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## Original Article

## Clinical Implications, Risk Factors and Mortality Following Community-onset Bacteremia Caused by Extended-spectrum $\beta$ -lactamase (ESBL) and non-ESBL Producing *Escherichia coli*

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**BACKGROUND/PURPOSE:** Infections caused by extended-spectrum  $\beta$ -lactamase (ESBL)-producing bacteria have become a serious clinical concern worldwide. The occurrence of ESBLs in Taiwan has been well-documented and is reviewed in recent publications. However, studies comparing community-onset bacteremia caused by ESBL- and non-ESBL-producing *Escherichia coli* are limited.

**METHODS:** We retrospectively reviewed the medical records of patients with *E. coli* bacteremia who visited the emergency department of Kaohsiung Chang Gung Memorial Hospital from January 2005 to December 2006. Clinical data were collected to compare the clinical features of patients with ESBL-producing *E. coli* with those of patients with non-ESBL-producers and to identify the risk factors associated with ESBL-producing *E. coli* bacteremia.

**RESULTS:** There were 404 episodes of community-onset *E. coli* bacteremia. The overall 30-day mortality rate was 11.4% (46/404) and the mortality rate of healthcare-associated infections was significantly higher than that of community-acquired infections [4/13 (30.8%) vs. 42/391 (10.7%);  $p=0.049$ ] Non-urinary focus was independently associated with an increased risk of fatality [47/178 (26.4%) vs. 4/226 (1.8%);  $p<0.001$ ]. The frequency of ESBL producers was 4.7% (19/404). Of these, four (21.1%) were associated with a long-term care facility. Significant risk factors associated with ESBL-producing *E. coli* bacteremia included recent antibiotic exposure (within 30 days) and urinary catheter placement. Although the trend was towards higher mortality in patients with ESBL-producing *E. coli* bacteremia, the difference did not reach statistical significance compared with the mortality of patients with non-ESBL *E. coli* bacteremia.

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**CONCLUSION:** Fewer than 5% of community-onset *E. coli* bacteremia episodes in Southern Taiwan were due to ESBL-producers. Prior antibiotic use within 30 days and urinary catheter placement were independently associated with ESBL-producing *E. coli* bacteremia.

**KEYWORDS:** bacteremia, community-onset, *Escherichia coli*, extended-spectrum  $\beta$ -lactamases, risk factors

## Introduction

Extended-spectrum  $\beta$ -lactamases (ESBLs) are a heterogeneous group of enzymes responsible for the resistance of enterobacteria to extended-spectrum  $\beta$ -lactam antibiotics.<sup>1</sup> ESBL were first identified in Germany in 1983,<sup>2</sup> and many reports of ESBLs quickly followed in the United States. The types of antimicrobial resistance pertaining to ESBLs have been recognized worldwide in the last 20 years. The majority of persons infected with ESBL-producing microorganisms have been exposed to hospital intensive care units.<sup>3,4</sup> Recent data have suggested that ESBL-producing *Enterobacteriaceae* are prevalent in community-based settings.<sup>5-7</sup> Unlike the nosocomial multidrug resistant organisms, ESBL-producing *Escherichia coli* are frequently community-onset, particularly those with the worldwide-spread of CTX-M-type ESBLs. Furthermore, foreign travel may be a major risk factor for developing community-onset ESBL-producing *E. coli* infections.<sup>8</sup>

As is the case with ESBL-producing *Klebsiella pneumoniae*, treatment with cephalosporins or fluoroquinolones for bloodstream infections caused by ESBL-producing *E. coli* is associated with a poorer prognosis than carbapenem therapy.<sup>9</sup> As the frequency of bacteremia caused by ESBL-producing *E. coli* is increasing, carbapenem use is rising, which may contribute to the spread of carbapenem resistance. As a result, ESBL-producing *E. coli* is an emerging and worrying.

The goal of the study was to evaluate the prevalence, clinical features and risk factors of community-onset ESBL-producing *E. coli* bacteremia in Southern Taiwan; thus we retrospectively studied all available community-onset bloodstream infections caused by *E. coli* from January 2005 to December 2006.

