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Original Article

Extended-spectrum β-lactamase–producing phenotype signifies a poor prognosis for patients with cefpodoxime-resistant *Escherichia coli* or *Klebsiella pneumoniae* bacteremia

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Background and purpose: Bloodstream infections caused by multidrug-resistant *Enterobacteriaceae* are a major concern. This study explored the clinical impact of extended-spectrum β-lactamase (ESBL) production among cefpodoxime-resistant *Escherichia coli* and *Klebsiella pneumoniae* bacteremia.

Methods: The medical charts and microbiological results of patients with cefpodoxime-resistant *E. coli* or *K. pneumoniae* bacteremia in a tertiary hospital in southern Taiwan between June 2003 and December 2006 were retrospectively reviewed. The clinical characteristics, medical histories, and clinical outcomes were evaluated. ESBL production was indicated by the double-disk synergy test.

Results: 278 episodes of bacteremia caused by cefpodoxime-resistant *K. pneumoniae* or *E. coli* were identified, of which 115 (41%) were ESBL producing. Compared with non-ESBL–producing bacteremia, bacteremic episodes caused by ESBL producers were less often community acquired (4.3% vs 26.4%; $p < 0.001$). Underlying diabetes mellitus (48.7% vs 35.0%; $p = 0.02$), liver cirrhosis (22.6% vs 11.7%; $p = 0.02$), or uremia (21.7% vs 3.7%; $p < 0.001$) were more common in ESBL-producing bacteremia. In contrast, solid tumors were more frequent in non-ESBL–producing bacteremia (44.8% vs 27.8%; $p = 0.004$). Overall, patients with ESBL-producing bacteremia had higher disease severity indicated by a Pittsburgh bacteremia score ≥4, longer duration of hospital stay (51.1 days vs 31.9 days; $p = 0.007$), more admission to intensive care units (19.1% vs 8.0%; $p = 0.006$), and a higher mortality rate at 28 days (34.8% vs 23.9%; $p = 0.03$).

Conclusion: ESBL production signifies a poor clinical outcome for patients with bacteremia caused by cefpodoxime-resistant *E. coli* or *K. pneumoniae*.

Key words: Bacteremia; beta-Lactamases; Cefpodoxime; Drug resistance, microbial; *Escherichia coli*; *Klebsiella pneumoniae*

Introduction

Escherichia coli and *Klebsiella pneumoniae* are major pathogens causing urinary tract infections, intra-abdominal infections, and primary bacteremia. Due to widespread use of broad-spectrum cephalosporins, including oxyimino-β-lactam agents, in the past 2 decades, antibiotic-resistant strains have emerged worldwide among the *Enterobacteriaceae*, and are mainly *E. coli* and *K. pneumoniae* [1]. Such a scenario is often found in daily clinical practice, especially in patients who are admitted to hospitals or intensive care units (ICUs).

Antibiotic resistance is recognized as an important clinical issue, and is a challenge for physicians when confronting infections, especially in the hospital setting.

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Bloodstream infections (BSI) caused by organisms that have antibiotic resistance are associated with increased rates of treatment failure and mortality [2]. Extended-spectrum β-lactamases (ESBLs), usually plasmid mediated, are β-lactamases that confer resistance to oxyimino cephalosporins and monobactams. Patients at high risk for infection by ESBL-producing organisms are often seriously ill, with histories of lengthy hospital stays and exposure to invasive medical devices and/or procedures [3]. Diseases caused by ESBL-producing strains of the *Enterobacteriaceae* family have a considerable impact on mortality rates and hospital costs [4].

If it was possible to identify ESBL-producing bacteremia as soon as possible after the primary results of drug susceptibility testing by the disk diffusion method become available, patients infected by possible ESBL-producing strains might be able to receive earlier adequate antimicrobial treatment. Therefore, this study was performed to ascertain the clinical impact and outcome of ESBL-producing isolates among cefpodoxime-resistant *E. coli* or *K. pneumoniae* bacteremia at the National Cheng Kung University Hospital (NCKUH), Tainan, Taiwan. NCKUH is a 900-bed teaching hospital, with 5 ICUs (67 beds), located in southern Taiwan.

Methods

Study design and patients

In this retrospective study, the blood culture records at the clinical microbiology laboratory were reviewed to identify bacteremia caused by cefpodoxime-resistant *K. pneumoniae* or *E. coli* between June 2003 and December 2006. Only adult patients (older than 18 years) were enrolled.

