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Nosocomial extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* bacteremia in hemodialysis patients and the implications for antibiotic therapy

Chih-Chao Yang [a,1], Chien-Hsing Wu [a,1], Chien-Te Lee [a], Han-Tsung Liu [b], Jin-Bor Chen [a], Chien-Hua Chiu [a], Chih-Hung Chen [c,2], Feng-Rong Chuang [a,2,*]

[a] *Division of Nephrology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, 123 Ta Pei Road, Niao Sung District, Kaohsiung City 833, Taiwan*

[b] *Division of Trauma and Emergency Surgery, Department of Surgery, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan*

[c] *Division of General Medicine, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan*

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SUMMARY

Background: In the face of increasing treatment options for extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* (ESBL-Kp) hemodialysis (HD) access-related bacteremia, the difference in clinical effectiveness between ertapenem and flomoxef remains unclear. We conducted this retrospective study to determine their efficacies and treatment outcomes.

Methods: Patients on maintenance HD with fistula-, graft-, or catheter-related ESBL-Kp bacteremia were enrolled. Data related to clinical features and antibiotic treatments were collected. Outcome was determined by mortality resulting from bacteremia during the 14-day period after the collection of the first positive blood culture for flomoxef-susceptible ESBL-Kp.

Results: The 64 patients studied had severe septicemia as determined by the Pitt bacteremia score; 50% (32/64) were in the intensive care unit (ICU) at the time of bacteremia. Old age (>65 years; 57.8%), malnutrition (albumin < 3.5 g/dl; 92.2%), a history of severe illnesses (defined by shock, intubation, or ICU stay; 82.5%), and prolonged hospitalization prior to the onset of bacteremia (>30 days; 75%) were also highly prevalent. The study population comprised nine fistula-, 10 graft-, and 45 HD catheter-related bacteremia cases, and the mortality rate was high (38/64, 59.4%). The mortality rate was significantly higher in the flomoxef treatment group than in the ertapenem treatment group (22/30, 73% vs. 16/34, 47%, $p < 0.05$). Among patients with catheter-related bacteremia, multivariate analyses revealed that flomoxef use (odds ratio (OR) 2.52, 95% confidence interval (CI) 1.34–35.17) and Pitt bacteremia score (OR 4.37, 95% CI 1.28–5.26) were independently associated with mortality.

Conclusions: In accordance with our previous study, our results have demonstrated the inferiority of flomoxef to carbapenems in the treatment of HD access-related ESBL-Kp bacteremia and provide an insight into the possibility of using ertapenem rather than flomoxef as an initial or de-escalating therapy for infections caused by ESBL-producing bacteria.

1. Introduction

Infectious complications of the vascular access are a major source of morbidity and mortality among hemodialysis (HD) patients. Numerous reports implicate the vascular access in up to 48–73% of all bacteremia in HD patients.[1,2] A previous study recognized HD access-related extended-spectrum beta-lactamase (ESBL)-producing *Klebsiella pneumoniae* (ESBL-Kp) bacteremia to cause high mortality in

* Corresponding author. Tel.: +886 7 7317123 ext. 8306; fax: +886 7 7322402.
E-mail address: noteofnephrology@gmail.com (F.-R. Chuang).

[1] CCY and CHW made an equal contribution.

[2] CHC and FRC made an equal contribution.

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patients on maintenance HD (MHD).[3] Unfortunately, most of these patients initially received ineffective empiric antibiotics and there was a discrepancy in outcomes between patients receiving different effective antibiotics. Group 2 carbapenems (imipenem or meropenem) showed superior efficacy than flomoxef in treating these vulnerable patients.

