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ORIGINAL ARTICLE

Risk factors and outcomes of carbapenem-nonsusceptible *Escherichia coli* bacteremia: A matched case–control study

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Background: Infections due to carbapenem-resistant Enterobacteriaceae have been the emerging problem worldwide. This primary object of this study was to understand the risk factors and clinical outcomes of carbapenem-nonsusceptible *Escherichia coli* (CNSEc) bacteremia.
Methods: We conducted a matched case–control study in a 3,715-bed tertiary care medical center in northern Taiwan. The controls were selected among patients with carbapenem-susceptible *E coli* and were matched with CNSEc for bacteremia.
Results: Fifty-one patients were included in this study (17 cases and 34 controls). Bivariate analysis showed that prior exposure to carbapenems ($p < 0.001$), stay in intensive care units ($p = 0.016$), placement of central venous catheters ($p = 0.001$), chronic liver diseases ($p < 0.001$), uremia with regular dialysis ($p = 0.004$), and mechanical ventilation ($p = 0.004$) were associated with CNSEc bacteremia. Multivariate analysis revealed that prior exposure to carbapenems [odds ratio (OR), 29.17; 95% confidence interval (CI), 1.76–484.70; $p = 0.019$], uremia with regular dialysis (OR, 98.58; 95% CI, 4.02–999; $p = 0.005$) and chronic liver diseases (OR, 27.86; 95% CI, 2.31–335.83; $p = 0.009$) were independent risk factors for CNSEc bacteremia. Compared with carbapenem-susceptible *E coli* group, CNSEc group had a longer hospital stay (68.4 days *vs.* 35.8 days; $p = 0.04$) and a higher disease severity, as

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indicated by a Pittsburgh bacteremia score greater than or equal to 4 (5.6% *vs.* 2.5%; $p = 0.015$). Patients with CNSEc bacteremia had a higher overall in-hospital mortality rate (94.12% *vs.* 50.00%; $p = 0.002$), but there was no difference in the 28-day mortality between these two groups.

Conclusions: CNSEc bacteremia would lead to a poor outcome among patients with prior exposure to carbapenems, chronic liver disease, and uremia with regular dialysis.

Introduction

Carbapenem antibiotics have been the cornerstone of treatment for serious infections because of multidrug-resistant gram-negative pathogens. Carbapenem resistance used to be uncommon in the past few years but has now been increasing among the *Enterobacteriaceae* worldwide,[1–4] particularly *Klebsiella pneumoniae*.[5] Infections caused by carbapenem-resistant *K pneumoniae* have been reported, and clinical outcomes and risk factors of carbapenem-resistant *K pneumoniae* infections have been well studied.[6–8]

The emergence and spread of carbapenem-nonsusceptible (intermediately resistant or resistant) *Escherichia coli* (CNSEc) is also becoming a clinical challenge for physicians.[4,9] The mechanism of producing carbapenem resistance in *E coli* is mostly attributable to an outer-membrane porin deficiency combined with CMY-2-/CMY-4-related AmpC enzymes, CTX-M-type/SHV-12 extended-spectrum-β-lactamases (ESBL) or IMP-8-type metallo-β-lactamase.[1,10–13] Recently, OXA-48-like carbapenemases and outer-membrane protein loss were also reported.[14]

To date, risk factors for CNSEc acquisition have not been well described. There were only limited observation and clinical experience in the treatment of infections caused by CNSEc, especially bacteremia. Bloodstream infections caused by organisms with highly antibiotic resistance are associated with increased rates of treatment failure and mortality.[15] Hence, we conducted a matched case—control study to identify the potential risk factors for the development of CNSEc bacteremia and to investigate the outcomes of patients with CNSEc bacteremia.