The medical charts of all identified patients were reviewed, and clinical information, including demographics, dates of hospital admission and discharge, and dates of blood cultures, were obtained. Medical histories were reviewed for underlying illnesses, invasive procedures within 1 week, and hospital admission within 6 months. The severity of bacteremia was evaluated by the Pittsburgh bacteremia score [5], and the clinical outcomes 14 and 28 days after the onset of the index bacteremic episode were analyzed.

Microbiological analysis

Blood cultures were processed in the clinical microbiology laboratory, using the BACTEC 9240 system (Becton Dickinson Diagnostic Instrument Systems, Sparks, MD, USA). *K. pneumoniae* and *E. coli* isolates were identified both by standard microbiological techniques and by the Vitek system (bioMérieux, Marcy L'Etoile, France). Antimicrobial susceptibility testing was determined by the disk diffusion technique in accordance with the criteria established by the Clinical and Laboratory Standards Institute (CLSI) [6].

ESBL production was determined by using the combination disks method according to the CLSI performance standards [6]. In brief, the diameters of inhibition zones around cefotaxime and ceftazidime disks (30 μg each), alone and in combination with clavulanic acid 10 μg, were determined. An increase of at least 5 mm in inhibition zone diameter when either drug was combined with clavulanic acid was considered to be evidence of ESBL production.

Definition

Health care–associated infections were defined as infection noted in patients who received regular hemodialysis, had transferred from a chronic care center, or had been admitted to hospital within the previous 6 months. A nosocomial infection was defined as an infection that occurred more than 48 h after admission to the hospital. The severity of illness was evaluated on the first day of bacteremia onset by means of the Pittsburgh bacteremia score.

Statistical analysis

The results were analyzed using the Statistical Package for the Social Sciences (SPSS) for Windows (Version 13.0; SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean values ± standard deviation (SD), and categorical variables as a percentage of the total number of patients analyzed. The categorical variables were compared by the Fisher's exact or chi-squared test, as appropriate, and the continuous variables by the Mann-Whitney *U* or Student's *t* test. All tests for statistical significance were 2-tailed. p Values <0.05 were considered to be statistically significant. Independent predictors for ESBL-producers were identified by means of logistic regression analysis. The Kaplan-Meier method was used for survival analysis.

Results

From June 2003 to December 2006, 278 episodes of cefpodoxime-resistant *K. pneumoniae* (30.2%) or *E. coli* (66.6%) bacteremia were identified, among which both *K. pneumoniae* and *E. coli* were isolated

at the same time in 9 (3.2%) episodes. 115 (41.3%) episodes were caused by ESBL-producing organisms.

Demographic characteristics

The patients' characteristics are presented in Table 1. There were no significant differences in age or sex between patients infected by ESBL-producing and non-ESBL–producing isolates. Compared with non-ESBL producers, bacteremic episodes caused by ESBL-producers were less often community acquired (4.3% vs 26.4%; $p < 0.001$) or found in patients recently admitted to hospital (29.6% vs 54.6%; $p < 0.001$), and were more usually hospital acquired and in patients undergoing regular hemodialysis (21.7% vs 3.7%; $p < 0.001$).

There were more patients with diabetes mellitus (48.7% vs 35.0%; $p = 0.02$), liver cirrhosis (22.6% vs 11.7%; $p = 0.02$), and end-stage renal disease (21.7% vs 3.7%; $p < 0.001$) in the group with ESBL-producing bacteremia, but solid tumors were more frequent in the group with non-ESBL–producing bacteremia (44.8% vs 27.8%; $p = 0.004$). Of 278 episodes of bacteremia caused by cefpodoxime-resistant *E. coli* or *K. pneumoniae*, 82.7% were associated with recent access to health care facilities, such as residence in a nursing home, receipt of regular hemodialysis, or recent hospital admission.

For the predisposing conditions of bacteremia, 108 patients (38.8%) had urinary indwelling catheters and

Table 1. Clinical characteristics of 278 patients with bacteremia caused by cefpodoxime-resistant *Escherichia coli* or *Klebsiella pneumoniae* with and without the extended-spectrum β-lactamase (ESBL)–producing phenotype.

