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ORIGINAL ARTICLE

Clinical manifestations and prognostic factors in cancer patients with bacteremia due to extended-spectrum β-lactamase-producing *Escherichia coli* or *Klebsiella pneumoniae*

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KEYWORDS
Bacteremia;
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Prognostic factor

Background: Clinical information about bacteremia due to extended-spectrum β-lactamase (ESBL)-producing pathogens in cancer patients was limited. The study was aimed to identify the clinical manifestations and risk factors for mortality in ESBL-producer bacteremia in cancer patients.
Methods: A retrospective study of bacteremia caused by ESBL-producing *Escherichia coli* or *Klebsiella pneumoniae* in adults with cancer in National Cheng Kung University Hospital and National Taiwan University Hospital from July 2002 to August 2007 was conducted. Clinical characteristics, initial manifestations, and antimicrobial therapy were analyzed for their association with crude mortality at 14 days after bacteremia onset.
Results: A total 113 episodes of bacteremia caused by *E coli* (59.3%), *K pneumoniae* (39.8%) or both (0.9%) were included. Patients with hematological malignancy were younger (55 ± 22 *vs.* 69 ± 14 years, $p < 0.003$) and had less co-morbidity, but were more likely to have neutropenia (73.1% *vs.* 4.6%, $p < 0.001$) than those with solid tumor. By the univariate analysis in 113

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episodes of ESBL-producer bacteremia, several risk factors, including pneumonia or soft-tissue infection as the bacteremia source, initial manifestations with high Pitt bacteremia scores, shock, respiratory failure or severe sepsis, and inappropriate definitive therapy were associated with 14-day crude mortality. By multivariate analysis, only pneumonia [adjusted odds ratio (AOR), 5.2; 95% confident interval (CI), 1.3—21.0; $p = 0.021$], severe sepsis (AOR, 24.3; 95% CI, 5.6—105.0; $p < 0.001$), and inappropriate definitive therapy (AOR, 11.3; 95% CI, 1.7—72.8; $p = 0.011$) were independently associated with a fatal outcome.

Conclusion: The presence of neutropenia or underlying hematological malignancy in cancer patients with ESBL-producer bacteremia was not associated with an increase in the mortality rate. Appropriate definitive antimicrobial therapy will be beneficial in improving clinical outcome.

Introduction

Although many potent and broad-spectrum antibiotics had been marketed in the past decades, bacterial infections still caused substantial mortality and morbidity among cancer patients with or without neutropenia. This may be related to more immunosuppressant medications and aggressive diagnostic or therapeutic tools in clinical management of various cancers. Gram-positive bacteria were predominant causative pathogens of bloodstream infections in cancer patients in western countries,[1] but Gram-negative bacilli could cause severe sepsis and mortality. Enterobacteriaceae, especially *Escherichia coli* and *Klebsiella pneumoniae*, remain the prevalent causes of bacterial infections in cancer patients.[2—5] Extended-spectrum β-lactamase (ESBL)-producing pathogens were considered to be related to a poor outcome.[6] The recognized risk factors for acquisition of ESBL-producing pathogens included previous antibiotics use, longer hospital stay, and intravascular devices, which were also characteristic in cancer patients.[7—9] Besides, the trend of increasing ESBL-producer bacteremia has been a great concern due to increasing medical expenditure and mortality.[6] Variable severity and outcome were observed in individuals with ESBL-producer bacteremia. There were few studies discussing in ESBL-producing bacteremia in cancer patients so far.[10,11] We are intended to identify clinical features and risk factors for the mortality in cancer patients with ESBL-producer bacteremia.

Methods

The retrospective cohort study was conducted at National Cheng Kung University Hospital and National Taiwan University Hospital in Taiwan, two medical centers with 1,100 and 2,000 beds, respectively. The study period was May 2002 through August 2007. All eligible patients were identified retrospectively through the records of clinical microbiology laboratory at both centers, where ESBL production was detected by the screening and then phenotypic confirmatory tests according to those recommended by the Clinical and Laboratory Standards Institute (CLSI).[12] Patients older than 18 years who had underlying malignancy and ESBL-producing *E coli* or *K pneumoniae* bacteremia were included. Growth of the same organism in blood cultures after at least 4 weeks from the initial bacteremia episode was considered to be a new infectious episode. The primary outcome in the study is the 14-day crude mortality rate, and crude mortality rate is defined as the rate of all death after bacteremia onset.