Materials and methods

Study design and patients

This study was conducted at the Chang Gung Memorial Hospital-Taoyuan, a 3,715-bed tertiary care medical center. In this retrospective study, the blood culture records at the microbiology laboratory databases were reviewed to identify all the bacteremia caused by CNSEc between January 2006 and December 2008. All identified patients were enrolled, and their medical charts were reviewed. The clinical information was collected, such as demographics, dates of hospital admission and discharge, and dates of blood cultures. For patients with more than one episode of infection because of *E coli*, only data relevant to the first episode were collected and analyzed. The exposure to various risk factors was taken into consideration in the analysis only if it had occurred before the development of the infection. Variables analyzed as risk factors are summarized in Table 1, including comorbid illness, recent hospitalization ($\leq$14 days) and surgery, intensive care unit (ICU) stay, mechanical ventilation, tracheotomy, placement of central venous catheters (CVCs), Foley catheter insertion, implantation of prosthesis, cardiovascular and endovascular catheterization, endoscopic procedures, the Pittsburgh bacteremia score for disease severity,[16] and previous exposure to various antibiotic agents. Exposure to a specific antimicrobial agent was considered significant in our analysis only if (1) that exposure had occurred only during the hospitalization in which infection developed and (2) the antibiotic had been administered for at least 3 consecutive days before the development of the infection.

Selection of controls

For each patient with CNSEc bacteremia, we selected two matched control patients from the pool of patients with carbapenem-susceptible *E coli* (CSEc) bacteremia. We used a stepwise matching technique to identify the appropriate control patient matched to a case for gender, age $\pm$ 5 years, year of hospital admission, and length of hospital stay up to the isolation of *E coli* $\pm$ 6 days.

Microbiological analysis

Blood cultures were processed in the clinical microbiology laboratory, using the automated blood culture system (BACTEC 9240 system; Becton Dickinson Diagnostic Instrument Systems, Sparks, MD, USA). The isolated organisms that grew on culture were identified according to routine bacteriological procedures. Antibiotic susceptibility testing was determined by the disk diffusion method in accordance with the criteria of the Clinical and Laboratory Standards Institute (CLSI).[17] The antibiotic disks (BD Microbiology Systems, Cockeysville, MD, USA) for Enterobacteriaceae included amoxicillin—clavulanic acid, piperacillin, piperacillin—tazobactam, cefazolin, cefuroxime, ceftriaxone, ceftazidime, aztreonam, gentamicin, amikacin, ciprofloxacin and ertapenem. Quality control was performed testing *E coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *K pneumoniae* ATCC 700603, and *E coli* ATCC 35218. Interpretations of disk diffusion results were made using CLSI document M100-S19.[18] Carbapenem nonsusceptibility was initially screened with ertapenem disk diffusion testing on the basis of the CLSI document M100-S19 and was

Table 1 Clinical characteristics of 51 patients with bacteremia caused by *Escherichia coli* with and without the carbapenem-nonsusceptible phenotype