## Methods

### Subjects

This retrospective study was conducted at Chang Gung Memorial Hospital, Kaohsiung, which is a 2,600-bed medical center facility located in Southern Taiwan, providing both primary and tertiary referral care. It receives more than 100,000 emergency room (ER) visits per year.

Patients were included if their blood cultures were drawn in the ER immediately prior to admission and if the culture results were found to be positive. Patients who had been admitted on a prior occasion within the preceding 30 days were excluded. We reviewed the medical records of 1,200 patients from January 2005 to December 2006. Demographic characteristics, underlying diseases, source of specimen (blood, urine, pus, and others), antimicrobial regimen, any antimicrobial therapy administered in the 30 days prior to the onset of bacteremia, laboratory data (e.g. leukocyte and platelet counts) and clinical outcome (e.g. length of hospitalization, mortality) were retrospectively collected for each patient.

### Microbiological testing

Bacterial susceptibility to antimicrobial agents was determined according to criteria of the National Committee for Clinical Laboratory Standards.<sup>10</sup> ESBL-producing *E. coli* was suspected if the disk-diffusion susceptibility test showed the inhibition zone of ceftriaxone was  $\leq 25$  mm or ceftazidime  $\leq 22$  mm. These isolates were subjected to cefotaxime (30  $\mu$ g) cefotaxime/clavulanate (30/10  $\mu$ g) and ceftazidime (30  $\mu$ g) ceftazidime/clavulanate (30/10  $\mu$ g) disk testing. ESBL production was evidenced if an increase of  $\geq 5$  mm in the diameter of the inhibition zone was found when clavulanate was combined with either

cefotaxime or ceftazidime. The reference strains used were *E. coli* ATCC 25922 and *K. pneumoniae* ATCC 700603.

### Definitions

All variable definitions were established prior to data collection. Bacteremia was defined as the finding of organisms in a blood culture specimen. Community-onset bacteremia was defined as a positive blood culture taken on, or within, 48 hours of admission. These patients, who had been hospitalized in the month prior to admission and had been transferred from another hospital, were defined as having a nosocomial infection. Antimicrobial therapy was defined as inappropriate when an active antimicrobial agent (as determined by *in vitro* susceptibility testing) at the usual recommended dosage had not been administered during the first 48 hours. Episodes of community-onset bacteremia were further classified as long term care facility-associated infections if the patient had been resident in a nursing home or long-term care facility. All other cases of community-onset bacteremia were classified as community-acquired infections. Length of hospital stay was calculated as the time from the onset of bacteremia to discharge home or transfer to a rehabilitation ward.

### Statistical analysis

Data analysis was performed using SPSS version 10.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were compared using  $\chi^2$  test or Fisher's exact test, as appropriate. Continuous variables were compared using the Student's *t* test. All *p* values were two-tailed; a *p* value <0.05 was considered statistically significant. Odd ratios (OR) and 95% confidence intervals (CI) were calculated for the significant factors.

### Results

We collected 50 samples per month for 2 years, all with a positive blood culture on admission to, or within 48 hours of admission to the ER. The total number was 1,200. *E. coli* and *K. pneumoniae* accounted for 37.5% and 22.9%, respectively. Data from 450 patients with *E. coli* bacteremia was collected but five patients were not enrolled owing to incomplete medical records. Forty-one patients with nosocomial bloodstream infections were excluded, leaving 404 patients with community-onset *E. coli* bacteremia.

The ESBL-producing strains included 4.7% (19/404) *E. coli* and 10.4% (26/249) *K. pneumoniae*. There was no apparent clustering of the case patients in terms of their geographical distribution. However, ESBL-producing *E. coli* bacteremia occurred mostly in August (5/32, 15.6%) and May (4/27, 14.8%).

The demographic and clinical characteristics of the patients with community-onset bacteremia caused by *E. coli* are shown in Table 1. In general, there were no statistical differences in the presumed origin of bacteremia between non-ESBL- and ESBL-producing *E. coli*: urinary tract infection (UTI; 55.6% vs. 63.2%), biliary tract infection (19.5% vs. 10.5%), respiratory tract infection (3.1% vs. 5.3%), and primary bloodstream infection (18.7% vs. 5.3%). However, soft tissue infection was caused more frequently by ESBL-producing strains than non-ESBL strains (10.5% vs. 0.5%; *p*=0.01).

