (39.7)
Antibiotics exposure within 60 d	24 (17.6)
Co-morbidity	
Hypertension	74 (54.4)
Diabetes mellitus	41 (30.1)
Old stroke	35 (25.7)
Chronic renal disease	18 (13.2)
Chronic hepatitis	18 (13.2)
Renal stones	2 (1.5)
Diagnosis	
UTI only	38 (27.9)
Complicated UTI only	23 (16.9)
UTI and bacteremia	38 (27.9)
Complicated UTI and bacteremia	37 (27.2)
Symptoms and signs	
Fever	100 (74.1)
Chills/rigor	48 (35.8)
Tachycardia	45 (33.1)
Pyuria	125 (94.0)
Hematuria	77 (57.9)
Thrombocytopenia	18 (13.4)
Acute kidney injury	18 (13.4)
Structural abnormality of urinary tract	30 (22.4)
Functional abnormality of urinary tract	20 (14.9)
Indwelling urinary catheter	12 (9.0)

Clinical variables associated with levofloxacin nonsusceptibility among uropathogens from patients with UTI

Clinical features of 136 patients were compared according to the levofloxacin susceptibility of isolated pathogens

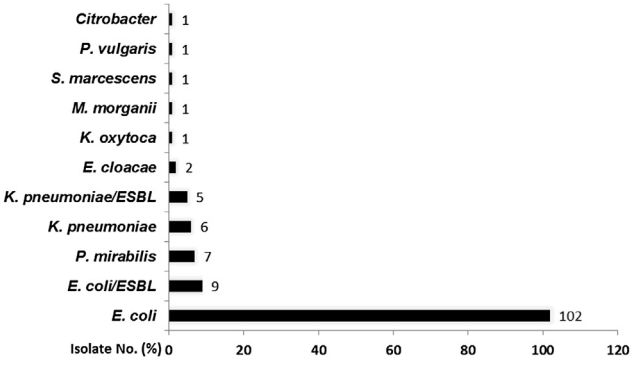

Figure 1. Bacterial species and isolate numbers of 136 uropathogens in the present study.

Table 2 Univariate analysis of clinical variables associated with levofloxacin nonsusceptibility in uropathogens obtained from adults with urinary tract infection (UTI)

Risk factors	Susceptible $n = 88$ (%)	Nonsusceptible $n = 48$ (%)	OR	95% CI	p
Age >65 y	48 (54.5)	37 (77.1)	2.8	1.3–6.2	0.01
Male gender	23 (26.1)	20 (41.7)	2.0	1.0–4.3	0.08
Recurrent UTI	12 (13.6)	15 (31.3)	2.9	1.2–6.8	0.02
Prior hospitalization in the past 6 mo	19 (21.6)	35 (72.9)	9.8	4.3–22.1	<0.01
Prior antibiotic in the past 60 d	8 (9.1)	16 (33.3)	5.0	1.9–12.8	<0.01
Urinary tract structure abnormality	19 (21.8)	11 (23.4)	1.1	0.5–2.5	0.83
Urinary function abnormality	8 (9.2)	12 (25.5)	3.4	1.3–9.0	0.02
Indwelling urinary catheter	3 (3.4)	9 (19.1)	6.6	1.7–25.9	<0.01
Co-morbidity					
Old stroke	12 (13.6)	23 (47.9)	5.8	2.5–13.4	<0.01
Diabetes mellitus	18 (20.7)	23 (47.9)	3.5	1.6–7.6	<0.01
Hypertension	47 (53.4)	27 (56.3)	1.1	0.6–2.3	0.86
Benign prostate hypertrophy	11 (12.5)	6 (12.5)	1.0	0.3–2.9	1.0
Renal disease	10 (11.4)	8 (16.7)	1.6	0.6–4.3	0.43
Renal stones	8 (9.2)	4 (8.3)	0.9	0.3–3.2	1.0
Solid tumor	4 (4.5)	6 (12.5)	3.0	0.8–11.2	0.17
Presentations of UTI					
Altered consciousness	10 (11.5)	12 (25.5)	2.6	1.0–6.7	0.05
Urinary symptoms	56 (64.4)	14 (29.8)	0.2	0.1–0.5	<0.01
Chills	39 (44.8)	9 (19.1)	0.3	0.1–0.7	<0.01
Fever	71 (81.6)	29 (60.4)	0.3	0.2–0.8	0.01
Pyuria	81 (93.1)	44 (95.7)	1.6	0.3–8.4	0.71
Hematuria	59 (67.8)	18 (39.1)	0.3	0.2–0.6	<0.01
Tachycardia	29 (33.3)	16 (34)	1.0	0.5–2.2	1.0
Thrombocytopenia	11 (12.6)	7 (14.9)	1.2	0.4–3.4	0.79
Abnormal liver function	8 (9.1)	5 (10.6)	1.2	0.4–3.9	0.77
Acute kidney injury	10 (11.4)	8 (17)	1.6	0.6–4.4	0.43

CI = confidence interval; OR = odds ratio.

