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**Original Article**

# Bacteremia due to extended-spectrum beta-lactamase-producing *Enterobacteriaceae* other than *Escherichia coli* and *Klebsiella*

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**Background and Purpose:** Carbapenems are considered the drugs of choice for the treatment of serious infections caused by extended-spectrum beta-lactamase (ESBL)-producing *Klebsiella* and *Escherichia coli*. However, controversy exists about the antibiotic choice for infections due to ESBL-producing organisms of other genera.
**Methods:** This retrospective study evaluated the risk factors and outcomes of 54 adult patients with bacteremia due to ESBL-producing *Enterobacteriaceae* other than *Klebsiella* spp. or *E. coli* treated at a tertiary care hospital in northern Taiwan from January 2001-December 2003. Patients were categorized into carbapenem (n = 22) and non-carbapenem (n = 32) treatment groups. All patients had at least one positive blood culture together with fever or other clinical features compatible with systemic infection.
**Results:** Higher Acute Physiology and Chronic Health Evaluation II score, glucocorticoid use, and presentation of septic shock were significant risk factors for mortality ($p<0.05$). Patients treated with a carbapenem had a better 14-day or overall survival rate (i.e., survived to discharge) than those treated with non-carbapenem antibiotics, although this difference was not significant. Among patients in the non-carbapenem group, the overall survival rates of ciprofloxacin, aminoglycoside, and ceftazidime were 70% (14/20), 62.5% (5/8), and 50% (2/4), respectively ($p=0.877$). The overall survival rates of the carbapenem (72.7%) and ciprofloxacin (70.0%) groups were similar.
**Conclusions:** The results suggest that ciprofloxacin, when indicated based on antimicrobial susceptibility testing, may serve as an alternative choice for infections caused by ESBL-producing *Enterobacteriaceae* other than *E. coli* or *Klebsiella* spp. and may not affect the clinical outcome at discharge.

**Key words:** Bacteremia, beta-lactamase, carbapenems

## Introduction

Extended-spectrum beta (β)-lactamases (ESBLs) have been found in all species of the family *Enterobacteriaceae*, and are most commonly produced by isolates of *Klebsiella pneumoniae* and, to a lesser extent, *Escherichia coli* [1,2]. Screening and confirmation tests issued by the National Committee for Clinical Laboratory Standards (NCCLS) currently apply to *E. coli*, *K. pneumoniae*, and *Klebsiella oxytoca* [3-5]. These are based on the minimal inhibitory concentration or disk diffusion results for 5 antimicrobial agents and testing with ceftazidime and cefotaxime in the presence and absence of clavulanic acid. According to NCCLS recommendation, laboratories should report ESBL-producing isolates of *E. coli* or *Klebsiella* spp. as resistant to all penicillins, cephalosporins (including cefepime and cefpirome), and aztreonam irrespective of the susceptibility results. This recommendation does not extend to ESBL-producing organisms of other genera.

Carbepenems are the suggested antibiotic for serious infections due to ESBL-producing *E. coli* and *Klebsiella* spp. (ESBL-EK) [6,7]; however, there is little information on the relative effectiveness of therapeutic options for serious infections due to ESBL-producing organisms of other genera [8]. This retrospective study

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evaluated the risk factors associated with mortality and treatment outcomes of patients with bacteremia caused by ESBL-producing *Enterobacteriaceae* other than *E. coli* or *Klebsiella* spp.

## Methods

### Patients

The patients included in this study were older than 18 years of age with at least one positive blood culture together with fever or other clinical features compatible with systemic infection. They had bacteremia due to ESBL-producing *Enterobacteriaceae* other than *E. coli* and *Klebsiella* spp. treated during a 3-year period from January 2001 to December 2003 and were identified based on the computerized microbiology database of Chang Gung Memorial Hospital-Linkou, a 3000-bed medical center in northern Taiwan. Only the first bacteremic episode of each patient was included. Data collected from medical charts included the following demographic characteristics: comorbid illnesses, clinical features, primary site of infection, laboratory test results, radiographic findings, Acute Physiology and Chronic Health Evaluation (APACHE) II score, presentation of septic shock, duration of intensive care unit stay, duration of hospital stay before the onset of bacteremia, use of intravenous devices (e.g., a central venous catheter), prior invasive procedures, surgery or steroid use before the onset of bacteremia, regimen and duration of antimicrobial therapy before and after the onset of bacteremia, and treatment response.