Characteristics	Carbapenem-nonsusceptible group ($n = 17$)	Carbapenem-susceptible group ($n = 34$)	p
Demographic			
Sex, male	10 (58.82)	20 (58.82)	1.000
Age	67.2 ± 14.7 (40—94)	67.4 ± 15.6 (36—94)	0.974
Length of hospital stay (d)	68.4 ± 56.4 (7—161)	35.8 ± 34.5 (4—141)	0.040*
Duration before bacteremia (d)	36.7 ± 39.6 (1—131)	21.9 ± 28.5 (0—125)	0.133
Comorbidities			
Heart diseases[a]	3 (17.65)	2 (5.88)	0.318
Malignancies (solid tumor)	6 (35.29)	12 (35.29)	1.000
COPD	2 (11.76)	3 (8.82)	1.000
Uremia with regular dialysis	6 (35.29)	1 (2.94)	0.004*
Diabetes mellitus	7 (41.18)	10 (29.41)	0.401
Chronic liver diseases[b]	13 (76.47)	6 (17.65)	<0.001*
Hematological diseases	2 (11.76)	2 (5.88)	0.530
Immunosuppressant use[c]	3 (17.65)	8 (23.53)	0.731
Previous transplantations	3 (17.65)	0	0.033*
Readmission within 14 d[d]	7 (41.18)	6 (17.65)	0.093
Intensive care unit stay	11 (64.71)	10 (29.41)	0.016*
Mechanical ventilation support	11 (64.71)	8 (23.53)	0.004*
Pittsburgh bacteremia score	5.6 ± 4.4 (1—14)	2.5 ± 2.6 (0—11)	0.015*
Invasive procedure or devices			
Central venous catheters	12 (70.59)	8 (23.53)	0.001*
Foley catheter insertion	6 (35.29)	5 (14.71)	0.147
Surgery	6 (35.29)	9 (26.47)	0.515
Prosthesis placement	6 (35.29)	6 (17.65)	0.181
Colostomy/gastrotomy	0	3 (8.82)	0.542
Tracheostomy	3 (17.65)	2 (5.88)	0.318
Prior antibiotic exposure			
Penicillin/ampicillin/amoxicillin	1 (5.88)	2 (5.88)	1.000
β-Lactam/β-lactam-lactamase inhibitor	1 (5.88)	2 (5.88)	1.000
Anti-pseudomonal penicillins	1 (5.88)	1 (2.94)	1.000
1st- and 2nd-generation cephalosporins	0	2 (5.88)	0.547
3rd-Generation cephalosporins	8 (47.06)	9 (26.47)	0.142
4th-Generation cephalosporins	4 (23.53)	3 (8.82)	0.203
Aminoglycosides	2 (11.76)	7 (20.59)	0.699
Fluoroquinolones	7 (41.18)	6 (17.65)	0.093
Metronidazole	3 (17.65)	1 (2.94)	0.102
Clindamycin	0	1 (2.94)	1.000
Carbapenems	9 (52.94)	1 (2.94)	<0.001*
Outcome			
Mortality, ≤14 d	8 (47.06)	13 (38.24)	0.546
Days from culture to death, ≤14 d	3.8 ± 3.8 (0—11)	5.8 ± 4.5 (1—12)	0.289
Mortality, ≤28 d	12 (70.59)	16 (47.06)	0.111
Days from culture to death, ≤28 d	9.8 ± 9.6 (0—24)	9.4 ± 8.6 (1—25)	0.895
Mortality, overall	16 (94.12)	17 (50.00)	0.002*
Days from culture to death, overall	34.5 ± 48.1 (0—160)	10.6 ± 9.7 (1—30)	0.069
Microbial eradication	7 (41.18)	22 (64.71)	0.110
Favorable (cure or improvement)	1 (5.88)	17 (50.00)	0.002*
Unfavorable (stationary or deterioration)	16 (94.12)	17 (50.00)	

[a] Heart diseases included congestive heart failure and valvular heart diseases.
[b] Chronic liver diseases included liver cirrhosis and chronic hepatitis.
[c] Immunosuppressant use included administration of steroids or immunosuppressant agents for non-hemaoncologic diseases.
[d] Readmitted from health care centers or hospitals within 14 d.
* Statistically significant, $p < 0.05$.
Data are presented as mean ± standard deviation (range) or n(%).
COPD = chronic obstructive pulmonary diseases.

confirmed by imipenem disk diffusion, according to established methods and breakpoints,[18] and by the Etest methods with imipenem and ertapenem, according to the manufacturer's instructions (AB Biodisk, Solna, Sweden).

Definition of outcomes

The primary outcome measure was in-hospital mortality. Secondary outcome was the outcome of the infection, and this was assessed as either favorable (cure or improvement) or unfavorable (stationary or deterioration).

Statistical methods

Descriptive statistics, including the number of observations, mean and standard deviation, were used to summarize the continuous variables. Frequency and proportion were used to summarize the categorical variables. For the continuous variables, Student *t* test or Wilcoxon test was considered for the test statistics, depending on the validity of the normality assumption. Chi-square test or Fisher's exact test was used to test the categorical variables. Multivariate analysis was performed using logistic regression to identify factors that independently and significantly affected the outcome. Variables with a *p* value less than 0.05 in bivariate analyses were considered for inclusion in a multivariate model. The Statistical Analysis System (SAS) (Version 9.1; SAS Institute Inc., Cary, NC, USA) was used as the programming software for performing the analysis.

Results

From January 2006 to December 2008, 51 patients were included in this study (17 cases with CNSEc and 34 controls with CSEc). The patients' characteristics are summarized in Table 1. Matching was achieved for all 17 cases with CNSEc bacteremia. Matching variables included gender, age, and length of hospital stay up to the isolation of *E coli*.