Characteristic	ESBL-producing isolates (n = 115) No. (%)	Non-ESBL–producing isolates (n = 163) No. (%)	All patients (n = 278) No. (%)	*p*
Age (years) [mean ± SD]	67.9 ± 16.0	65.5 ± 14.8	66.5 ± 15.3	0.20
Men	58 (50.0)	90 (55.2)	148 (53.2)	0.43
Escherichia coli isolates	64 (55.7)	121 (74.2)	185 (66.6)	0.002
Place of acquisition				
Community	5 (4.3)	43 (26.4)	48 (17.3)	<0.001
Health care facility	110 (95.7)	120 (73.6)	230 (82.7)	<0.001
Hospital (>48 h)	69 (60.0)	71 (43.6)	140 (50.4)	0.007
Nursing home	12 (10.4)	8 (4.9)	20 (7.2)	0.08
Regular hemodialysis	25 (21.7)	6 (3.7)	31 (11.2)	<0.001
Recent admission (<6 months)	34 (29.6)	89 (54.6)	123 (44.2)	<0.001
Comorbidity				
Diabetes mellitus	56 (48.7)	57 (35.0)	113 (40.6)	0.02
Liver cirrhosis	26 (22.6)	19 (11.7)	45 (16.2)	0.02
End-stage renal disease	25 (21.7)	6 (3.7)	31 (11.2)	<0.001
HIV/AIDS	2 (1.7)	2 (1.2)	4 (1.4)	0.72
Solid tumor	32 (27.8)	73 (44.8)	105 (37.8)	0.004
Hematological malignancy	4 (3.5)	9 (5.5)	13 (4.7)	0.43
Steroid therapy	13 (11.3)	16 (9.8)	29 (10.4)	0.69
Predisposing conditions				
Urinary Foley catheter	36 (31.3)	72 (44.2)	108 (38.8)	0.03
Central venous catheter	30 (26.1)	59 (36.2)	89 (32.0)	0.08
ICU admission	34 (29.6)	31 (19.0)	65 (23.4)	0.04
Previous surgery	13 (20.0)	22 (13.5)	45 (16.2)	0.15
Portal of entry				
Primary bacteremia	23 (20.0)	95 (58.3)	118 (42.4)	<0.001
Urinary tract infections	31 (27.0)	36 (22.1)	67 (24.1)	0.35
Pneumonia	36 (31.3)	3 (1.8)	39 (14.0)	<0.001
Intra-abdominal infections	12 (10.4)	17 (10.4)	29 (10.4)	1.00
Catheter-related infections	7 (6.1)	6 (3.7)	13 (4.7)	0.35
Skin and soft tissue infections	4 (3.5)	3 (1.8)	7 (2.5)	0.39
Other	2 (1.7)	3 (1.8)	5 (1.8)	0.95

Abbreviations: SD = standard deviation; HIV/AIDS = human immunodeficiency virus/acquired immunodeficiency syndrome; ICU = intensive care unit.

Table 2. Clinical manifestations of 278 patients with bacteremia caused by cefpodoxime-resistant *Escherichia coli* or *Klebsiella pneumoniae* with and without the extended-spectrum β-lactamase (ESBL)–producing phenotype.

Clinical manifestation	ESBL-producing isolates (n = 115) No. (%)	Non-ESBL–producing isolates (n = 163) No. (%)	All patients (n = 278) No. (%)	*p*
Polymicrobial bacteremia	30 (26.1)	40 (24.5)	70 (25.2)	0.77
Duration of hospital stay before bacteremia (days)				
Range	0-398	0-115	0-398	<0.001
Mean ± SD	27.6 ± 51.8	11.2 ± 19.3	18.0 ± 37.3	
Duration of hospital stay (days)				
Range	0-734	0-180	0-734	0.007
Mean ± SD	51.1 ± 82.0	31.9 ± 31.2	39.9 ± 58.5	
ICU admission after bacteremia onset	22 (19.1)	13 (8.0)	35 (12.6)	0.006
Pittsburgh bacteremia score ≥4	45 (39.1)	42 (25.8)	87 (31.3)	0.02
Crude mortality				
14 days	33 (28.7)	30 (18.4)	63 (22.7)	0.04
28 days	40 (34.8)	39 (23.9)	79 (28.4)	0.03
Overall	49 (42.6)	40 (24.5)	89 (32.0)	0.001

Abbreviations: SD = standard deviation; ICU = intensive care unit.

65 (23.4%) had been admitted to an ICU at the onset of bacteremia. Both conditions were noted more often in patients with ESBL-producing bacteremia than in those with non-ESBL–producing bacteremia. The most common primary infection site in patients with ESBL-producing bacteremia was the lung (31.3%), but most patients with non-ESBL–producing bacteremia (58.3%) had no identified infection site. As shown in Table 2, ESBL-producing bacteremia was usually acquired late in a hospital admission period (27.6 days vs 11.2 days; $p < 0.001$), and was associated with higher disease severity, as indicated by a Pittsburgh bacteremia score ≥4 (39.1% vs 25.8%; $p = 0.02$). The clinical course after the onset of bacteremia was different between the 2 groups. Patients with ESBL-producing bacteremia had more need for admission to an ICU after the onset of bacteremia (19.1% vs 8.0%; $p = 0.006$), and had a worse prognosis at 28 days than those with non-ESBL–producing bacteremia (Fig. 1).