(Table 2). UTIs due to levofloxacin-nonsusceptible isolates occurred more often in the elderly. Patients with diabetes mellitus and a prior history of stroke were more likely to be infected by levofloxacin-susceptible isolates.

Patients with any one of the following: prior history of UTI, hospitalization, nursing home residence or regular visit to dialysis centers within 6 months, recent exposure to antibiotics in the previous 2 months, functional abnormalities of urinary tract, or indwelling urinary catheter, were more likely to be infected by levofloxacin-nonsusceptible isolates (Table 2).

Clinical isolates with levofloxacin nonsusceptibility were significantly associated with nonsusceptibiluty to other antibiotics, including ampicillin, ampicillin/sulbactam, gentamicin, cephalosporins, and associated with ESBL production (Fig. 2). In contrast, typical presentations of UTIs, such as dysuria, frequency, urgency, flank pain, fever, chills, or hematuria, were more often noted in those with UTIs due to levofloxacin-susceptible isolates. There were no differences in terms of the frequency of pyuria, thrombocytopenia, abnormal liver enzymes, or acute kidney injury between patients with UTI due to levofloxacin-susceptible and their corresponding nonsusceptible comparators.

Using the multivariate analysis, recent hospitalization or nursing home residence within 6 months, diabetes mellitus, male, and old stroke were independently associated with the acquisition of levofloxacin-nonsusceptible uropathogens (Table 3). However, patients presenting with fever, hematuria, and urinary symptoms (such as burning sensation, flank soreness, frequency and urgency), were less likely to be infected with levofloxacin-nonsusceptible uropathogens (Table 3).

Clinical variables associated with cefazolin nonsusceptibility among uropathogens from patients with UTI

Likewise UTIs due to cefazolin-nonsusceptible isolates occurred more often in males than females (48.8%, 21/43 vs. 23.7%, 22/93; $p < 0.01$). Prior stroke (51.2%, 22/43 vs. 14.0%, 13/93; $p < 0.01$), recent hospitalization within 6 months (76.7%, 33/43 vs. 22.6%, 21/93; $p < 0.01$), and indwelling urinary catheter (16.3%, 7/43 vs. 5.4%, 5/93; $p < 0.05$) were more often associated with UTIs due to cefazolin-nonsusceptible isolates. Cefazolin-nonsusceptible isolates were more often associated with nonsusceptibility to other antibiotics, including ampicillin, ampicillin/sulbactam, gentamicin, cefuroxime, and ceftriaxone (Fig. 3). Furthermore, multivariate analysis revealed that recent hospitalization [adjusted odds ratio (aOR) 8.9], male gender (aOR 4.6) and old stroke (aOR 3.9) were independently related to

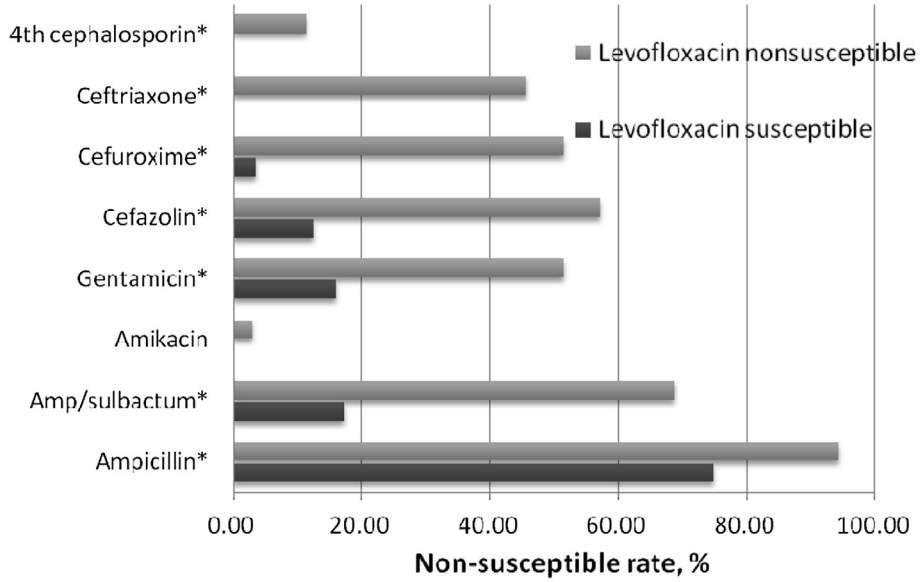

Figure 2. The nonsusceptible rates of eight antimicrobial agents among 122 isolates that were not extended-spectrum β-lactamase-producing uropathogens, stratified by levofloxacin susceptibility (*indicates a significant difference with $p < 0.05$).