The overall mean length of hospital stay was 13.4 ± 14.0 days (range, 0–120 days). The overall 30-day mortality rate was 11.4%. In addition, there was no statistical significance between 30-day mortality for ESBL- and non-ESBL-producing *E. coli* (21.1% vs. 10.9%), as shown in Table 2. The mean length of hospital stay for the 30-day mortality patients with ESBL- and non-ESBL producing *E. coli* were 15.5 ± 8.5 days and 6.1 ± 6.9 days, respectively (*p*<0.05). It may be that the length of hospital stay was longer for patients with ESBL-producing *E. coli* bacteremia, leading to an overestimation.

We limited our analysis of antibiotic use to the 30 days prior to the onset of bacteremia; 46 patients received antibiotics according to their medical records. There was an association between ESBL production and prior antibiotic use (ESBL vs. non-ESBL group, 27.8% vs. 10.8%, respectively; *p*=0.044). The other significant risk factors for ESBL production were residence in a long-term care facility and insertion of a Foley catheter (Table 1).

Of 19 episodes of ESBL-producing *E. coli* bacteremia, four (21.1%) were associated with a long-term care facility, which was significantly higher than that of the non-ESBL-producing strains [9/385 (2.3%); *p*<0.05]. There was no statistical significance in the overall median length of hospital stay for the 13 patient's resident in a long-term care facility compared with the 391 patients with community-acquired infections (12.9 ± 10.7 days vs. 13.4 ± 12.1 days; data not shown). However, the 30-day mortality

**Table 1.** Demographic characteristics and potential risk factors of patients with community-onset bacteremia caused by non-extended-spectrum beta-lactamase and extended-spectrum beta-lactamase-producing *Escherichia coli*<sup>a</sup>

Characteristics	Total (n=404)	Non-ESBL (n=385)	ESBL (n=19)	p
Age	61.5±18.3	61.3±18.6	66.1±11.0	0.080
Range	0–93	0–93	37–82	
≤50	83 (20.5)	82 (21.3)	1 (5.3)	0.140
>50	321 (79.5)	303 (78.7)	18 (94.7)	
Sex				0.093
Male	168 (41.6)	164 (42.6)	4 (21.1)	
Female	236 (58.4)	221 (57.4)	15 (78.9)	
Long-term care facility	13 (3.2)	9 (2.3)	4 (21.1)	0.002
Comorbid condition				
Malignancy	94 (23.3)	89 (23.1)	5 (26.3)	0.780
Diabetes mellitus	147 (36.4)	139 (36.1)	8 (42.1)	0.600
Hypertension	147 (36.4)	140 (36.4)	7 (36.8)	0.970
BPH	33 (8.2)	33 (8.6)	0 (0)	0.390
Pancreatic and/or hepatic disease	111 (27.5)	107 (27.8)	4 (21.1)	0.520
Renal disease	77 (19.1)	72 (18.7)	5 (26.3)	0.390
Heart disease	53 (13.1)	49 (12.7)	4 (21.1)	0.290
Stroke	56 (13.9)	51 (13.2)	5 (26.3)	0.160
Primary infection site				
Urinary tract infection	226 (55.9)	214 (55.6)	12 (63.2)	0.640
Biliary tract infection	77 (19.1)	75 (19.5)	2 (10.5)	0.550
Sepsis	73 (18.1)	72 (18.7)	1 (5.3)	0.220
Lung (pneumonia)	13 (3.2)	12 (3.1)	1 (5.3)	0.470
Cellulitis	4 (1.0)	2 (0.5)	2 (10.5)	0.010
Clinical presentation				
Fever	328 (81.2)	312 (81.0)	16 (84.2)	1.000
Neutropenia <1.2×10 <sup>9</sup> /L <sup>b</sup>	10 (2.5)	9 (2.4)	1 (5.3)	0.390
Band % >15 <sup>b</sup>	9 (2.3)	8 (2.1)	1 (5.3)	0.360
Foley insertion	18 (4.5)	14 (3.6)	4 (21.1)	0.007
Prior use of antibiotics within 30 d <sup>c</sup>	46 (11.4)	41 (10.8)	5 (27.8)	0.044