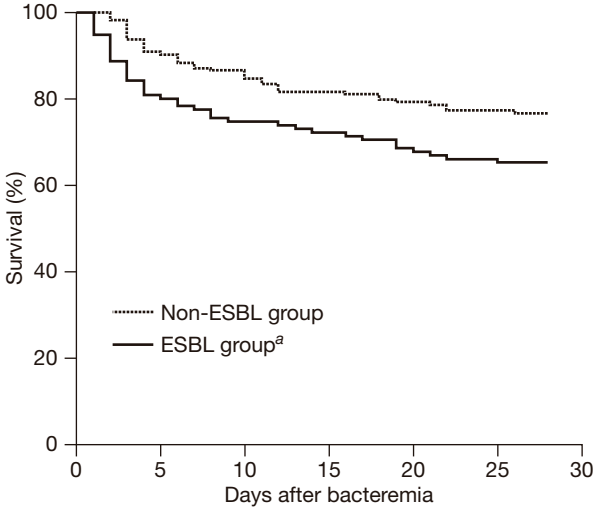

Fig. 1. Survival analysis of patients with bacteremia caused by cefpodoxime-resistant *Escherichia coli* or *Klebsiella pneumoniae* with or without extended-spectrum β-lactamase (ESBL) production.
[a]$p = 0.03$.

Prediction of extended-spectrum β-lactamase production

Using the clinically significant parameters shown in Table 1 and Table 2, multivariate analysis was performed to delineate the factors associated with ESBL production (Table 3). Longer hospital admission, higher disease severity (Pittsburgh bacteremia score ≥4), presence of underlying end-stage renal disease, recent access to health care facilities, and pneumonia were independently associated with an ESBL-producing phenotype among cefpodoxime-resistant bacteremic isolates.

Microbiological data

Different combinations of study drugs for in vitro antimicrobial susceptibility tests were assigned during different periods. Therefore, the total number of isolates tested for individual drugs were varied. As shown in Table 4, all isolates were resistant to cefpodoxime, as

Table 3. Predictors of extended-spectrum β-lactamase (ESBL)–producing isolates among bloodstream infections caused by cefpodoxime-resistant *Escherichia coli* or *Klebsiella pneumoniae* by multivariate analysis.

Factor	Odds ratio (95% confidence interval)	*p*
Time to acquisition (days)	1.02 (1.01-1.03)	0.001
Pittsburgh bacteremia score ≥4	2.55 (1.13-5.73)	0.024
End-stage renal disease	3.19 (1.03-9.83)	0.044
Health care–associated infections	11.54 (3.35-39.81)	<0.001
Pneumonia	17.92 (4.40-72.91)	<0.001

Table 4. Antimicrobial susceptibility of cefpodoxime-resistant *Escherichia coli* or *Klebsiella pneumoniae* with or without the extended-spectrum β-lactamase (ESBL)–producing phenotype.

Antimicrobial agent	Susceptible isolates/isolates tested		*p*
	ESBL-producing No. (%)	Non-ESBL–producing No. (%)	
Ampicillin	0/115 (0)	0/163 (0)	
Amoxicillin-clavulanic acid or ampicillin-sulbactam	16/115 (13.9)	0/163 (0)	<0.001
Piperacillin-tazobactam	78/114 (68.4)	91/133 (68.4)	0.54
Cefpodoxime	0/115 (0)[a]	0/163 (0)	
Ceftazidime	49/115 (42.6)[a]	23/132 (17.4)	<0.001
Cefpirome	42/92 (45.7)[a]	154/154 (100)	<0.001
Aztreonam	29/115 (25.2)[a]	34/130 (26.2)	0.46
Imipenem	115/115 (100)	134/135 (99.3)	0.54
Meropenem	115/115 (100)	135/135 (100)	
Gentamicin	24/115 (20.9)	88/163 (53.7)	<0.001
Amikacin	81/115 (70.4)	144/151 (95.4)	<0.001
Cotrimoxazole	25/114 (21.9)	33/135 (24.4)	0.39
Ciprofloxacin	23/115 (20.0)	42/137 (30.7)	0.04

[a]According to the Clinical and Laboratory Standards Institute, ESBL-producing isolates should be reported as being resistant to penicillins, cephalosporins, and aztreonam.

for the essential criterion for study inclusion. Almost all isolates were susceptible to imipenem and meropenem. All 163 isolates without the ESBL-producing phenotype were susceptible to cefpirome. Among non-β–lactam antibiotics, non-ESBL–producing isolates were more often susceptible to gentamicin, amikacin, and ciprofloxacin than ESBL-producing isolates. Similar proportions of ESBL-producing and non-ESBL–producing isolates were susceptible to cotrimoxazole (21.9% and 24.4%, respectively).

