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Mortality caused by extended-spectrum beta-lactamase-producing Enterobacteriaceae bacteremia: Alert to Enterobacteriaceae strains with high minimum inhibitory concentrations of piperacillin/tazobactam

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Abstract

Purpose. The incidence of infections caused by extended-spectrum beta-lactamase-producing Enterobacteriaceae (ESBL-PE) has been recently increasing worldwide. ESBL-PE bacteremia has been associated with high mortality and has thus become a clinically critical issue. Accordingly, ESBL-PE strains with low susceptibility to piperacillin/tazobactam (PTZ) are a concern in clinical practice. This study aimed to assess the prognostic factors of patients with bacteremia due to ESBL-PE as well as the antimicrobial susceptibility, particularly to PTZ, among ESBL-PE strains.

Methods. A total of 65 patients with ESBL-PE bacteremia who were admitted to Osaka City University Hospital between January 2011 and April 2017 were enrolled and divided into the survivor group (n=52) and nonsurvivor group (n=13). The medical records of these patients were retrospectively reviewed.

Results: The survivor group (mean age: 66.2 years) included 26 men, while the nonsurvivor group (mean age: 45.2 years) included 5 men. The male-to-female ratio, age, underlying disease, leukocyte count, C-reactive protein level, and treatment did not differ between the two groups. Multivariate analysis showed that the independent predictors associated with hospital mortality of ESBL-PE bacteremia were sepsis ($p=0.047$) and febrile neutropenia (FN) ($p=0.008$). Further, the minimum inhibitory concentration values of ESBL-PE isolates in nonsurvivors tended to be higher than

those in survivors.

Conclusions: Sepsis and FN were independent predictors of hospital mortality in ESBL-PE bacteremia; thus early assessment of these conditions is important. Furthermore, PTZ should be used with caution in cases of ESBL-PE strains with low susceptibility to the drug.

Keywords

bacteremia, extended-spectrum beta-lactamase, febrile neutropenia, piperacillin/tazobactam, sepsis

Introduction

Extended-spectrum beta-lactamase (ESBL) are enzymes that confer resistance to most beta-lactam antibiotics including penicillins, cephalosporins, and monobactams [1]. ESBL are produced by the Enterobacteriaceae, predominantly in *Escherichia coli* and *Klebsiella pneumoniae* [2]. In recent years, the incidence of infections caused by ESBL-producing Enterobacteriaceae (ESBL-PE) are increasing worldwide [3]. ESBL-PE bacteremia has been associated with high mortality and has thus become a clinically critical issue. Previous studies reported a mortality rate of approximately 15%–30% in patients with ESBL-PE bacteremia [4-7]. Therefore, determining the predictors of ESBL-PE bacteremia mortality is important in clinical practice.

Carbapenems have become widely used as the primary drug of choice for treating severe infections caused by ESBL-PE [8]. However, because of the emergence and spread of carbapenemase-producing bacteria, there has been increasing interest in determining potential alternatives to carbapenems [9]. Previous reports showed that β-lactam/β-lactamase inhibitors, including piperacillin/tazobactam (PTZ), are clinically reliable for the treatment of infections caused by ESBL-PE [10, 11]. The 2016 Clinical and Laboratory Standards Institute (CLSI) set a PTZ breakpoint of ≤16 μg/mL for ESBL-PE [12]. However, some studies have recently reported a decreased clinical efficacy of PTZ for bacteremia caused by ESBL-PE in the presence of isolates with high

minimum inhibitory concentrations (MICs) [9, 13, 14]. Some studies reported that the 30-day mortality in patients treated with PTZ as empiric therapy for bacteremia caused by ESBL *E. coli* was lower for isolates with low MIC than those with high MIC [9, 13]. Furthermore, another report suggested that a lower PTZ MIC value was recommended as a breakpoint for bacteremia caused by ESBL-PE [14].

In the present study, we investigated the clinical characteristics of patients with bacteremia due to ESBL-PE in a tertiary hospital, including the prognostic factors for infection and isolate antimicrobial susceptibility, particularly to PTZ.