<sup>a</sup>Data presented as mean ± standard deviation or n (%); <sup>b</sup>Only 400 results showed absolute neutrophil counts and band form count; <sup>c</sup>only 399 cases had medical records showing that antibiotics were used within the preceding 30 days. ESBL=extended-spectrum β-lactamase; BPH=benign prostatic hyperplasia.

of patients from long-term care facilities was significantly higher than that of patients with community-acquired infections (33.3% vs. 10.7%;  $p < 0.05$ ). Furthermore, when we analyzed the association between the primary site of infection and mortality, non-urinary focus (47/178, 26.4%;  $p < 0.001$ ) was independently associated with an increased risk of death.

In this study, 67 episodes of *E. coli* bacteremia were combined with other pathogens, but there were no statistical difference between the proportion of those with or

without ESBL [62/385 (16.1%) vs. 5/19 (26.3%);  $p = 0.22$ ]. However, we found that, among UTIs, ESBL *E. coli* bacteremia seemed to be accompanied by other pathogens compared with non-ESBL *E. coli* bacteremia ( $p < 0.05$ ; Table 3).

The antibiograms of the 404 isolates with non-ESBL and ESBL-producing *E. coli* are shown in the Figure. Imipenem was the only antibiotic agent to which all isolates were susceptible. In our study, the susceptibility of *E. coli* to gentamicin, trimethoprim/sulfamethoxazole and

**Table 2.** Differences of outcome between non-extended-spectrum  $\beta$ -lactamase and extended-spectrum  $\beta$ -lactamase-producing *Escherichia coli* bacteremia<sup>a</sup>

Outcomes	Total (n=404)	Non-ESBL (n=385)	ESBL (n=19)	p
Crude mortality	51 (12.6)	47 (12.2)	4 (21.1)	0.28
3-day mortality	25 (6.2)	24 (6.2)	1 (5.3)	NS
15-day mortality	39 (9.7)	38 (9.9)	1 (5.3)	NS
Hospital stay (d)	13.4±14.0	13.1±13.0 (0–96)	21.0±27.1 (1–120)	0.22
30-day mortality	47 (11.4)	42 (10.9)	4 (21.1)	0.25
Hospital stay (d)	6.7±7.4	6.1±6.9 (0–27)	15.5±8.5 (3–22)	<0.05

<sup>a</sup>Data presented as n (%) or mean ± standard deviation. ESBL=extended-spectrum  $\beta$ -lactamase; E.coli=Escherichia coli; NS=not significant.

**Table 3.** Frequency of *Escherichia coli* bacteremia with or without extended-spectrum  $\beta$ -lactamase combined with other pathogens in different primary infection site

	Total (n=404)	Non-ESBL (n=385)	ESBL (n=19)	p
Number of case	67 (16.7)	62 (16.1)	5 (26.3)	0.220
Primary infection site				
Urinary tract infection	14/226 (6.2)	10/214 (4.7)	4/12 (33.3)	0.004
Biliary tract infection	26/77 (33.8)	26 (34.7)	0 (0)	0.550
Sepsis	19/73 (26)	19 (26.4)	0 (0)	1.000
Lung	5/13 (38.5)	5/12 (92.3)	0 (0)	1.000
Others <sup>b</sup>	2			

<sup>a</sup>Data presented as n (%); <sup>b</sup>one case of cellulitis caused by non-ESBL *E. coli*; one case of pelvic inflammatory disease caused by ESBL-producing *E. coli*. ESBL=extended-spectrum  $\beta$ -lactamase; *E. coli*=*Escherichia coli*.

piperacillin was poor, even against non-ESBL-producers. Isolates of ESBL-producing *E. coli* were more resistant to gentamicin [11/19 (57.9%) vs. 87/385 (22.6%);  $p < 0.05$ ] and ciprofloxacin [10/19 (52.6%) vs. 54/385 (14.0%);  $p < 0.05$ ] than isolates of non-ESBL-producing *E. coli*, as shown in Table 4. Among non-ESBL *E. coli* bacteremia, resistance to aztreonam (3.38%), ceftazidime (5.71%), ceftriaxone (5.97%) and cefuroxime (7.01%) was an independent risk factor for mortality ( $p < 0.05$ ; Table 5).