The currently recommended therapy for infection caused by ESBL-producing organisms consists of group 2 carbapenems (e.g., imipenem and meropenem).[4,5] More recent studies have shown that ertapenem, a group 1 carbapenem, may be used successfully for ESBL-associated infection with favorable clinical response and microbiological cure rates[6] and provides comparable efficacy to group 2 carbapenems.[7] Cephamycins (i.e., cefmetazole, cefotetan, and flomoxef), characterized by their 7-α-methoxy β-lactam, have been reported to be highly active in vitro against both low inocula (10^5–10^6 CFU/ml) and high inocula (10^7–10^8 CFU/ml) of TEM- or SHV-producing *Enterobacteriaceae*.[8] In a retrospective study, treatment with either flomoxef or a group 2 carbapenem in patients with flomoxef-susceptible ESBL-Kp bacteremia was reported to be similarly effective.[9] Unfortunately, controversy remains regarding the optimal treatment, and few clinical reports comparing the treatment efficacy of cephamycins and carbapenems have been published.[10]

Because the differences in clinical effectiveness between ertapenem and flomoxef for HD access-related ESBL-Kp bacteremia in patients on MHD have not yet been studied, we conducted this 9-year retrospective study to compare the outcomes of patients treated with either flomoxef or ertapenem.

2. Subjects and methods

2.1. Study population and design

Adult MHD patients admitted during the 9-year period from January 2001 to December 2009 who developed a nosocomial HD access-related infection secondary to ESBL-Kp were included. The eligibility criteria was the presence of HD access (including arteriovenous fistula, graft or catheter) -related flomoxef-susceptible ESBL-Kp bacteremia. The following details were obtained from the medical charts: patient clinical characteristics, biochemical data, sites of ESBL-Kp infection (blood, HD catheter tip, pus from HD catheter exit site, and pus from fistula or graft wounds), and outcomes. Only patients treated with either flomoxef or ertapenem were included. For each patient included, flomoxef or ertapenem was administered for at least 2 days, starting within 5 days after receiving the finalized blood culture results. Individual patients without blood cultures that grew ESBL-Kp and severely ill patients who died rapidly without having received ertapenem or flomoxef for at least 2 days were excluded. Variables used for the assessment of severity of illness included the Pitt bacteremia score and comorbid conditions (e.g., poor nutrition, length of prior hospital stay (LOS), and intensive care unit (ICU) stay at the time of bacteremia). Mortality resulting from bacteremia within 14 days after the day the first positive blood culture that grew flomoxef-susceptible ESBL-Kp was collected, was used to determine the outcome. The study was approved by the institutional review board of Kaohsiung Chang Gung Memorial Hospital (study ID: CGMH-IRB-101-1595B).

2.2. Microbiology

All *K. pneumoniae* isolates were identified by standard methods, and the presence of ESBLs was evaluated using the Clinical and Laboratory Standards Institute (CLSI) criteria for ESBL screening and the disk confirmation test.[11] Minimum inhibitory concentrations (MICs) $\leq$2 mg/l for ertapenem and $\leq$8 mg/l for flomoxef were considered to indicate susceptibility.[12,13]

2.3. Definitions

Nosocomial bacteremia was defined as bacteremia occurring $>$ 48 h after admission to the hospital. HD access infections were defined in the presence of local signs (pus or redness) at the vascular access site, with or without a positive culture from the catheter tip or pus, or a positive blood culture with no known source other than the vascular access. ESBL-Kp bacteremia was defined by the isolation of ESBL-Kp from blood cultures. Empiric antibiotic was defined as the antibiotic therapy started at the time blood cultures were drawn. Definitive antibiotic was defined as the antibiotic therapy administered subsequent to the receipt of final blood culture results. Effective antimicrobial therapy for flomoxef-susceptible ESBL-Kp bacteremia in this study was defined as treatment with ertapenem or flomoxef—after determining the antibiotic susceptibility of the blood isolates. Significant underlying diseases were defined as a medical history of diabetes mellitus, liver cirrhosis, malignancy, or congestive heart failure.

2.4. Statistical analyses

All statistical analyses were performed using SPSS software program for Windows version 11.5 (SPSS Inc., Chicago, IL, USA). Continuous variables were each expressed as the mean $\pm$ standard deviation (SD) and were analyzed using the Student's *t*-test. The statistical difference in the frequency of occurrence of the variants in patients with HD catheter-related bacteremia (CRB) between subgroups was assessed with the Chi-square test or Fisher's exact test. A logistic regression model was used to estimate the effects of multiple factors associated with mortality in the univariate analyses. Variables with $p \leq 0.1$ in the univariate analysis between patients who died and those who survived were entered for further assessment. Estimated odds ratios (ORs) and 95% confidence intervals (CIs) were obtained from this model. For all analyses, two-sided tests of significance were used, with $p < 0.05$ considered significant.