Data collection

Retrieved from medical chart records was clinical information, including sex, age, classification of malignancy type, clinical manifestations, co-morbidity, primary site of infection, serum biochemistry, laboratory data, antimicrobial therapy, and clinical outcome. Besides, host factors regarded as being immunosuppressive, such as systemic steroid, immunosuppressant therapy, neutropenia status, were also recorded.

Definitions

Hematological malignancies referred to the types of cancer that affect blood, bone marrow, and lymph nodes, and solid tumors were malignant tumors that develop in virtually any tissue or organ. ESBL-producer bacteremia is the bacteremic episode due to *E coli* or *K pneumoniae* with ESBL production phenotypically detected according to the CLSI criteria.[12] Breakthrough bacteremia was defined as the development of bacteremia caused by the same ESBL-producer while at least one *in vitro* active antimicrobial agent has been used for at least 5 days. Recent immunosuppressant therapy included corticosteroid use (10 mg or an equivalent dosage daily dosage) for more than 2 weeks, and chemotherapy or anti-rejected therapy within 4 weeks before bacteremia onset. Neutropenia was defined as absolute neutrophil counts less than 500/mm^3 at the bacteremia onset. Pitt bacteremia score was measured at the bacteremia onset to evaluate the severity of bacteremia.[13] Extreme body temperature (BT) indicates BT below 36°C or more than 39°C. Organ dysfunction was defined according to organ dysfunctions and/or infection model, and categorized as respiratory, cardiovascular, renal, neurologic, hepatic, or hematological failure.[14] Severe sepsis means sepsis associated with organ dysfunction, hypoperfusion, or hypotension which could be reversed after adequate fluid resuscitation.[15]

The date of the first positive blood culture was regarded as the date of bacteremia onset. Antibiotic therapy was considered to be appropriate, if the prescribed antibiotic was *in vitro* active against the causative organism. Antibiotic

therapy was classified as empirical or definitive therapy. The former was defined as antimicrobial agents given before the susceptibility result was available, and the latter as antimicrobial agent adjusted after the susceptibility data are available.

Statistical analysis

All statistical data were analyzed with SPSS software, version 13.0 for Windows (SPSS Inc, Chicago, IL, USA). Continuous variables were compared by Student *t* test while categorical variables were compared by χ^2 test or two-tail Fisher's exact test. The *p* values <0.05 were considered to be statistically significant. Variables considered significant in univariate analysis were the candidates included in multivariate analysis. Logistic regression analysis was used to identify the independent risk variables for mortality. The Kaplan–Meier method was used for the survival analysis.

Results

Study population

A total of 113 (32.2%) episodes of ESBL-producer bacteremia in patients with underlying malignancy were identified among 351 episodes of bacteremia due to ESBL-producing *E coli* and *K pneumoniae* during the study period. Clinical characters of 113 episodes among 110 patients were shown in Table 1. There were two major types of malignancy. Hematological malignancy included leukemia or lymphoma, and solid tumors a variety of malignancies, such as lung, colon, liver, breast, gastric, or bile duct cancer. Twenty-six (23%) episodes occurred in patients with hematological malignancy and 87 (77%) episodes solid tumors. Their mean age among them was 65 ± 18 years. Patients with hematological malignancy were younger than those with solid tumor (53 *vs.* 68 years respectively, $p = 0.003$). Neutropenia was present in 20.4% of all patients, and 82.6% occurred in patients with hematological malignancy. Although co-morbidities, including diabetes mellitus (0% *vs.* 29.9%, $p < 0.001$), chronic kidney disease (0% *vs.*18.4%, $p=0.021$), or liver cirrhosis (0% *vs.* 18.4%, $p = 0.021$), were less often noted in patients with hematological malignancy, more immunosuppressant therapy, such as chemotherapy (84.6% *vs.* 18.4%, $p < 0.001$) and steroid (30.8% *vs.* 10.3%, $p = 0.024$) was recently used in these patients. The severity of bacteremia, as indicated by severe sepsis ($p = 0.45$) or Pitt bacteremia score ($\geq$4 points, $p = 1.0$) did not vary significantly between two patient groups.