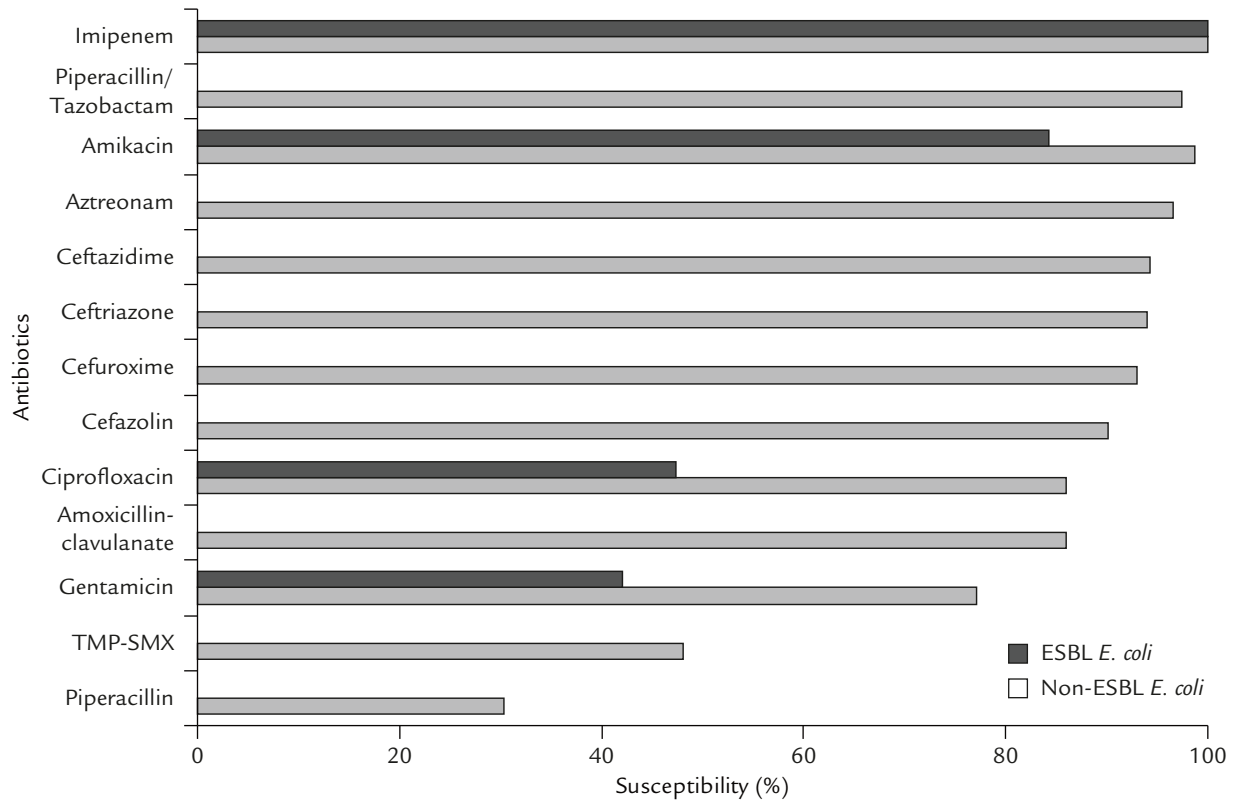
## Discussion

Infections caused by ESBL-producing bacteria have become a serious clinical concern worldwide. The occurrence of ESBLs in Taiwan has been well-documented and is reviewed in recent publications.<sup>11</sup> Relatively high incidence figures for ESBL phenotypes were reported for three centers in Northern Taiwan, contributing to the 1998–2002

SENTRY programs, with overall rates of ESBL production of 13.5% for *K. pneumoniae* and 5.6% for *E. coli*.<sup>12</sup> However, our study was undertaken to evaluate the risk factors and the prevalence of ESBL-producing *E. coli* bacteremia at the community level, to distinguish the clinical manifestations of *E. coli* bacteremia with and without ESBL, and to detect the antimicrobial resistance patterns in Southern Taiwan.