3. Results

A total of 64 MHD patients with HD access-related bacteremia who met the inclusion criteria were identified during the study period. The demographic and clinical data of these patients are summarized in Table 1. In addition to 45 patients with HD CRB, there were nine patients with fistula-related bacteremia and 10 patients with graft-related bacteremia. Most of these patients were male (47/64, 73.4%), and old age (>65 years; 57.8%), malnutrition (albumin $<$ 3.5 g/dl; 92.2%), a history of severe illness (defined by shock, intubation, or ICU stay; 82.5%), and prolonged hospitalization prior to the onset of bacteremia (>30 days; 75%) were highly prevalent. Many patients also had significant underlying diseases (diabetes mellitus 46.9%, liver cirrhosis 14.1%, congestive heart failure 31.3%, and malignancy 10.9%) and prior use of broad-spectrum antibiotics (third-generation cephalosporin 64.1%). Most patients were initially hospitalized due to the onset of an infectious disease (39/64, 60.9%). At the onset of bacteremia, these patients had a critical illness (defined as a Pitt bacteremia score $\geq$4 points), with a mean $\pm$ SD Pitt bacteremia score of 5.3 $\pm$ 1.78. Thirty-two (32/64, 50%) patients were accommodated in an ICU at the time of bacteremia. The overall mortality rate was high (38/64, 59.4%), and patients with graft infection had the highest Pitt bacteremia score and the highest rate of mortality (7/10, 70%). With regard to the use of empiric antibiotics, the majority (38/64, 59.4%) did not receive effective antibiotic therapy, consisting of either flomoxef or ertapenem within 5 days after blood cultures were obtained, at the onset of bacteremia. A total of 53.1% (34/64) of patients were treated with ertapenem and 46.9% (30/64) with flomoxef as the definitive effective antibiotic.

Table 1
Comparisons of demographic and clinical data between the groups of different hemodialysis access-related ESBL-Kp bacteremia

	Source of infection			
	HD catheter	Fistula	Graft	All
Number of cases	45	9	10	64
Male, *n* (%)	34 (75.6)	6 (66.7)	7 (70)	47 (73.4)
Age, years, mean ± SD	65.2 ± 11.2	62 ± 9.3	67.1 ± 8.6	65.0 ± 10.1
Patients aged > 65 years, *n* (%)	26 (57.8)	4 (44.4)	7 (70)	37 (57.8)
Admission for infectious diseases, *n* (%)	25 (55.6)	6 (66.7)	8 (80)	39 (60.9)
Significant underlying diseases, *n* (%)				
Diabetes mellitus	17 (37.8)	5 (55.6)	8 (80)	30 (46.9)
Liver cirrhosis	5 (11.1)	2 (22.2)	2 (20)	9 (14.1)
Congestive heart failure	11 (24.4)	4 (44.4)	5 (50)	20 (31.3)
Malignancy	4 (8.9)	2 (22.2)	1 (10)	7 (10.9)
Comorbid conditions, *n* (%)				
Poor nutrition[a]	42 (93.3)	8 (88.9)	9 (90)	59 (92.2)
Prior antibiotic use[b]	38 (84.4)	7 (77.8)	7 (70)	52 (81.3)
Previous severe illness[c]	35 (77.8)	6 (66.7)	6 (75)	47 (82.5)
Prolonged hospitalization (>30 days), *n* (%)	35 (77.8)	6 (66.7)	7 (70)	48 (75)
Prior use of third-generation cephalosporin, *n* (%)	28 (62.2)	6 (66.7)	7 (70)	41 (64.1)
ICU stay at the time of bacteremia, *n* (%)	21 (46.7)	5 (55.6)	6 (60)	32 (50)
Pitt bacteremia score, mean ± SD	5.1 ± 1.41	5.3 ± 1.52	6.2 ± 2.6	5.3 ± 1.78
Antibiotics after onset of bacteremia, *n* (%)				
Effective antibiotics within 5 days	18 (40)	4 (44.4)	4 (40)	26 (40.6)
Use of flomoxef/ertapenem as effective antibiotic	19 (42.2)/26 (57.8)	5 (55.6)/4 (44.4)	6 (60)/4 (40)	30 (46.9)/34 (53.1)
Mortality, *n* (%)	27 (60)	4 (44.4)	7 (70)	38 (59.4)