Materials and methods

The medical records of 65 patients with ESBL-PE bacteremia who had been admitted to Osaka City University Hospital between January 2011 and April 2017 were retrospectively reviewed. The age, sex, underlying disease, clinical features, patient medication records, and prognosis were evaluated. If ESBL-PE had been isolated on multiple occasions within a six-year period in the same patient, only the first episode of ESBL-PE bacteremia was reviewed. This study was approved by the Ethics Committee of Osaka City University, and the thesis was approved on October 4, 2017 (Approval number: 3868). The need for written informed consent was waived owing to the retrospective nature of the study.

115

116 Definition of bacteremia

117 Bacteremia was defined as one or more positive blood cultures from patients with

118 clinical signs of infection, such as fever, shaking chills, and sweats with or without local

119 signs and symptoms [15]. A patient was diagnosed with ESBL-PE urinary tract infection

120 (UTI) when the clinical and diagnostic findings included two more of following: 1)

121 ESBL-PE confirmed in a urine specimen, 2) clinical manifestations suggestive of UTI,

122 and 3) imaging findings suggestive of pyelonephritis. Symptoms and urinary findings

123 including dysuria, suprapubic pain, hematuria, flank pain, costovertebral-angle

124 tenderness, nausea or vomiting, and pyuria or bacteriuria are characteristic of UTI [16].

125 Further, the imaging findings including perinephric stranding, renal swelling, thickening

126 of Gerota's fascia, and a segmental poor enhancement region are characteristic of

127 pyelonephritis [17]. The diagnosis of ESBL-PE biliary tract infection was made when

128 the clinical and diagnostic findings included three or more of the following: 1) fever

129 and/or chills, 2) laboratory evidence of an inflammatory response, 3) jaundice or

130 abnormal liver chemistries,4) biliary dilation or evidence of an etiology observed on

131 imaging, 5) ESBL-PE isolated from a bile specimen.

132

133 Assessment of laboratory data

If the initial blood culture was positive, then the leukocyte count, the neutrophil count, C-reactive protein levels, and albumin levels were assessed within 2 days of the culture. Neutropenia was defined as a neutrophil count of <500/μL. The 2016 Sepsis-3 definitions were applied in the present study [18].

Identification of bacteria

All ESBL-PE isolates were identified via colony morphologic analysis and gram staining. Isolate identification and antimicrobial susceptibility were confirmed using the MicroScan WalkAway-96 SI (Beckman Coulter, Inc., Brea, CA, USA). The MICs were determined using a dilution antimicrobial susceptibility test in accordance with the manufacturer's instructions (Eiken Chemical, Japan). All plates were incubated at 35°C overnight (16–20 hours). The results were interpreted according to the 2016 CLSI breakpoints.

Antimicrobial treatments

The attending physician determined the appropriate initial antimicrobial treatment regimen. Antimicrobial treatment administered within five days after bacteremia onset was defined as empirical therapy and that administered afterward as definitive therapy [19]. Inappropriate antibiotic therapy was defined as not matching in vitro susceptibility

according to the criteria of CLSI.

Statistical analysis

Patient characteristics, blood examination data, and treatments were compared between the survivor group and nonsurvivor group. Chi-square tests were used for univariate comparison of categorical data. Variables with a p-value <0.1 in the univariate analyses were considered for inclusion in the backward, stepwise, multivariate logistic regressions using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical interface for R (The R Foundation for Statistical Computing, Vienna, Austria, version 3.3.1), to determine the independent predictors of hospital mortality of ESBL-PE bacteremia. More precisely, it is a modified version of R commander (version 2.3-0) that includes the statistical functions frequently used in biostatistics. P values <0.05 indicated a statistically significant difference.

Results

Clinical characteristics and laboratory findings

The clinical characteristics and laboratory findings of the 65 patients with ESBL-PE bacteremia are summarized in Table 1. The cohort included 31 men and 34 women, and the mean age was 62.0 years. Of all infections, 55 (84.6%) were caused by *E. coli*, 6

(9.2%) by *K. pneumoniae*, 2 (3.1%) by *Proteus mirabilis*, 1 (1.5%) by *Enterobacter cloacae*, and 1 (1.5%) by *Citrobacter amalonaticus*. Of the 65 patients with ESBL-PE bacteremia, 42 (64.6%) had malignancy; 14 (21.5%) had diabetes mellitus; 20 (30.8%) had sepsis; and 12 (18.5%) had febrile neutropenia (FN). A total of 28 (43.1%) patients had received immunosuppressive drug or corticosteroid, and 23 (35.4%) were treated with antibiotics 60 days prior to isolation. The most frequent clinical manifestation of ESBL-PE infection was UTI (n=29 patients; 44.6%). The hospital mortality rates of the infected patients was 20.0%.