In this study, 4.7% (19/404) of cases had ESBL-producing *E. coli* bacteremia; a similar frequency to that reported by Kang et al.<sup>13</sup> The prevalence of ESBL-producing *E. coli* bacteremia was higher in patients who acquired bacteremia while in a long term care facility than in those who acquired it in the community (30.8% vs. 3.8%;  $p < 0.05$ ).

Previous studies have recognized potential risk factors for community-onset ESBL-producing *E. coli* bacteremia, including diabetes mellitus, previous fluoroquinolone use, recurrent UTIs, previous hospital admission, older



**Figure.** Antimicrobial susceptibility of extended and non-extended spectrum  $\beta$ -lactamase producing *Escherichia coli* at Chang-Gung Memorial Hospital, Kaohsiung. Sensitivity of *E. coli* and ESBL-*E. coli* to antimicrobial drugs was as follows: Imipenem = 100%; ciprofloxacin = 86% vs. 47.7%; gentamicin = 77.4% vs. 42.1%; amikacin = 98.7% vs. 84.2%. ESBL = extended-spectrum beta-lactamase; TMP-SMX = trimethoprim-sulfamethoxazole.

**Table 4.** Comparison of the antimicrobial susceptibility of non-extended and extended-spectrum  $\beta$ -lactamase-producing *Escherichia coli*<sup>a</sup>

Antibiotics	Non-ESBL (n=385)	ESBL (n=19)	p
Ciprofloxacin			<0.001
R	54 (14.0)	10 (52.6)	
S	331 (86.0)	9 (47.7)	
Gentamicin			0.001
I	4 (1.0)	1 (5.3)	
R	83 (21.6)	10 (52.6)	
S	298 (77.4)	8 (42.1)	
Amikacin			<0.001
I	2 (0.5)	0 (0)	
R	3 (0.8)	3 (15.8)	
S	380 (98.7)	16 (84.2)	
Imipenem			
S	385 (100)	19 (100)	

<sup>a</sup>Data presented as n (%). ESBL = Extended-spectrum  $\beta$ -lactamase; *E. coli* = *Escherichia coli*.

age, and male sex.<sup>14</sup> Our present study revealed residence in a long-term care facility, cellulitis and Foley catheter insertion were significantly risk for ESBL production in patients with community-onset *E. coli* bacteremia. In terms of cellulitis, one site was over the left foot and another was a peritoneal abscess. Although Gram-negative cellulitis is not particularly common, there are several case reports published in the literature.<sup>15,16</sup> To our knowledge, there are no reports of cellulitis caused by ESBL-producing *E. coli*.

Pedersen et al demonstrated that previous antibiotic prescriptions were strongly associated with antimicrobial resistance in community-onset bacteremia, especially with *E. coli*.<sup>17</sup> In addition, recent studies show that previous use of oxyimino- $\beta$ -lactams or fluoroquinolones is a risk factor for ESBL-producing isolates in patients with bacteremia caused by *E. coli*.<sup>18,19</sup> We limited our analysis of antibiotic use to 30 days before the onset of bacteremia and we only assessed the association between ESBL-producing *E. coli* and previous antibiotic use ( $p=0.044$ ).