ESBL-Kp, extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae*; HD, hemodialysis; SD, standard deviation; ICU, intensive care unit.
[a] Albumin < 3.5 g/dl.
[b] Including extended-spectrum cephalosporins, aztreonam, fluoroquinolones, trimethoprim/sulfamethoxazole, or aminoglycosides.
[c] Includes shock, intubation, and ICU stay.

Patient clinical characteristics, variables used for the assessment of severity of illness, and outcomes were compared between the two treatment groups (Table 2). When compared with the ertapenem group, patients treated with flomoxef had more fistula- and graft-related infections and carried a higher risk of mortality ($p < 0.05$). For patients with fistula or graft infections, surgical interventions (wound debridement and/or removal of the infected fistula or graft) were performed in eight (8/11, 73%) patients treated with flomoxef and in three (3/8, 38%) treated with ertapenem. Since the extent and perioperative risk of surgery might affect the survival of patients with fistula or graft infections, we only analyzed patients with CRB.

The demographic and clinical data of patients with CRB are summarized in Table 3. Most of the patients were elderly and the overall mortality rate was high (27/45, 60%). Patients who died had significantly lower levels of serum albumin, a longer LOS, and longer duration of catheter-dependent HD (all $p < 0.05$). A significantly higher Pitt bacteremia score (4.12 vs. 5.75) and prevalence of ICU stay (27.8% vs. 59.3%), both reflecting the severity of the septicemia, were also noted in the group of patients who died (both $p < 0.05$). The prescription of appropriate empiric and definitive antibiotic therapy indeed significantly affected the outcome. Mortality was significantly associated with flomoxef treatment and not having received effective antibiotic therapy within 5 days after the onset of bacteremia.

The results of the multivariate analysis examining risk factors for mortality associated with CRB are given in Table 4. Variables that were determined to be significantly associated with mortality at 14 days after the date the first positive blood culture was collected on univariate analysis were subjected to multivariate analysis. Flomoxef treatment (OR 2.52, 95% CI 1.34–35.17) and Pitt bacteremia score (OR 4.37, 95% CI 1.28–5.26) were independently associated with increased mortality.

Table 2
Comparisons of patient clinical characteristics, variables used for the assessment of illness severity, and outcomes between the ertapenem and flomoxef treatment groups

	Ertapenem	Flomoxef
Number of cases	34	30
Source of infection, *n*		
HD catheter	26	19
Fistula	4	5
Graft	4	6
Comorbid conditions, *n* (%)		
Poor nutrition[a]	31 (91)	28 (93)
Previous severe illness[b]	24 (71)	23 (77)
Prolonged hospitalization (>30 days)	25 (74)	23 (77)
ICU stay at the time of bacteremia	17 (50)	15 (50)
Pitt bacteremia score, mean ± SD	5.3 ± 1.37	5.4 ± 1.65
Effective antibiotics within 5 days, *n* (%)	14 (41)	12 (40)
Mortality, *n* (%)[c]	16 (47)	22 (73)

HD, hemodialysis; ICU, intensive care unit; SD, standard deviation.
[a] Albumin < 3.5 g/dl.
[b] Includes shock, intubation, and ICU stay.
[c] $p < 0.05$.