Discussion

Infections due to antibiotic-resistant organisms are associated with increased mortality, morbidity, duration of hospital admission, and cost of health care, compared with infections due to antibiotic-susceptible organisms [7,8]. Awareness of antimicrobial resistance is growing, and the impact of antimicrobial resistance on clinical and economic outcomes is important [9]. An investigation of clinical outcomes associated with infections caused by antibiotic-resistant organisms is valuable, as it could provide practical information for clinicians to improve infection control, to find better interventions for infection prevention, and to avoid the spread of antibiotic-resistant organisms [8].

In Europe and the United States, episodes of bacteremia caused by ESBL-producing *Enterobacteriaceae* are increasing [4]. Bacteremia caused by ESBL-producing organisms is frequently noted in nosocomial infections [4,10] and is considered to be associated with exposure to third-generation cephalosporins [11,12]. In this study, comparison with cefpodoxime-resistant non-ESBL–producing bacteremia, bacteremia caused by ESBL–producing isolates is often noted in patients with nosocomial bacteremia (60% vs 43.6%; $p = 0.007$) and those receiving regular hemodialysis (21.7% vs 3.7%; $p < 0.001$).

ESBLs have been found in all species of the *Enterobacteriaceae* family, and are most commonly

produced by *K. pneumoniae* isolates and, to a lesser extent, *E. coli* [13]. Typically, infections caused by ESBL-producing organisms are associated with increased mortality [14]. Bacteremia caused by ESBL-producing *Enterobacteriaceae*, including *E. coli* and *K. pneumoniae*, is recognized to be associated with an increased rate of treatment failure and death [1,15,16]. Delay in appropriate therapy has been demonstrated to be a risk factor for mortality in serious infections [17,18]. As limited appropriate antibiotics can be introduced, delayed institution of effective therapy for ESBL-producing often occurs, a scenario that supports a causal association between ESBL production and mortality [14].

This study targeted bacteremic episodes caused by either cefpodoxime-resistant *E. coli* or *K. pneumoniae*. Cefpodoxime is a third-generation cephalosporin, and *Enterobacteriaceae* resistance to cefpodoxime represents some degree of antibiotic resistance. Cefpodoxime susceptibility is usually obtained 1 day before the documentation of ESBL production by the double-disk synergy test. According to the multivariate analysis in this study, if patients have cefpodoxime-resistant *E. coli* or *K. pneumoniae* bacteremia, empirical carbapenem therapy may be preferred if patients have a longer duration of hospital stay, higher disease severity (Pittsburgh bacteremia score ≥4), underlying end-stage renal disease or pneumonia, or recent access to health care facilities. Such information could help clinicians to initiate appropriate broad-spectrum antimicrobial agents for high-risk individuals as early as possible.

Due to the limited number of effective antimicrobial agents, treatment of infections caused by ESBL-producing organisms has been based on in vitro susceptibility data and observational studies. Carbapenems, specifically imipenem and meropenem, are considered to be the treatment of choice [19]. The clinical strategy for treating ESBL-producing infections with β-lactam/β-lactamase inhibitor combinations (such as piperacillin/tazobactam) and non-β–lactam antibiotics (such as cotrimoxazole, aminoglycosides, and fluoroquinolones) remains controversial [20-22]. According to the in vitro data from this study, non-β–lactam susceptibility rates in ESBL-producing isolates are relatively low: amikacin (70.4%), gentamicin (20.9%), cotrimoxazole (21.9%), and ciprofloxacin (20.0%). Therefore, carbapenem is the drug of choice for ESBL-producing *E. coli* or *K. pneumoniae* bacteremia. In contrast, cefpodoxime-resistant non-ESBL–producing isolates were often susceptible to amikacin (95.4%), imipenem (99.3%), meropenem (100%), and cefpirome (100%). Therefore, the therapeutic options for bacteremia caused by these isolates might include amikacin or cefpirome (a fourth-generation cephalosporin), in addition to carbapenems.

In summary, bacteremia caused by cefpodoxime-resistant ESBL-producing *E. coli* or *K. pneumoniae* is associated with increased disease severity and adverse clinical outcome compared with that caused by cefpodoxime-resistant non-ESBL–producing isolates.

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