Empirical carbapenem therapy was prescribed more often to patients with hematological malignancy than those with solid tumors (53.8% *vs.* 32.2%, $p = 0.064$). Administration of appropriate empirical therapy was more frequent in patients with hematological malignancy, though the difference is not statistically significant (57.7% *vs.* 40.2%,$p = 0.123$).

Mortality and predictors of outcome

Of 113 episodes, 27 (24%) episodes died within 14 days after onset of bacteremia. The mortality rate of ESBL-producing *E coli* was 19.4% and *K pneumoniae* was 28.8% ($p = 0.26$). The primary outcome, 14-day mortality rate, of those with solid tumors, tended to be higher than that of hematological malignancy (37.6% *vs.* 11.5%, $p = 0.12$). Of 79 monomicrobial bacteremic episodes, 20 (25.3%) died within 14 days, and 7 (20.6%) of 34 polymicrobial episodes did ($p = 0.064$) (Table 2).

By the univariate analysis, factors associated with 14-day mortality among ESBL-producer bacteremia were pneumonia, urosepsis, skin and soft-tissue infection, respiratory failure, shock, extreme BT, severe sepsis, higher Pitt bacteremia score, appropriate definitive therapy, and carbapenem use (Table 2). The presence of inappropriate empirical therapy, polymicrobial bacteremia, fluoroquinolone (levofloxacin, ciprofloxacin, or lomefloxacin) resistance, had no impact on mortality. Multivariate analysis with a logistic regression model found some independent factors positively associated with mortality, including clinical presentations with severe sepsis [adjusted odds ratio (AOR), 24.3; 95% confident interval (CI), 5.6–105.0; $p < 0.001$] and pneumonia (AOR, 5.2; 95% CI, 1.3–21.0; $p = 0.021$). The receipt of appropriate definitive therapy was negatively associated with mortality (AOR, 0.1; 95% CI, 0.01–0.6; $p = 0.011$) (Table 3). The survival curve plotted by Kaplan–Meier method did not showed a survival benefit among those with appropriate versus inappropriate empirical therapy ($p = 0.93$, Fig. 1A). However, there is a higher survival rate in patients with appropriate definitive therapy than those with inappropriate definitive therapy ($p < 0.001$, Fig. 1B).

Discussion

Since human pathogens with ESBL production were identified in 1983, they had been found to distribute globally,[7] and their clinical threat was increasing emphasized due to multiple drug resistance and their adverse impact of mortality.[9,10] Specific clinical information of ESBL-producer bacteremia in cancer patients is limited.[10,11] Neutropenia and recent immunosuppressant with steroid or chemotherapy have been reported as host factors associated with increasing mortality in the cases of bacteremia,[10,11] and not surprisingly these factors or conditions were more prevalent in patients with hematological malignancy. In accordance with the finding that Gudiol et al. has demonstrated that solid tumors as underlying disease wound influence the mortality rate in ESBL-producing *E coli* bacteremia,[10] mortality rates, irrespective of sepsis-related or crude mortality rates at 14 or 30 days after bacteremia onset, there was a trend that patients with solid tumors had a worse prognosis than those with hematological malignancy. Younger age and less co-existing chronic illness in individuals with hematological malignancy were the possible reasons for such a finding. Another relevant issue is that according to IDSA guideline, more broad-spectrum β-lactam drugs would be prescribed for febrile neutropenic cancer patients,[3] and this clinical practice promoted more and early use of carbapenems. A carbapenem was used in 91% of neutropenic patients and 70% of non-neutropenic patients ($p = 0.04$), and definitive antimicrobial therapy was earlier shifted to appropriate therapy among neutropenic patients than non-neutropenic

Table 1 Clinical characters and outcome of 113 episodes of bacteremia caused by extended-spectrum β-lactamase-producing *Escherichia coli* or *Klebsiella pneumoniae* in adults with hematological malignancy or solid tumor