Treatment

The empirical and definitive therapies against ESBL-PE bacteremia are summarized in Table 2. The most frequently used antibiotic as both empirical and definitive therapy was carbapenems (35.4% and 58.1%, respectively).

Antimicrobial susceptibility

The MIC_{50} and MIC_{90} values of the various antimicrobial agents against ESBL-PE are shown in Table 3. The MIC_{50} and MIC_{90} values of meropenem were both ≤0.06 μg/mL and that of doripenem were both ≤0.06 μg/mL. Meanwhile, The MIC_{50} and MIC_{90} values of PTZ were 2 μg/mL and 4 μg/mL, respectively. The MICs of PTZ against the

ESBL-PE in survivors or nonsurvivors are shown in Table 4. The percentage of ESBL-PE isolates with MIC ≤1 was lower in nonsurvivors than that in survivors (10.0% vs 23.3%). By contrast, the percentage of ESBL-PE isolates with MIC ≥8 was higher in nonsurvivors than that in survivors (20.0% vs 6.7%).

Prognostic factors

Univariate analysis of predictors associated with hospital mortality of ESBL-PE bacteremia are shown in Table 5. The male-to-female ratio, mean age, underlying disease, and treatment did not differ between survivors and nonsurvivors. However, FN was a predictor of hospital mortality (p=0.01). The independent predictors of hospital mortality of ESBL-PE bacteremia according to multivariate analysis were sepsis (p=0.047) and FN (p=0.008) (Table 6). The use of PTZ as empirical or definitive therapy was not associated with hospital mortality.

Discussion

The results of our study revealed the following. First, sepsis and FN were independent predictors of hospital mortality in ESBL-PE bacteremia. Second, ESBL-PE MICs of PTZ in nonsurvivors tended to be higher than those in survivors.

Some studies reported that the presence of sepsis or septic shock is an independent

predictor of mortality in patients with ESBL-PE bacteremia [5, 20, 21]. Wang et al. [20] reported that gram-negative bacilli could cause severe sepsis and death, in particular, ESBL-PE bacteremia was associated with severe outcomes. A previous report has shown that endotoxin, a toxin of gram-negative bacilli, induced inflammatory cytokines and caused sepsis and progression to multiple organ dysfunction [22]. Furthermore, Lee et al. [23] reported that inappropriate empirical antibiotic therapy was strongly related to poor outcomes in patients with ESBL-PE bacteremia. These findings suggest that sepsis caused by ESBL-PE bacteremia has high mortality rate. In our study, the percentage of nonsurvivors with sepsis or inappropriate empirical antibiotic therapy were relatively high (53.8% and 46.2%, respectively). However, many of the previous studies have used the conventional definition of sepsis, and the relationship between the mortality of ESBL-PE bacteremia and sepsis as defined in the 2016 CLSI guidelines has not been adequately investigated. In the present study, although mortality of ESBL-PE bacteremia was suggested to be related to sepsis, we believe that more cases should be collected to confirm this relationship.

A previous report showed that the presence of neutropenia was associated with 30-day mortality in patients with ESBL-producing *E. coli* bacteremia [7]. Kim et al. [24] reported that patients with neutropenic fever tended to have prolonged hospital stay and prior use of broad-spectrum cephalosporins, thus increasing the risk for acquiring

ESBL-PE and ESBL-PE bacteremia in this patient population. Furthermore, some studies reported that neutropenia was a prevalent complication in immunocompromised patients and was associated with the increased risk of life-threatening bacteremia infection and high morbidity and mortality [25, 26]. The findings of previous reports suggested high mortality due to ESBL-PE bacteremia in patients with febrile neutropenia. By contrast, Wang et al. [20] reported that the presence of neutropenia in patients with ESBL-PE bacteremia was not associated with an increase in the mortality rate. This result was attributed to the use of carbapenem, which is the most recommended antibiotic for bacteremia in FN patients, in 91% of patients and the early shift of definitive antimicrobial therapy to appropriate therapy. In our study, although most FN patients with ESBL-PE bacteremia received appropriate therapy against ESBL-PE, the utilization rates of carbapenems as both an empirical and definitive therapy were relatively low (50.0% and 60.0%, respectively). Therefore, we speculated that FN was an independent predictor of hospital mortality of ESBL-PE bacteremia.