UTI due to cefazolin-nonsusceptible isolates. But those presented with urinary symptoms and chills were less likely to be infected with cefazolin-nonsusceptible pathogens (Table 3).

Clinical variables associated with ESBL production among *E. coli*, *Klebsiella* and *Proteus* species from patients with UTI

Among 131 isolates of *E. coli*, *Klebsiella* and *Proteus* spp., which would be tested for ESBL-production phenotype if decreased zone diameters of cefotaxime or ceftazidime discs were noted, according to the recommendations of CLSI, clinical characters of 14 (10.7%) ESBL-producing isolates were compared with those of 117 isolates without ESBL. Patients with ESBL-producer UTIs more often had recurrent UTI (8/14, 57.1% vs. 18/117, 15.4%; $p < 0.01$), prior hospitalization within 6 months (12/14, 85.7% vs. 39/117, 33.3%; $p < 0.01$), prior antibiotics within 60 days (8/14, 57.1% vs. 16/117, 12.7%; $p < 0.01$), urinary function abnormalities (7/14, 50% vs. 12/117, 10.3%; $p < 0.01$), indwelling urinary catheter (5/14, 35.7% vs. 7/117, 6%; $p < 0.01$), underlying old stroke (8/14, 57.1% vs. 26/117, 22.2%; $p < 0.01$), and receipt of immunosuppressive therapy (2/14, 14.3% vs. 1/117, 0.9; $p = 0.03$) than those

Table 3 Multivariate analysis of clinical variables associated with levofloxacin or cefazolin nonsusceptibility and extended-spectrum beta-lactamase (ESBL) production in uropathogens obtained from adults with urinary tract infection

Risk factors	Levofloxacin nonsusceptibility			Cefazolin nonsusceptibility			ESBL production[a]		
	aOR	95% CI	*p*	aOR	95% CI	*p*	aOR	95% CI	*p* value
Male gender	3.1	1.1–8.6	0.03	4.6	1.7–12.2	<0.01			
Prior hospitalization in the past 6 months	4.8	1.8–12.9	<0.01	8.9	3.4–23.6	<0.01	7.4	1.5–37.6	0.02
Prior antibiotic in the past 60 days							4.2	1.2–14.8	0.03
Co-morbidity									
Old stroke	3.1	1.1–8.2	0.03	3.9	1.4–10.6	<0.01			
Diabetes mellitus	3.8	1.5–9.9	<0.01						
Presentations of urinary tract infection									
Altered consciousness	3.2	1.0–9.7	0.04						
Chills	0.4	0.2–0.9	0.03	0.4	0.2–1.0	0.04			
Fever				0.3	0.1–0.8	0.01			
Pyuria	0.3	0.1–0.7	<0.01						
Tachycardia	0.3	0.1–0.6	<0.01						

aOR = adjusted odds ratio; CI = confidence interval.
[a] The analytic population of ESBL production is the patients with UTIs due to *Escherichia coli*, *Klebsiella* or *Proteus* species.

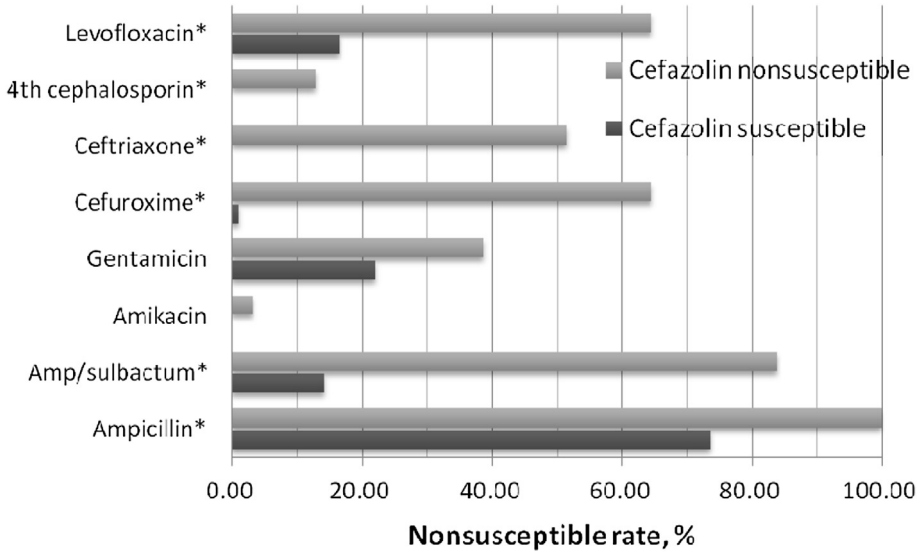

Figure 3. The nonsusceptible rates of eight antimicrobial agents among 122 isolates that were not extended-spectrum β-lactamase-producing uropathogens, stratified by levofloxacin susceptibility (*indicates a significant difference with $p < 0.05$).

due to non-ESBL-producing isolates. In the multivariate analysis, only recent hospitalization and antimicrobial therapy were independently related to ESBL-producer UTIs (Table 3).