Characters	Case no. (%) or mean ± SD		*p*
	Solid tumor $n = 87$	Hematology malignancy $n = 26$	
Age (yr)	68.6 ± 14.2	55.4 ± 22.5	0.003
Elderly (age > 60 yr)	59 (67.8)	10 (38.5)	0.011
Male	44 (50.6)	17 (65.4)	0.262
Nosocomial infection	63 (72.4)	23 (88.5)	0.118
Co-morbidity			
Diabetes mellitus	26 (29.9)	0 (0)	<0.001
Liver cirrhosis	16 (18.4)	0 (0)	0.021
Chronic kidney disease	16 (18.4)	0 (0)	0.021
Recent chemotherapy	16 (18.4)	22 (84.6)	<0.001
Steroid use	9 (10.3)	8 (30.8)	0.024
Chronic hemodialysis	5 (5.7)	0 (0)	0.588
Neutropenia (ANC < 500)	4 (4.6)	19 (73)	<0.001
Organ transplantation	2 (2.3)	3 (10.3)	0.079
Source of bacteremia			
Pneumonia	23 (26.4)	6 (23.1)	0.804
Urosepsis	22 (25.3)	2 (7.7)	0.06
Intra-abdomen infection	18 (20.7)	0 (0)	0.012
Primary bacteremia	12 (13.8)	14 (53.8)	<0.001
Vascular catheter-related infection	11 (12.6)	3 (11.5)	1.000
Skin and soft-tissue infection	3 (3.4)	1 (3.8)	1.0
Pathogens			
Escherichia coli	49 (56.3)	18 (69.2)	0.362
Klebsiella pneumonia	37 (38.1)	8 (30.8)	
Both	1	0	
Clinical manifestations			
Shock	33 (37.9)	9 (34.6)	0.821
Extreme body temperature[a]	5 (5.7)	7 (26.9)	0.006
Respiratory failure	19 (21.8)	3 (11.5)	0.395
Renal failure	18 (20.7)	3 (11.5)	0.395
Hepatic failure	21 (24.1)	4 (15.4)	0.428
Hematological failure	17 (19.5)	18 (66.7)	<0.001
Neurological failure	8 (9.2)	1 (3.8)	0.682
Severe sepsis	25 (28.7)	5 (19.2)	0.45
Pitt bacteremia score ≥ 4	22 (25.3)	6 (23.1)	1.00
Laboratory data			
Blood leukocyte, ×1,000 cells/mm^3	10.68 ± 6.74	3.28 ± 7.14	<0.001
Blood platelet, ×1,000 cells/mm^3	158.57 ± 125.74	36.24 ± 38.65	<0.001
Serum albumin, g/dL	2.9 ± 0.68	3.12 ± 0.53	0.328
Treatment			
Appropriate empirical therapy	35 (40.2)	15 (57.7)	0.123
Empirical carbapenem	28 (32.2)	14 (53.8)	0.064
Appropriate definitive therapy	75 (86.2)	25 (96.2)	0.292
Outcome			
ESBL breakthrough bacteremia	1 (3.8)	3 (3.4)	1.000
14-day crude mortality rate	24 (27.6)	3 (11.5)	0.118
Sepsis-related mortality rate	22 (25.3)	3 (11.5)	0.182
30-day crude mortality rate	30 (34.5)	5 (19.2)	0.157

[a] Body temperature below 36°C or more than 39°C.
ANC = absolute neutrophil count; SD = standard deviation.

patients (1.9 *vs.* 2.2 days; $p = 0.025$). Therefore neutropenia, although well known for predisposing to bacterial infections in cancer patients, was commonly noted in patients with hematological malignancy, but did not result in a poor outcome.