Patients with CNSEc bacteremia were mostly health care associated, either by nosocomial acquisition or by being transferred from nursing home or regional hospitals. Among the 17 patients with CNSEc bacteremia, 13 came from different wards, and no outbreaks were detected during the study period. Cross infection in hospital wards seemed less likely. As for the rest of the four patients, two were admitted in the medical intensive care unit, but the dates of their positive blood cultures for CNSEc were 9 months apart. Another two patients were admitted to the same gastrointestinal ward, but the culture dates were 4 months apart. Therefore, the 17 CNSEc isolates were unlikely from the limited clones. Besides, an earlier study using eight of our studied patients investigated the development of carbapenem resistance in *E coli*. Eight pairs of *E coli* isolates with various carbapenem susceptibilities from eight patients were prospectively collected to study. Identical pulsed-field gel electrophoresis patterns were found in carbapenem-susceptible and -resistant isolates, but different pulsed-field gel electrophoresis patterns occurred among the patients.[1]

Compared with the CSEc group, the CNSEc group had more patients with uremia on regular dialysis (35.29% *vs.* 2.94%; $p = 0.004$), with chronic liver diseases (76.47% *vs.* 17.65%; $p < 0.001$), and receiving transplantation (including liver and kidney transplantation, 17.65% *vs.* 0%; $p = 0.033$). Of 17 patients with CNSEc bacteremia, seven (41.18%) had recent access to health care facilities, such as residence in a nursing home, or recent hospital admission. However, there was no statistically significant difference of this parameter in comparison with that in the CSEc group (41.18% *vs.* 17.65%; $p = 0.093$).

For the patients with CNSEc bacteremia, 12 (70.59%) had the placement of CVCs and 11 (64.71%) had been admitted to an ICU with mechanical ventilator support at the onset of CNSEc bacteremia. Both conditions were seen to a lesser extent in patients with CSEc bacteremia [8 (23.53%) and 10 (29.41%), respectively]. Previous antibiotic exposure, particularly to carbapenems, was more frequently seen in patients with CNSEc bacteremia (52.94% *vs.* 2.94%; $p < 0.001$). As shown in Table 1, CNSEc bacteremia group had a longer hospital stay (68.4 days *vs.* 35.8 days; $p = 0.04$) and a disease severity, as indicated by a Pittsburgh bacteremia score greater than or equal to 4 (5.6% *vs.* 2.5%; $p = 0.015$). The clinical course after the onset of bacteremia was different between these two groups. Patients with CNSEc bacteremia had a higher overall in-hospital mortality rate (94.12% *vs.* 50.00%; $p = 0.002$) and more unfavorable outcome than those with CSEc bacteremia, but there was no statistical difference in the 28-day mortality between these two groups (Fig. 1).

Using the statistically significant parameters ($p < 0.05$) shown in Table 1, bivariate analysis showed that prior exposure to carbapenems ($p < 0.001$), ICU stay ($p = 0.016$), CVC placement ($p = 0.001$), chronic liver diseases ($p < 0.001$), uremia with regular dialysis ($p = 0.004$), and mechanical ventilation ($p = 0.004$) were associated with CNSEc bacteremia. Multivariate analysis showed that prior exposure to carbapenems [odds ratio (OR), 29.17; 95% confidence interval (CI), 1.76–484.70; $p = 0.019$]; uremia with regular dialysis (OR, 98.58; 95% CI, 4.02–999; $p = 0.005$); and chronic liver diseases (OR, 27.86; 95% CI, 2.31–335.83; $p = 0.009$) were independent risk factors for the development of CNSEc bacteremia (Table 2).

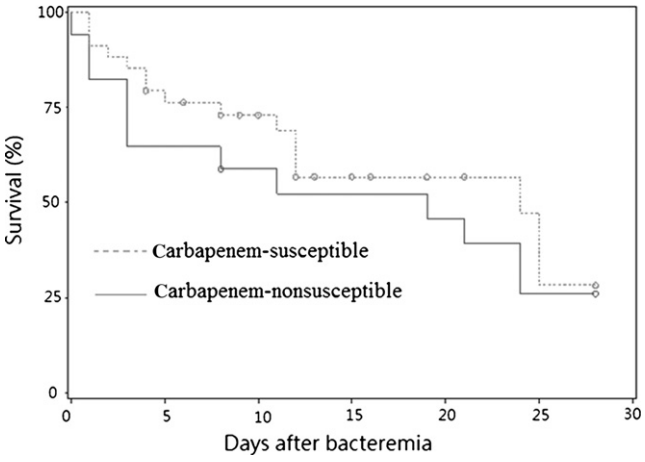

Figure 1. Survival analysis of patients with bacteremia caused by *Escherichia coli* with and without the carbapenem-nonsusceptible phenotype ($p = 0.3994$).