**Table 5.** Difference between drug susceptibility of *Escherichia coli* and mortality rate ( $n=385$ )

Drug	Alive	Dead	<i>p</i>	Odds ratio	95% confidence interval
Aztreonam					(0.064, 0.651)
S	330	42	0.013	0.204	
R	8	5			
Ceftazidime					(0.126, 0.916)
S	322	41	0.039	0.340	
R	16	6			
Ceftriaxone					(0.110, 0.732)
S	322	40	0.014	0.284	
R	16	7			
Cefuroxime					(0.143, 0.903)
S	318	40	0.034	0.359	
R	20	7			

With regard to the clinical impact of ESBL-producing *E. coli* bacteremia, a number of studies observed that patients with infection caused by ESBL-producing *E. coli* tended to have poorer outcomes, longer length of stay, higher mortality, and excess hospital charges than those caused by non-ESBL producers.<sup>20,21</sup> In our study, there was no statistical difference in the 30-day mortality rate and of length of hospital stay for non-ESBL and ESBL-producing *E. coli* bacteremia. The question of whether ESBL-production significantly increases the risk of death remains unresolved.<sup>22</sup> Compared with other studies,<sup>19,20</sup> our crude mortality rate was lower, but the length of hospital stay was longer. Nevertheless, long-term care facility-associated infections had a higher 30-day mortality rate than community-acquired bloodstream infections. The mortality rate between long-term care facility and community-acquired *E. coli* bacteremia seems to be similar to that in a previous report.<sup>23</sup>

Interestingly, in our study, mortality was higher if the non-ESBL producing *E. coli* was resistant to oxyimino- $\beta$ -lactams (Table 5). The reason for this may be that our empiric therapy for *E. coli* infection was cephalosporins, with or without aminoglycosides, meaning that the inappropriate antibiotic was used initially. The antibiograms in our study showed that imipenem was the only antibiotic agent to which all isolates were susceptible. Of the ESBL producers, resistance to gentamicin

(11/19, 57.9%) and amikacin (3/19, 15.8%) was higher than in previous reports.<sup>18,21</sup> However, resistance to ciprofloxacin (10/19, 52.6%) was lower than in a previous study.<sup>21</sup> In cases of non-ESBL *E. coli* bacteremia, resistance to amoxicillin/clavulanate, ciprofloxacin, trimethoprim/sulfamethoxazole, gentamicin, and amikacin was higher than in other studies.<sup>17</sup> Therefore, resistance rates need to be kept in mind when selecting antibiotics to treat *E. coli* infections.

As to the source of the bloodstream infections, more than half of the patients had UTI. We found that non-urinary tract focus was associated with an increasing risk of death, regardless of whether non-ESBL or ESBL-producing *E. coli* was the pathogen; this is similar to a previous study.<sup>24</sup>

Notably, in our study, 67 patients (16.6%) had polymicrobial bloodstream infections, and we found that UTI caused by ESBL-producing *E. coli* were frequently present alongside polymicrobial bloodstream infections. In other words, if a UTI is caused by ESBL-producing *E. coli*, other pathogens must also be considered, and broad spectrum antibiotics should be used. To our knowledge, there are few reports about the association between polymicrobial bloodstream infections, primary site of infection and the ESBL producer, and more research is needed.

The main limitation of our study is that the small sample size might not allow for the evaluation of risk

factors for some subgroups of patients, and might have been insufficient to detect other relevant risk factors for ESBL-producing *E. coli* infections. In addition, as this study was of a retrospective nature, the possibility of the limitation in precluding accurate comparisons should be kept in mind. In fact, some selection bias may have occurred during the review process. Since the study was carried out in a tertiary hospital, many of our patients had serious underlying illness, including neoplastic diseases and chronic liver disease. Thus the results may not be applicable to other institutions.

In conclusion, this study showed that the prevalence of ESBL-producing *E. coli* in community-onset bacteremia of Southern Taiwan was 4.7%. Independent risk factors for ESBL-producing *E. coli* were residence in a long term care facility, urinary catheterization, possible previous antibiotic use and older age. *In vitro*, ESBL-producing *E. coli* were susceptible to flomoxef and amikacin, but whether these antibiotics are a reliable alternative to carbapenems in clinical practice is a question that needs further study. Therefore, the physician should be aware of such high-risk patients and target the initial appropriate empirical antimicrobial therapy to minimize the mortality of those with community-onset bloodstream infections due to ESBL-producing *E. coli*.

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