4. Discussion

No strict guidelines or consensus indicates the preferred therapeutic treatment for ESBL-producing *Enterobacteriaceae*-related infections, especially in immunocompromised individuals like HD patients. For infections secondary to ESBL-producing organisms, a higher clinical failure rate[14] and mortality rate[15] have been associated with cephalosporin treatment, and the overuse of cephalosporins has been shown to lead to increased bacterial resistance to many classes of beta-lactam and non-beta-lactam antibiotics. Although a few small retrospective trials have demonstrated that group 2 carbapenems show relative superiority over other agents for the treatment of infections caused by ESBL-producing organisms,[7] the extensive use of these antibiotics may result in the outbreak of infections related to carbapenem-resistant strains such as *Acinetobacter baumanii*,[16] *Pseudomonas aeruginosa*,[17] and *Stenotrophomonas maltophilia*.[18] The emergence of multi-drug resistance in these virulent pathogens poses challenging infection-control issues and has significantly hampered efforts to devise effective empiric or directed antibiotic treatment regimens.

Table 3
Comparisons of demographic and clinical data between patients who died and those who survived of the 45 patients with catheter-related bacteremia

Variable	Survived ($n=18$)	Died ($n=27$)	p-Value	Total ($n=45$)
Age, years, mean ± SD	64.2 ± 7.2	65.9 ± 12.1	NS	65.2 ± 11.2
Male, *n* (%)	13/18 (72.2)	21/27 (77.8)	NS	34/45 (75.6)
Patients aged > 65 years, *n* (%)	9/18 (50)	17/27 (63)	NS	26/45 (57.8)
Flomoxef treatment, *n* (%)	3 (16.7)	16 (59.3)	0.015	19 (42.2)
Treatment within 5 days, *n* (%)	11 (61.1)	7 (25.9)	0.029	18 (40)
Pitt bacteremia score, mean ± SD	4.12 ± 1.14	5.75 ± 1.67	0.007	5.1 ± 1.41
Serum albumin, g/dl, mean ± SD	2.83 ± 0.54	2.32 ± 0.75	0.037	2.52 ± 0.71
Hemoglobin, g/dl, mean ± SD	9.21 ± 0.65	9.33 ± 1.81	NS	9.28 ± 1.51
Hospital days before onset, mean ± SD	52 ± 31.2	112.9 ± 64.5	0.045	88.5 ± 59.1
Duration of catheter-dependent HD, days, mean ± SD	26.2 ± 8.9	41.6 ± 13.1	0.031	35.4 ± 11.2
ICU stay at the time of bacteremia, *n* (%)	5 (27.8)	16 (59.3)	0.022	21 (46.7)

SD, standard deviation; NS, not significant; HD, hemodialysis; ICU, intensive care unit.

Flomoxef is unique among cephamycins in having a difluoromethylthioacetamido group at position 7, which improves its in vitro activity against ESBL-producing *Enterobacteriaceae*.[8,19] Ertapenem is a new carbapenem with superior pharmacokinetics and shares similar structural features with meropenem, allowing it to have broad-spectrum activity with resistance to nearly all β-lactamases.[20] However, both ertapenem and flomoxef have limited activity against *P. aeruginosa* and *A. baumannii*, which makes them not optimal for infections caused by nosocomial pathogens. In HD patients, both intravenous ertapenem and flomoxef can be given once-daily at dosages of 500 mg and 1 g, respectively, which may be an advantage of prescription. However, their efficacies for the treatment of HD access-related ESBL-Kp bacteremia in MHD patients are still unclear.

Although our study was limited by its retrospective design and small sample size, it indeed demonstrated that the prescription of an appropriate antibiotic is critical in the light of our finding that treatment with flomoxef was an independent risk factor for increased mortality (on multivariate analysis) in these vulnerable patients. As in our previous study,[3] the research data in this study were derived from our population of HD patients with HD access-related ESBL-Kp bacteremia and most of them were treated with flomoxef, imipenem, meropenem, or ertapenem. After an extensive literature review, we found there to be very limited data regarding this issue, therefore we conducted these two studies using a similar methodology and statistical analysis methods.