Rodríguez-Baño et al. [13] reported that the 30-day mortality in patients empirically treated with PTZ for bacteremia caused by ESBL *E. coli* was only 4.5% if MIC was ≤4 μg/mL, or 23% if the MIC was >4 μg/mL. Retamar et al. [9] showed that the 30-day mortality in patients who received PTZ as empiric therapy for bacteremia with a non-urinary focus caused by ESBL *E. coli* was significantly lower for isolates with MIC

of ≤2 μg/mL than those with higher MIC (0% vs 41.1%). Furthermore, a previous study reported that the microbiological and clinical efficacy of PTZ with MICs of ≤8 μg/mL for bacteremia caused by ESBL-PE was significantly higher than that of MICs of ≥16 μg/mL and suggested the need to revise the PTZ breakpoint for ESBL-PE [14]. These findings suggest that the clinical efficacy of PTZ for bacteremia caused by ESBL-PE was higher for isolates with low PTZ MIC than those with high PTZ MIC. In the present study, the PTZ MICs against ESBL-PE in nonsurvivors were higher than those of survivors (MIC_{50}: 4, 2 and MIC_{90}: 8, 4, respectively). Furthermore, two (20.0%) ESBL-PE isolates in nonsurvivors exhibited low susceptibility to PTZ (MICs ≥8 μg/mL). One corresponding patient received PTZ therapy until the end of treatment and died. Although PTZ may be administered for bacteremia caused by ESBL-PE, the findings of previous reports suggest that PTZ should be administered with caution in ESBL-PE strains with low susceptibility to the antibiotic.

Our study had several limitations. First, we primarily assessed *E. coli* bacteremia, which accounted for majority of ESBE-PE bacteremia in our cohort. It is necessary to determine the numbers of patients with bacteremia caused by other ESBL-PE such as *K. pneumoniae* and *P. mirabilis*. Second, as this study was conducted only in patients in a tertiary hospital, there was a selection bias. Future studies are necessary to determine the numbers of patients with bacteremia caused by ESBL-PE in a community hospital

setting. Third, we conducted this retrospective study primarily with the aim of investigating the predictors of hospital mortality of ESBL-PE bacteremia. Future prospective studies are necessary to compare the efficacy of carbapenems and PTZ for the treatment of bacteremia caused by ESBL-PE.

Conclusion

The results of our study demonstrated that sepsis and FN were independent predictors of hospital mortality in ESBL-PE bacteremia. Therefore, early assessment of sepsis or FN is important in patients with ESBL-PE bacteremia. Although PTZ may be administered for bacteremia caused by ESBL-PE, it should be administered with caution in ESBL-PE strains with low susceptibility to the antibiotic.

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Conflict of interest: We declare no conflicts of interest.

Informed consent: Not applicable to this study.

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378

Tables

Table 1. Clinical characteristics and laboratory findings of the patients with ESBL-PE bacteremia

Variables	Value
Sex (male/female)	31/34
Mean age (years)	62.0 ± 18.5
Bacterial strains, n(%)	
Escherichia coli	55 (84.6%)
Klebsiella pneumoniae	6 (9.2%)
Proteus mirabilis	2 (3.1%)
Enterobacter cloacae	1 (1.5%)
Citrobacter amalonaticus	1 (1.5%)
Underlying disease, n(%)	
Malignancy	42 (64.6%)
Hematological	15 (23.1%)
Immunosuppressive drug or corticosteroid use	28 (43.1%)
Diabetes mellitus	14 (21.5%)
Chronic renal failure	12 (18.5%)
Cardiovascular disease	10 (15.4%)
Digestive disease	10 (15.4%)
Central nervous system disease	9 (13.8%)
Respiratory disease	8 (12.3%)
Endocrine disease	5 (7.7%)
Autoimmune disease	3 (4.6%)
Others	18 (27.7%)
Leukocyte count (/μL)	9007.7 ± 6603.3
Neutrophil count (/μL)	7484.6 ± 5775.2
CRP (mg/dL)	11.1 ± 9.2
Alb (g/dL)	2.9 ± 0.7
Sepsis, n(%)	20 (30.8%)
Febrile neutropenia, n(%)	12 (18.5%)
Use of antibiotics prior to isolation, n(%)	52 (80.0%)
Quinolones	23 (35.4%)