In concordance with several published reports that mortality rate in ESBL-producing *E coli* or *K pneumoniae* bacteremia was about 16—42%,[10,11,16—19] the mortality rate in the present study was 24%. Three independent prognostic factors in our study were pneumonia as the source of

Table 2 Risk factors for 14-day crude mortality by univariate analysis of 113 episodes of bacteremia caused by extended-spectrum β-lactamase-producing *Escherichia coli* or *Klebsiella pneumoniae* in adults with cancer

	Episode number (%)			*p*
	Total, $n = 113$	Survival, $n = 86$	Fatal, $n = 27$	
Male	61 (54)	43 (50)	18 (66)	0.184
Elderly (age $>$ 60 yr)	69 (61)	51 (59)	18 (67)	0.652
Underlying cancer				
Solid tumor	87 (77)	63 (73)	24 (89)	0.118
Hematological malignancy	26 (23)	23 (27)	3 (11)	0.118
Recent chemotherapy	38 (34)	28 (33)	10 (37)	0.816
Neutropenia (ANC $<$ 500 cells/mm^3)	23 (20)	16 (19)	7 (26)	0.420
Organ transplant	5 (4)	4 (5)	1 (4)	1.000
Underlying condition other than cancer				
Diabetes mellitus	26 (23)	22 (26)	4 (15)	0.303
Recent steroid therapy	17 (15)	11 (13)	6 (22)	0.233
Liver cirrhosis	16 (14)	12 (14)	4 (15)	1.000
Chronic kidney disease	16 (14)	11 (13)	5 (19)	0.528
Hemodialysis	5 (4)	4 (5)	1 (4)	1.000
Infection site				
Pneumonia	29 (26)	15 (17)	14 (52)	0.001
Primary bacteremia	26 (23)	21 (24)	5 (19)	0.609
Urosepsis	24 (21)	22 (26)	2 (8)	0.058
Intra-abdomen infection	18 (16)	16 (19)	2 (8)	0.233
Vascular catheter-related infection	14 (12)	13 (15)	1 (4)	0.184
Skin and soft-tissue infection	4 (4)	0 (0)	4 (15)	0.003
Etiological pathogen				
Escherichia coli	67 (59)	54 (63)	13 (48)	0.262
Klebsiella pneumonia	45 (40)	32 (37)	13 (48)	
Polymicrobial infection	34 (30)	27 (31)	7 (26)	0.640
Fluoroquinolone resistance	87/106	67/81	20/25	1.000
Clinical manifestations				
Hematological failure	35 (31)	24 (28)	11(13)	0.237
Hepatic failure	25 (22)	17 (20)	8 (30)	0.296
Renal failure	23 (20)	17 (20)	4 (15)	0.778
Respiratory failure	21 (19)	12 (14)	9 (33)	0.044
Neurological failure	9 (8)	5 (6)	4 (15)	0.214
Severe sepsis	30 (27)	11 (13)	19 (70)	$<$0.001
Shock	42 (37)	23 (27)	19 (70)	$<$0.001
Extreme body temperature	12 (11)	12 (14)	0 (0)	0.067
Pitt bacteremia score $\geq$ 4	28 (24)	16 (19)	12 (44)	0.010
Breakthrough bacteremia	4 (4)	2 (2)	2 (7)	0.241
Antimicrobial treatment				
Appropriate empirical therapy	50 (44)	38 (44)	12 (44)	1.000
Appropriate definitive therapy	99 (88)	80 (95)	19 (70)	0.004
Empirical carbapenem use	42 (37)	33 (38)	9 (33)	0.820
Carbapenem use	83 (74)	68 (79)	15 (56)	0.024

ANC = absolute neutrophil count.

bacteremia, severe sepsis, and the use of drugs other than carbapenem as definitive therapy. The former two factors were difficult to be amendable, but the prescription of in time and appropriate antimicrobial therapy, according to the *in vitro* susceptibility results from the clinical microbiology laboratory, can improve the short-term outcome of cancer patients with ESBL-producer bacteremia. Although the emergence of fluoroquinolone resistance has been a concern as an independent prognostic factor in *E coli* and *K pneumoniae* infections,[11,20] the causative isolates in the present study exhibited a high extent of fluoroquinolone resistance (82%). However, fluoroquinolone resistance had no significant impact on mortality in the study.