Table 2 Multivariable analysis of risk factors for carbapenem-nonsusceptible *Escherichia coli* bacteremia

Factors	Odds ratio	95% Confidence interval	*p*
Uremia with regular dialysis	98.58	4.02—999.99	0.005*
Chronic liver diseases	27.86	2.31—335.83	0.009*
Previous use of Carbapenems	29.17	1.76—484.70	0.019*

Only risk factors in Table 1 with *p* value less than 0.05 were considered for inclusion in a multivariable analysis.
A multivariable regression model was constructed by using a stepwise selection procedure.
* Statistically significant ($p < 0.05$).

Discussion

Emergence of imipenem resistance after long-term imipenem—meropenem therapy for a case with recurrent urosepsis because of ESBL-producing *E coli* has been reported.[4] The occurrence of an outer-membrane porin deficiency and the expression of a plasmid-mediated class C β-lactamase[1,13] or carbapenem-hydrolyzing enzymes[1,4,19] were reported to be responsible for carbapenem resistance in *E coli*.

Risk factors for the development of bacteremia or non-bacteremic infections caused by carbapenem-resistant *E coli* (CREc) or CNSEc have been rarely well described in the English-language literature. One earlier study by Jeon et al[20] surveyed the risk factors for the acquisition of CREc among hospitalized patients. A total of 46 patients with nosocomially acquired CREc isolates were studied. Previous use of carbapenem and metronidazole, the presence of biliary drainage catheter, and prior hospital stay were associated with CREc acquisition.[20] The causal association between metronidazole exposure and acquisition of CREc was not actually identified by conditional logistic regression analyses, but most (25 of 46, 54.3%) of the patients were indeed exposed to metronidazole. Similar to the findings of Jeon et al,[20] our study revealed that prior use of carbapenem was an independent risk factor for the emergence of CNSEc infections but metronidazole was not. That is because only three patients with CNSEc bacteremia had biliary drainage and metronidazole exposure.

Multivariate analysis in our study revealed that uremia with regular dialysis and chronic liver diseases were also independent risk factors. The greater disease severity, placement of CVCs, and higher incidence of invasive procedures might contribute to the acquisition of bloodstream infections. Vascular devices—related bloodstream infections may be the major transmission route of CNSEc bacteremia. Patients with such risk factors may also have repeated hospitalization and longer hospital stay.[21]

The overall in-hospital mortality in the case group was almost two times higher than that of the matched controls (94.12% *vs*. 50.00%), but there was no statistical difference in the 28-day mortality between these two groups. It could be difficult to assess the attributable mortality in this study when both groups had such a high overall mortality. Limited patient numbers may be another factor for this difficulty. Greater disease severity and poor patient condition may contribute to the poor outcome, not the infection itself. Notably, 17.6% (6 of 34) of the matched controls had bacteremia caused by ESBL strains, which had been reported to have high mortality rate.[22] However, whether the infection of multidrug-resistant gram-negative bacilli is associated with increasing mortality is still controversial.[23,24]

Our study has limitations. First, the sample size of patients included in this study is relatively small, although this is a common problem in studies assessing risk factors of infections because of multidrug-resistant pathogens.[25] Second, molecular epidemiology investigations using PCR for resistance genes or sequencing of PCR products were not performed in our study. Thus, details on the kind of carbapenemase are not available. Identifying the specific carbapenemase of the bacterial strains in our study will be necessary because the minimal inhibitory concentrations vary with the type of carbapenemase and may have influences on treatment results.[7] Our study afforded the preliminary data for risk factors of the acquisition of CNSEc infections and the outcome of patients with such infections.

In summary, CNSEc bacteremia led to a worse outcome than CSEc bacteremia. To our knowledge, our study is the first to show the association between CNSEc bacteremia and the underlying comorbid illness (i.e. chronic liver diseases and uremia with regular dialysis).

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