Anti-MRSA agents	17 (26.2%)
Third-generation cephalosporins	16 (24.6%)
Carbapenems	13 (20.0%)
Fourth-generation cephalosporins	12 (18.5%)
Sulfamethoxazole/trimethoprim	12 (18.5%)
Second-generation cephalosporins	10 (15.4%)
Sulbactam/ampicillin	7 (10.8%)
Piperacillin/Tazobactam	5 (7.7%)
None	13 (20.0%)
Others	7 (10.8%)
Nosocomial infection, n(%)	50 (76.9%)
Hospitalization within 90 days, n(%)	23 (35.4%)
Central venous catheter, n(%)	25 (38.5%)
Urinary catheter, n(%)	22 (33.8%)
Surgery, n(%)	17 (26.2%)
Polymicrobial infection, n(%)	4 (6.2%)
Infection site, n(%)	
Urinary tract	29 (44.6%)
Biliary tract	6 (9.2%)
Wound infection	5 (7.7%)
Intravascular device	2 (3.1%)
Others	6 (9.2%)
Unknown	17 (26.2%)
Hospital mortality, n(%)	13 (20.0%)

*Data are presented as mean ± SD

Abbreviations: Alb: albumin, CRP: C-reactive protein, ESBL-PE: extended-spectrum beta-lactamase-producing Enterobacteriaceae, MRSA: methicillin-resistant *Staphylococcus aureus*, SD: standard deviation

Table 2. Empiric and definitive therapy against ESBL-PE bacteremia

Antibiotic	Empiric therapy, n(%)	Definitive therapy, n(%) [a]
Carbapenems	23 (35.4%)	36 (58.1%)
Piperacillin/Tazobactam	9 (13.8%)	9 (14.5%)
Fourth-generation cephalosporins	6 (9.2%)	1 (1.6%)
Third-generation cephalosporins	8 (12.3%)	3 (4.8%)
Cefmetazole	4 (6.2%)	8 (12.9%)
Quinolones	4 (6.2%)	1 (1.6%)
Flomoxef	3 (4.6%)	2 (3.2%)
Others	8 (12.3%)	2 (3.2%)

[a]Three patients died before definitive therapy.

Abbreviation: ESBL-PE: extended-spectrum beta-lactamase-producing Enterobacteriaceae

Table 3. ESBL-PE MICs

Antibiotic	MIC range (μg/mL)	MIC_{50}	MIC_{90}
Piperacillin/Tazobactam	≤1–8	2	4
Cefmetazole	≤0.25–8	1	4
Flomoxef	≤1	≤1	≤1
Levofloxacin	≤0.06–≥4	≥4	≥4
Sitafloxacin	≤0.06–≥4	1	1
Meropenem	≤0.06	≤0.06	≤0.06
Doripenem	≤0.06–0.12	≤0.06	≤0.06
Faropenem	≤0.5–2	1	2
Fosfomycin	≤0.5–≥8	2	≥8
Amikacin	≤1–≥8	4	4
Gentamicin	≤0.5–≥4	2	≥4
Sulfamethoxazole/trimethoprim	≤0.5–≥4	≥4	≥4
Minocycline	≤0.25–≥4	2	≥4

*40 strains were preserved.