Clinical impact of nonsusceptibility in uropathogens among patients with UTIs

Since there was no 14-day mortality among enrolled patients, clinical impact will be referred to the length of hospital stays. The hospital stay was longer in UTI due to levofloxacin-nonsusceptible (16.1 ± 10.9 vs. 7.5 ± 3.6 days; $p < 0.01$), cefazolin-nonsusceptible (15.4 ± 9.8 vs. 8.4 ± 6.2 days; $p < 0.01$), or ESBL-producing (16.7 ± 10.9 vs. 9.6 ± 7.3 days; $p < 0.01$) uropathogens, as compared with those due to antimicrobial-susceptible comparators.

Discussion

In this study, among selected hospitalized adults with microbiologically documented CoUTIs, we identified several host factors that are helpful in the differentiation of UTIs due to antimicrobial-nonsusceptible uropathogens from antimicrobial susceptible uropathogens. In general, male gender, recent hospitalization, and underlying old stroke were independently associated with the acquisition of levofloxacin- or cefazolin-nonsusceptible uropathogens. Typical presentations of urosepsis, such as urinary symptoms, fever, chills, though with variable statistical significance in the multivariate analysis, were related to UTIs due to levofloxacin- or cefazolin-susceptible uropathogens. Moreover, the acquisition of levofloxacin- or cefazolin-nonsusceptible uropathogens, although no short-term survival impact was seen in our study, was related to a longer hospital stay, which could be anticipated to increase medical cost. A similar impact was observed in the population acquiring ESBL-producer UTIs, in which they were independently associated with prior hospitalization, nursing home residence or regularly visiting dialysis centers and recent antibiotic exposure, comparable to the findings of a Canadian study.[9]

Our study population was designed to include the patients with CoUTIs. As evidenced by the frequent presence of a history of recent visits to healthcare facilities and functional or structural disorders in the urinary tract, our patients were not initially healthy, as defined in the patients with community-acquired infections. More precisely, some of our enrolled patients had community-onset, healthcare-associated UTIs, rendering a certain degree of heterogeneity in the study cohort. However, such a heterogeneous population was frequently encountered in the referral tertiary hospitals.

Although cefazolin is not recommended as empirical therapy for community-acquired UTIs in the clinical guidelines from western countries, in Taiwan it still plays an important role as one of the drugs of choice for acute uncomplicated or complicated pyelonephritis in adults.[10] Although clinical data of antimicrobial therapy and antimicrobial susceptibility among uropathogens in adults are scarce, such information from pediatric population in Taiwan is available. Among 446 *E. coli* isolates obtained from 597 pediatric cases of UTIs, cefazolin resistance was noted in 24% of patients, but nearly 40% of the affected children had underlying GU tract anomalies, which predisposed them to recurrent UTI and previous antimicrobial therapy.[11] Moreover, in a retrospective analysis of 338 children with the first episodes of symptomatic UTIs, cefazolin, or cephalexin alone was regarded to be an appropriate treatment for community-acquired UTIs,[12] supporting the rationale that cefazolin can be one of the alternative drugs for CoUTIs in adults without the risk factors of cefazolin nonsusceptibility identified in our study.

The interaction between clinical presentations of UTIs and antimicrobial susceptibility of causative pathogens was

rarely mentioned. We found that UTIs due to antimicrobial-nonsusceptible isolates cause less local or systemic symptoms/signs such as urinary irritation, fever, or chills, as compared with UTIs caused by susceptible comparators. There is a possibility that antimicrobial-nonsusceptible UTIs are often present in relatively debilitated elderly with underlying chronic illness, and therefore their localized symptoms are less evident clinically and febrile responses are blunted.[13] However, another plausible reason may be the variable pathogenicity among bacterial isolates with varied degrees of antimicrobial resistance.[8]

There were several limitations in the present study. First, the reported clinical impact of decreased antimicrobial susceptibility among uropathogens was limited to the hospital stay, but in fact may involve increasing medical cost and morbidity and mortality which were not investigated in our study. Second, the appropriateness of therapeutic regimens for CoUTIs, which in theory would influence clinical responses of medical therapy and thereafter the hospital stay, were not examined. However, none of our study population had in-hospital mortality or needed intensive care for critical illness.

With the knowledge of host factors associated with antimicrobial nonsusceptibility in uropathogens, physicians can select appropriate empirical therapy for patients with UTIs due to these pathogens. The clinical impact posed by these antimicrobial-resistant uropathogens warrants further studies.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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