An infection was considered nosocomial if it occurred after 48 h of admission or within 14 days after hospital or health care facility discharge. Neutropenia was defined as an absolute neutrophil count of below 500/mm$^3$. Nosocomial bloodstream infections were defined according to the criteria proposed by the Centers for Disease Control and Prevention [9].

The 14-day survival rate was calculated as the total number of survivors on day 14 of the hospital day/total number of patients. The overall survival rate was calculated as the total number of patients who survived until discharge from the hospital without fever, leukocytosis, and any evidence of systemic or focal infection regardless of the duration of hospital stay/total number of patients. Patients who died within 3 days after blood was drawn for cultures or before the antimicrobial susceptibility results became available were excluded from the study.

### Microbiologic methods

Antibiotic susceptibility testing of each isolate was performed by the disk diffusion method using the NCCLS criteria [3] to determine the diameters of the inhibition zones around cefotaxime and ceftazidime disks (30 μg each), alone and in combination with clavulanic acid (10 μg). An increase in zone diameter by ≥5 mm when either of the antimicrobial agents was combined with clavulanic acid was considered evidence of ESBL production. However, as the NCCLS criteria did not apply to ESBL-producing *Enterobacteriaceae* other than *Klebsiella* spp. or *E. coli* at the time of this study, our laboratory did not report isolates as resistant to ceftazidime and ceftriaxone if they were initially susceptible to either of these agents.

Monomicrobial bacteremia was defined as the isolation of only 1 organism from the blood culture, and polymicrobial bacteremia as the isolation of at least 2 species of organisms from the same blood culture.

### Antibiotics

Monotherapy was defined as the use of only 1 antibiotic active in vitro against the isolate and combination therapy as the use of 2 or more antibiotics. Empirical antimicrobial therapy was defined as the regimen given before the results of blood culture were available. Definitive antimicrobial therapy was the regimen continued or commenced on the day that the susceptibility results were reported. Empirical antimicrobial therapy was defined as inappropriate when given after a pathogen was identified as resistant by in vitro susceptibility testing. All patients included in this study received antimicrobial therapy for at least 7 days. The carbapenem treatment group included patients who received imipenem-cilastatin or meropenem as definitive therapy for at least 7 days. The non-carbapenem group included patients who received definitive therapy for 7 days or more with antibiotics other than carbapenems that were active against the isolate, such as aminoglycosides, cephalosporins, or ciprofloxacin.

### Statistical analysis

Univariate analysis was performed using two-tailed chi-square test or Fisher's exact test. Continuous variables were compared using Student's *t* test. The Kaplan-Meier method was used for survival analysis. All *p* values were two-tailed; a *p* value of $<0.05$ was considered statistically significant. Variables with a *p* value of $<0.05$ in the univariate analysis were included in the multivariate

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analysis. Statistical Package for the Social Sciences (SSPS) for Windows (Version 10.07; SPSS, Chicago, IL, USA) software was used for statistical analyses.

## Results

The prevalence of ESBL production among isolates of ESBL-producing *Enterobacteriaceae* spp. from patients with bacteremia treated at this hospital from 2001-2003 was as follows: 7.4% (117/1586) of *Citrobacter* isolates; 7.7% (1890/24,670) of *E. coli* isolates; 21.7% (824/3797) of *Enterobacter* isolates; 14.5% (90/621) of *K. oxytoca* isolates; 17.6% (1696/9639) of *K. pneumoniae* isolates; 2.2% (44/2068) of *Morganella morganii* isolates; and 3.3% (138/4223) of *Proteus mirabilis* isolates.

Among the 59 patients with bacteremia due to ESBL-producing *Enterobacteriaceae* other than *E. coli* or *Klebsiella* during the study period, 5 were excluded because of missing or incomplete medical records. The remaining 54 patients were included in the study. These patients were divided into the carbapenem and non-carbapenem groups depending on the antimicrobial treatment they received. There was no significant difference between these 2 groups in the clinical and demographic characteristics, including age, patient numbers, recent steroid use or surgery, placement of central venous catheter, neutropenia, presentation of septic shock, APACHE II score, and polymicrobial bacteremia (Table 1). The most common focus of infection was at a surgical site (14/54, 25.9%).