Our study results have demonstrated an inferiority of flomoxef to carbapenems in the treatment of HD access-related ESBL-Kp bacteremia. Although flomoxef is stable to hydrolysis by ESBL-producing *Enterobacteriaceae*, there is a general reluctance to use this agent because some isolates may decrease the expression of outer membrane proteins, thus creating resistance to this agent during therapy.[10] It is not surprising that the loss of effectiveness of flomoxef, if present, while treating ESBL-Kp bacteremia in critically ill HD patients leads to increased treatment failure and mortality. As a result of this major concern, the carbapenems have become widely recognized as the drug class of first choice for the treatment of serious infections caused by ESBL-producing *Enterobacteriaceae*. Our study indicates the possibility of using ertapenem rather than flomoxef as an initial or de-escalating therapy for infections caused by ESBL-producing bacteria. Because of the risk of selecting for resistance, initial empirical broad-spectrum treatment with imipenem or meropenem should be de-escalated to a narrow-spectrum agent once the identity and susceptibility profiles of the infecting pathogens are known. Limiting the use of imipenem and meropenem may consequently prevent the emergence of carbapenem resistance in *A. baumannii* and *P. aeruginosa*.

Table 4
Results of the multivariate analysis examining risk factors for mortality associated with catheter-related bacteremia

Mortality risk factor	p-Value	OR (95% CI)
Flomoxef treatment (vs. ertapenem)	0.021	2.52 (1.34–35.17)
Pitt bacteremia score (per 1-point increment)	0.009	4.37 (1.28–5.26)

OR, odds ratio; CI, confidence interval.

In addition to the risk of immunocompromise, HD patients may be rendered susceptible to ESBL-related infection by frequent vascular catheterization, catheter manipulation, and the need for broad-spectrum antibiotics during prolonged hospitalization. Although HD has been recognized as a risk factor for the acquisition of ESBL infections,[4,21] there is limited information regarding the clinical characteristics associated with HD access-related ESBL-Kp bacteremia in MHD patients. Most of the patients with bacteremia in the present study were elderly, malnourished, and had a history of severe illness and prolonged hospitalization. These patients were also critically ill, as determined by the Pitt bacteremia score, and had high prevalence rates of significant underlying diseases and were in the ICU at the time of bacteremia; therefore, they had a high mortality rate (38/64, 59.4%). Only 40.6% of these critically ill patients received effective antibiotics within 5 days after the date the first positive blood culture for ESBL-Kp was collected, which may have contributed to the high mortality rate.

Prolonged hospitalization has been recognized as a risk factor for ESBL infection,[15] and hypoalbuminemia has also been found to increase the likelihood of CRB in HD patients.[22] In the present study, both longer LOS and a lower serum albumin level were associated with high mortality in patients with CRB. A longer duration of catheter-dependent HD was additionally determined to be a risk factor for increased mortality. These findings suggest that shortening the duration of catheter-dependent HD may decrease the probability of CRB secondary to ESBL-producing bacteria and improve the prognosis. The significantly higher Pitt bacteremia score and prevalence rate of ICU stay at the time of bacteremia in the group of patients who died was not surprising. Because MHD patients with HD access-related ESBL-Kp bacteremia were mostly immunocompromised and critically ill, their mortality rate was determined by these parameters, which reflected the severity of the septicemia.

The use of effective antibiotics such as carbapenems during the 5-day period after the onset of bacteremia due to an ESBL-producing organism has been reported to be associated with lower mortality.[23] Unfortunately, most of our patients initially received ineffective empiric antibiotics and the limitation of the retrospective design of this study made a comparison of quantitative outcomes between treatment groups infeasible. However, the lower percentage of patients receiving effective empiric antibiotics reflects our collective unawareness of the significance of these emerging strains and the very limited information regarding this

issue in this special population. In the present study, treatment with effective antibiotics within 5 days after the onset of bacteremia and the use of ertapenem improved the prognosis in patients with CRB.

In conclusion, this is the first study to suggest ertapenem rather than flomoxef as the first choice for the empiric or directed therapy of critically ill MHD patients with HD access-related ESBL-Kp bacteremia. We stress that HD patients with a critical illness are susceptible to ESBL-Kp HD access-related bacteremia and have poor outcomes.

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