As for the source of *E coli* and *K pneumonia* bacteremia, some studies revealed intra-abdominal infections heralded a poor prognosis in affected patients.[16,17] In accordance with a recently proposed score for the prediction of early death in adults with cancer and bloodstream infections which highlighted the clinical significance in presence of pulmonary infiltrates,[21] pneumonia as the potential source of bacteremia, especially the presence of respiratory failure, independently signified a grave outcome, and may justify the

Table 3 Independent risk factors for mortality in adults with bacteremia caused by extended-spectrum β-lactamase-producing *Escherichia coli* or *Klebsiella pneumoniae*, based on multivariate analysis with logistic regression

Variables	Adjusted odds ratio	95% confident interval	*p*
Severe sepsis	24.29	5.62—104.98	<0.001
Pneumonia	5.20	1.29—20.95	0.021
Respiratory failure	3.45	0.40—29.89	0.261
Shock	2.81	0.43—18.42	0.280
Pitt bacteremia score ≥ 4	2.63	0.47—14.64	0.269
Appropriate empirical therapy	0.345	0.06—2.03	0.239
Appropriate definitive therapy	0.089	0.01—0.58	0.011

Variables with a p value < 0.05 in the univariate analysis, as well as the variables presumably to influence the mortality, i.e. appropriate empirical therapy, neutropenia, or hematological malignancy, were the candidates for multivariate analysis.

early use of carbapenems for the life-threatening infections caused by ESBL-producing *Enterobacteriaceae*.

Many studies evaluated the role of appropriateness antimicrobial therapy in the outcome analysis and emphasized the importance of appropriate empirical therapy.[5,16,17] However, our study noted that initial inappropriate therapy was not related to a grave outcome when compared with initial appropriate therapy. However, it is important to adjust antimicrobial therapy according to susceptibility results, as echoed in two studies.[10,17] Appropriate definitive therapy for ESBL-producer bacteremia would be beneficial, as evidenced in the present study.

In summary, the presence of neutropenia or the underlying hematological malignancy in cancer patients with ESBL-producer bacteremia was not significantly associated with an increase in the mortality rate. Appropriate definitive antimicrobial therapy will be beneficial in improving clinical outcome.

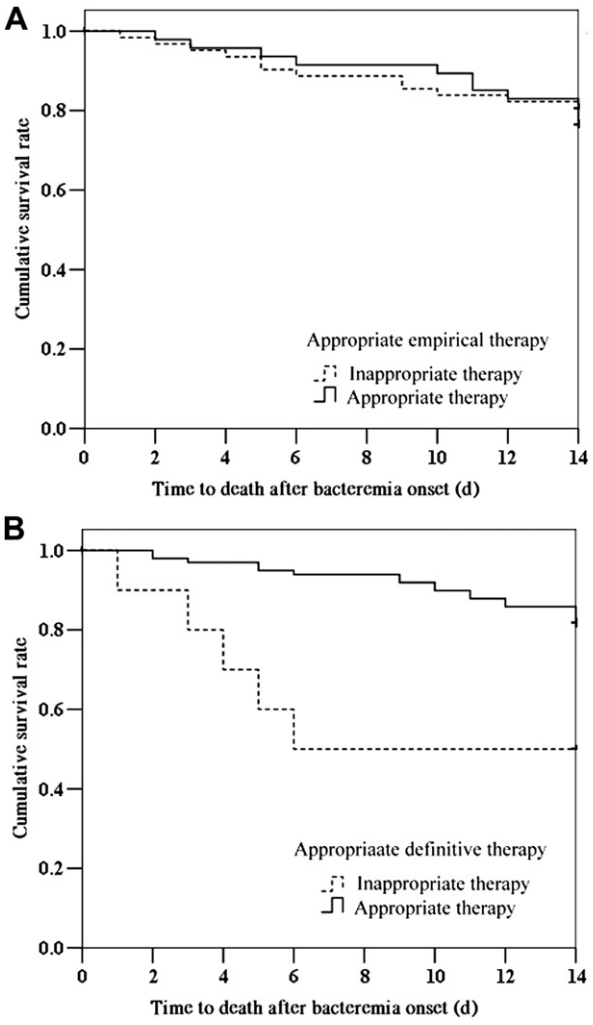

Figure 1. Impact of appropriateness of empirical and definitive antibiotics on 14-day survival rates analyzed by the Kaplan—Meier method. (A) Appropriateness of empirical antimicrobial therapy had no impact on 14-day outcome ($p = 0.93$). (B) Inappropriate definitive therapy led to higher mortality rate than appropriate definitive therapy ($p < 0.001$).

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