Table 2 lists the strains of ESBL-producing bacteria found in the 54 patients. *Enterobacter cloacae* was the predominant species that was isolated in 39 patients (72.2%) , followed by *Enterobacter aerogenes* in 6 (11.2%), *P. mirabilis* in 5 (9.3%), *Citrobacter diversus* in 2 (3.8%), *Serratia marcescens* in 1 (1.9%), and *Citrobacter freundii* bacteremia in 1 (1.9%). Among these 54 patients, 6 had polymicrobial bacteremia. The in vitro susceptibility of blood isolates of ESBL-producing *Enterobacteriaceae* other than *E. coli* and *Klebsiella* spp. to various antibiotics is listed in Table 3. All these isolates were sensitive to imipenem/cilastatin; however, only 75% of isolates (6/8) were sensitive to cefepime and 64.8% of isolates (35/54) were sensitive to ciprofloxacin.

In the non-carbapenem treatment group, 90.63% of patients (29/32) received monotherapy, including ciprofloxacin in 17 patients, an aminoglycoside in 8 patients, and ceftazidime in 4 patients. Combination therapy was given in 9.37% of patients (3/32) in the non-carbapenem treatment group, including 2 patients who were treated with ciprofloxacin and ceftazidime, and 1 patient with ciprofloxacin and aminoglycoside.

**Table 1.** Basic and clinical characteristics of 54 patients with bacteremia due to extended-spectrum beta-lactamase-producing *Enterobacteriaceae* other than *Escherichia coli* and *Klebsiella*

| | Non-carbapenem | Carbapenem | *p* |
|---|---|---|---|
| Age (mean ± SD) [range] | 61.47 ± 18.66 (19-87) | 58.46 ± 20.40 (22-83) | 0.398 |
| No. of patients (male:female) | 32 (21:11) | 22 (13:9) | 0.784 |
| No. of patients in ICU | 7 | 11 | 0.031 |
| Recent steroid use (%) | 3 (9.4) | 3 (13.6) | 0.624 |
| Recent surgery (%) | 17 (53.1) | 12 (54.5) | 0.918 |
| Neutropenia (%) | 2 (6.3) | 0 (0) | 0.232 |
| Nosocomial infection (%) | 23 (71.9) | 16 (72.7) | 0.945 |
| Septic shock (%) | 7 (21.9) | 2 (9.1) | 0.215 |
| Foley indwelling (%) | 22 (68.8) | 15 (68.2) | 0.965 |
| Placement of central venous catheter (%) | 19 (59.4) | 17 (77.3) | 0.170 |
| Invasive procedure within 14 days prior to admission (%) | 18 (56.3) | 18 (81.8) | 0.05 |
| Prior use of any antibiotics within 30 days (%) | 25 (78.1) | 16 (72.7) | 0.648 |
| Hospital stay (%) | 10 (31.25) | 11 (50.0) | 0.202 |
| White blood cell (/μL) [mean ± SD] | 12,619 ± 8112 | 10,822 ± 7591 | 0.384 |
| Platelet (× 1000/μL) [mean ± SD)] | 224.59 ± 185.88 | 244.05 ± 378.05 | 0.396 |
| APACHE II score (mean ± SD) | 11.88 ± 5.68 | 14.14 ± 5.83 | 0.235 |
| Hospital stay before bacteremia (range) | 13.53 ± 15.39 (0-73) | 26.64 ± 29.20 (0-95) | 0.202 |
| Duration[a] (days) [mean ± SD] | 12.31 ± 5.31 | 21.10 ± 17.34 | 0.598 |
| Polymicrobial bacteremia (%) | 3 (9.4) | 3 (13.6) | 0.624 |

Abbreviations: SD = standard deviation; ICU = intensive care unit; APACHE II = Acute Physiology and Chronic Health Evaluation II
[a]Duration of definitive antimicrobial therapy.


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**Table 2.** Comparison of pathogens of carbapenem and non-carbapenem treatment groups

| Strains of ESBL-producing bacteria | Carbapenem No. (%) | Non-carbapenem No. (%) | Total No. (%) |
|---|---|---|---|
| *Enterobacter cloacae* | 15 (68.2) | 24 (75) | 39 (72.2) |
| *Enterobacter aerogenes* | 2 (9.1) | 4 (12.5) | 6 (11.2) |
| *Proteus mirabilis* | 4 (18.1) | 1 (3.1) | 5 (9.3) |
| *Citrobacter diversus* | - | 2 (6.3) | 2 (3.8) |
| *Serratia marcescens* | 1 (4.5) | - | 1 (1.9) |
| *Citrobacter freundii* | - | 1 (3.1) | 1 (1.9) |

Abbreviation: ESBL = extended-spectrum beta-lactamase

Identified foci of infection in the non-carbapenem group included surgical wound infection (8 cases, 25%), urosepsis (7 cases, 21.9%), catheter-related infection (6 cases, 18.8%), intra-abdominal infection (IAI) [7 cases, 21.9%], and pneumonia (3 cases, 9.4%). In the carbapenem group, all 22 patients received monotherapy (19 with imipenem/cilastatin, 3 with meropenem), and the identified foci of infection were surgical wound infection (6 cases, 27.3%), urosepsis (3 cases, 13.6%), catheter-related infection (4 cases, 18.2%), IAI (4 cases, 18.2%), and pneumonia (4 cases, 18.2%).