Abbreviations: ESBL-PE: extended-spectrum beta-lactamase-producing Enterobacteriaceae, MICs: minimum inhibitory concentrations

Table 4. MICs of piperacillin/tazobactam against the ESBL-PE in survivors and nonsurvivors

Variables	MIC (μg/mL)						
	≤1	2	4	8	16	MIC_{50}	MIC_{90}
Survivors [a]	7 (23.3%)	14 (46.7%)	7 (23.3%)	2 (6.7%)	0 (0%)	2	4
Nonsurvivors [b]	1 (10.0%)	4 (40.0%)	3 (30.0%)	2 (20.0%)	0 (0%)	4	8

[a]30 strains were preserved.

[b]10 strains were preserved.

ESBL-PE: extended-spectrum beta-lactamase-producing Enterobacteriaceae, MICs: minimum inhibitory concentrations

Table 5. Univariate analysis of predictors of hospital mortality of ESBL-PE bacteremia

Variables	Survivors (n=52)	Nonsurvivors (n=13)	p-value [a]
Male sex	26 (50.0%)	5 (38.5%)	0.66
Age ≥ 70 years	23 (44.2%)	2 (15.4%)	0.11
Non *Escherichia coli*	8 (15.4%)	2 (15.4%)	1.00
Underlying disease			
Malignancy	33 (63.5%)	9 (69.2%)	0.95
Hematological	9 (17.3%)	21 (46.2%)	0.06
Immunosuppressive drug or corticosteroid use	19 (36.5%)	9 (69.2%)	0.06
Diabetes mellitus	11 (21.1%)	3 (23.1%)	1.00
Chronic renal failure	11 (21.1%)	1 (7.7%)	0.47
Cardiovascular disease	8 (15.4%)	2 (15.4%)	1.00
Digestive disease	10 (19.2%)	0 (0%)	0.20
Central nervous system disease	8 (15.4%)	1 (7.7%)	0.79
Respiratory disease	6 (11.5%)	2 (15.4%)	1.00
Endocrine disease	4 (7.7%)	1 (7.7%)	1.00
Autoimmune disease	2 (3.8%)	1 (7.7%)	1.00
Leukocyte count ≥ 12000 (/μL)	16 (30.8%)	2 (15.4%)	0.45
CRP ≥ 10 (mg/dL)	22 (42.3%)	6 (46.2%)	1.00
Alb ≤ 2.5 (g/dL)	18 (34.6%)	6 (46.2%)	0.65
Sepsis	13 (25.0%)	7 (53.8%)	0.09
Febrile neutropenia	6 (11.5%)	6 (46.2%)	0.01

Nosocomial infection	38 (73.1%)	12 (92.3%)	0.27
Hospitalization within 90 days	19 (36.5%)	4 (30.8%)	0.95
Central venous catheter	18 (34.6%)	7 (53.8%)	0.34
Urinary catheter	16 (30.8%)	6 (46.2%)	0.47
Surgery	13 (25.0%)	4 (30.8%)	0.94
Polymicrobial infection	4 (7.7%)	0 (0%)	0.70
Non-urinary tract infection	27 (52.0%)	9 (69.2%)	0.42
Empirical therapy			
Carbapenems	18 (34.6%)	5 (38.5%)	1.00
Piperacillin/tazobactam	7 (13.5%)	2 (15.4%)	1.00
Definitive therapy [b]			
Carbapenems	29 (55.8%)	7 (70.0%)	0.63
Piperacillin/tazobactam	8 (15.4%)	1 (10.0%)	1.00
Inappropriate empirical therapy	19 (36.5%)	6 (46.2%)	0.75
Inappropriate definitive therapy [b]	2 (3.9%)	1 (10.0%)	0.98

[a] Chi-square test.

[b] Three patients died before definitive therapy.

Alb: albumin, CRP: C-reactive protein, ESBL-PE: extended-spectrum beta-lactamase producing Enterobacteriaceae

Table 6. Multivariate analysis of predictors associated with hospital mortality of ESBL-PE bacteremia

Predictor	OR (95% CI)	p-value
Hematological malignancy	ND	ND
Immunosuppressive drug or corticosteroid use	ND	ND
Sepsis	4.08 (1.02–16.4)	0.047
Febrile neutropenia	7.52 (1.70–33.1)	0.008

CI: confidence interval, ESBL-PE: extended-spectrum beta-lactamase-producing Enterobacteriaceae, ND: not detected, OR: odds ratio