The 14-day survival rate of the carbapenem group (90.9%, 20/22) was superior to that of the non-carbapenem group (71.9%, 23/32), but this difference was not significant ($p$=0.088). The overall survival rate at discharge of the carbapenem group (72.7%, 16/22) was superior to that of the non-carbapenem group (65.6%, 21/32), but this difference was also not significant ($p$=0.581) [Fig. 1]. Among patients in the non-carbapenem group, the 14-day survival rates of those who received ciprofloxacin, aminoglycoside, and ceftazidime were 75% (15/20), 75% (6/8), and 50% (2/4), respectively ($p$=0.415). The overall survival rates of patients treated with ciprofloxacin, aminoglycoside, and ceftazidime were 70% (14/20), 62.5% (5/8), and 50% (2/4), respectively ($p$=0.877). Among the foci of infection, urinary tract infection had the best outcome, with overall survival rate of 85.7% (6/7) in the non-carbapenem group and 100% (3/3) in the carbapenem group. Among the 6 patients with polymicrobial bacteremia, 3 received ciprofloxacin as definitive antimicrobial therapy and all of them survived. Among the 3 patients who received imipenem/cilastatin as definitive antimicrobial therapy, 1 survived and 2 patients with polymicrobial infections died at 9 and 40 days after admission, respectively (Table 4).

The independent risk factors associated with overall mortality were glucocorticoid use, APACHE II score of ≥16, and presentation of septic shock (Table 5). Postoperative status, nosocomial infection, intensive care unit stay, indwelling Foley catheter, prior invasive procedure, prior use of broad-spectrum cephalosporin, and hospital stay over 14 days were not significantly associated with overall mortality. Inappropriate empirical antimicrobial therapy was not associated with a higher mortality rate (15/48, 31.3%) as compared

**Table 3.** In vitro susceptibilities of 54 blood isolates of extended-spectrum beta-lactamase-producing *Enterobacteriaceae* other than *Escherichia coli* and *Klebsiella*

| Drugs | Susceptible No. (%) | Intermittent No. (%) | Resistant No. (%) |
|---|---|---|---|
| Amikacin | 17 (31.5) | 14 (25.9) | 23 (42.6) |
| Gentamicin | 4 (7.4) | - | 50 (92.6) |
| Ceftazidime | 9 (16.7) | 2 (3.7) | 43 (79.6) |
| Ciprofloxacin | 35 (64.8) | 12 (22.2) | 7 (13.0) |
| Cefepime[a] | 6 (75.0) | - | 2 (25.0) |
| Flomoxef | 23 (57.5) | 1 (2.5) | 16 (40.0) |
| Imipenem | 54 (100) | 0 (0) | 0 (0) |

[a]Only 8 isolates were tested with cefepime in the present study.

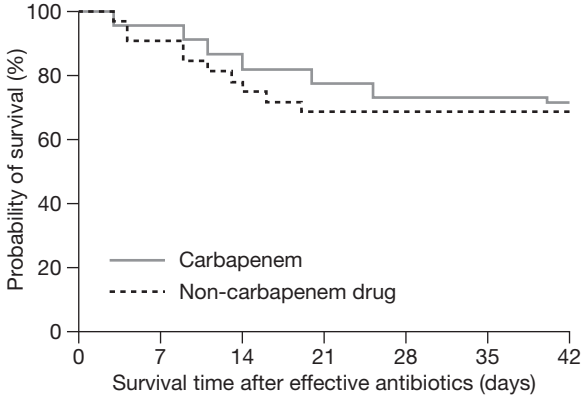


**Fig. 1.** Survival curve obtained by Kaplan-Meier method for bacteremia caused by extended-spectrum beta-lactamase-producing *Enterobacteriaceae* other than *Escherichia coli* and *Klebsiella* spp. according to definitive antimicrobial therapy regimens.

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**Table 4.** Treatment outcome of 6 patients with polymicrobial bacteremia

| Age/ gender | Primary site of infection | Organisms | Definitive regimen | Duration (days) | Clinical outcome[a] |
|---|---|---|---|---|---|
| 28/F | Urosepsis | *Enterococcus faecalis*<br>*Enterobacter cloacae*[b] | CIP | 14 | Cure |
| 76/M | Urosepsis | *Pseudomonas aeruginosa*<br>*Enterobacter cloacae*[b] | CIP | 12 | Cure |
| 62/F | Diabetic foot wth secondary infection | *Enterobacter cloacase*[b]<br>*Acinetobacter junii* | CIP | 12 | Cure |
| 24/F | Intra-abdominal infection | *Enterobacter cloacae*[b]<br>*Acinetobacter haemolyticus* | IPM | 10 | Cure |
| 78/M | Intra-abdominal infection | *Klebsiella pneumoniae*[b]<br>*Enterobacter cloacae*[b]<br>*Pseudomonas aeruginosa* | IPM | 9 | Failure |
| 80/F | Pressure sore with secondary infection | *Escherichia coli*<br>*Proteus mirabilis*[b]<br>*Enterococcus faecalis* | IPM | 40 | Failure |

Abbreviations: F = female; M = male; CIP = ciprofloxacin; IPM = imipenem-cilastatin

[a]Clinical outcome at discharge.

[b]Extended-spectrum beta-lactamase-producing strain.

to appropriate empirical antimicrobial therapy (2/6, 33.3%, $p$=0.92) if effective definitive therapy was initiated immediately after the susceptibility testing results became available.

The overall survival rates at discharge of the carbapenem and non-carbapenem groups in patients with monomicrobial bacteremia were 78.9% (15/19) and 62.0% (18/29), respectively ($p$=0.781). The 14-day survival rates of the carbapenem and non-carbapenem groups were 94.7% (18/19) and 68.9% (20/29), respectively ($p$=0.068).

## Discussion

ESBLs were first described in 1983 [10]. These agents can hydrolyze oximino-cephalosporin antibiotics such as cefotaxime, ceftriaxone, ceftazidime, cefpodoxime, and aztreonem. The NCCLS has issued recommendations for ESBL screening and confirmation for the isolates of *E. coli* and *Klebsiella* spp. Patients with infections caused by an ESBL-producing organism are at greater risk of treatment failure with an extended-spectrum β-lactam antibiotic.

ESBLs have also been found in other members of *Enterobacteriaceae*, which have become more and more common and can cause severe infections [11]. Carbapenem is the prudent antibiotic choice for serious

**Table 5.** Independent risk factors for mortality of patients with bacteremia due to extended-spectrum beta-lactamase-producing *Enterobacteriaceae* other than *Escherichia coli* and *Klebsiella*

| Risk factor | Mortality rate at discharge (%) | OR (95% CI) | *p* |
|---|---|---|---|
| Diabetes mellitus | | | |
| Yes | 1/14 (7.1) | 0.06 (0.01-0.71) | 0.027 |
| No | 16/40 (40) | | |
| Steroid use | | | |
| Yes | 5/6 (83.5) | 38.16 (2.25-647.09) | 0.012 |
| No | 12/48 (25) | | |
| APACHE II score of ≥16 | | | |
| Yes | 9/18 (50.0) | 3.74 (0.74-18.88) | 0.038 |
| No | 8/36 (22.2) | | |
| Presentation of septic shock | | | |
| Yes | 5/9 (55.6) | 10.25 (1.51-69.38) | 0.017 |
| No | 12/45 (26.7) | | |

Abbreviations: OR = odds ratio; CI = confidence interval; APACHE II = Acute Physiology and Chronic Health Evaluation II

[a]Multivariate analysis with a logistic regression model was used.


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infections due to ESBL-producing *E. coli* and *Klebsiella* spp., but there is little information about the antibiotic treatment indicated for serious infections due to ESBL-producing organisms of other genera. The NCCLS does not recommend ESBL screening for ESBL-producing *Enterobacteriaceae* other than *E. coli* and *Klebsiella* spp. because some of these strains (*Enterobacter*, *Citrobacter*, and *Serratia*) may produce a chromosomally encoded inducible AmpC β-lactamase that hydrolyzes most β-lactam antibiotics except cefepime [12]. A reliable method of screening for ESBL production in inducible AmpC-producing organisms based on susceptibility to cephalosporins is yet to be developed. Aztreonam is inappropriate for use as an indicator drug for ESBL detection in these organisms because it could be hydrolyzed by ESBLs [11]. Clavulanate may also act as an inducer of high level AmpC production that causes resistance to the screening drugs and may thereby produce a false negative result in the ESBL screening test.

We set the 14-day survival rate as the primary outcome according to general principles in clinical practice for the treatment duration of antibiotics for bacteremia [13]. Although there was no significant difference in the 14-day survival and overall survival rates between the carbapenem and non-carbapenem groups, the carbapenem group had a better survival rate (14 days, 90.9%; overall, 72.7%). Three patients in the non-carbapenem group died of underlying diseases (breast cancer with brain, lung, and liver metastasis; duodenal ulcer with massive bleeding; hepatocellular carcinoma with tumor thrombus). As far as impacting the overall survival rate (70%), ciprofloxacin, when the isolate was susceptible in vitro, seemed as effective as carbapenem for the treatment of bacteremia due to ESBL-producing *Enterobacteriaceae* other than *E. coli* and *Klebsiella* spp.

As the NCCLS criteria did not apply to ESBL-producing *Enterobacteriaceae* other than *Klebsiella* spp. or *E. coli* at the time of this study, our laboratory did not report isolates as resistant to ceftazidime and ceftriaxone if they were initially susceptible to either of these agents. The overall survival rate of the 4 patients who received ceftazidime as definitive antimicrobial therapy was only 50%, which was much lower than the rate for those who received ciprofloxacin as definitive treatment (70%). Ceftazidime thus did not appear to be an appropriate antimicrobial choice for infections caused by the non-EK ESBL-producing strains, even those which were susceptible in vitro.

The overall survival rate of the 8 patients receiving aminoglycoside treatment (62.5%, 5/8) was lower than that of the ciprofloxacin treatment group (70%, 14/20). This suggests that aminoglycoside may not be an appropriate antimicrobial choice for infections caused by non-EK ESBL-producing strains.

In the non-carbapenem group, the overall survival rates of patients who had urosepsis (87.7%, 6/7) and IAIs [71.4%, 5/7] were higher than for those with infections at other sites. Ciprofloxacin was prescribed for the treatment of urosepsis and IAI in most cases (11/14). Ciprofloxacin treatment leads to a higher concentration in the urinary tract and peritoneum, and the agent has a higher volume of distribution and limited biotransformation according to its pharmokinetics [14]. Ciprofloxacin may be used instead of carbapenem for the treatment of *Enterobacter* bacteremia or severe infections. These findings may explain why patients treated with ciprofloxacin had a higher survival rate than those treated with ciprofloxacin.

The independent risk factors for mortality were APACHE II score of ≥16, glucocorticoid use, and septic shock (Table 5). A higher APACHE II score and development of septic shock reflect greater disease severity. Administration of glucocorticoids can decrease the levels of proinflammatory cytokines and synthesis of cyclooxygenase-2, which is responsible for the production of prostaglandins at the area of tissue injury and affects phagocytosis [15]. The finding that diabetes mellitus was a negative predictive factor for mortality in this study may be attributable to the acquisition of non-EK ESBL-producing strains from obstructive uropathy with urosepsis or simple wound infection which was comparatively easily cured after management of the underlying source of infection such as patent urination, catheter removal, adequate debridement, or limb amputation.

The most frequently used non-carbapenem antibiotic in this study was ciprofloxacin (20/32). Sensitivity testing included cefepime in only 8 isolates in this study, and 75% of them were susceptible to cefepime. Cefepime has been successfully used in the treatment of infection by *Enterobacter* spp. with reduced susceptibility or resistance to ceftazidime [16]; however, none of the clinicians in this study chose cefepime as a single treatment regimen or in combination therapy.

This study found no significant difference in treatment outcome between patients who received carbapenem and ciprofloxacin, suggesting that ciprofloxacin is an alternative choice for infections

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caused by non-EK ESBL-producing strains. Awareness of this alternative may reduce the use of carbapenems, and facilitate a decline in the emergence of pan-drug resistant *Acinetobacter* spp. [17] and the cost for hospitalization [18].

In conclusion, patients with non-EK ESBL-producing bacteremia treated with a carbapenem had better 14-day or overall survival rate than those treated with non-carbapenem antibiotics, although this difference was not significant. Further studies involving a larger number of cases over a longer period of follow-up using a prospective, observational, or randomized design are needed to establish a clearer basis for the treatment of these infections.

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