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Original Article

Clinical characteristics and outcomes of non-cystic fibrosis patients with *Burkholderia cepacia* complex bacteremia at a medical center in Taiwan

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Abstract *Background: Burkholderia cepacia complex* (*BCC*) represents a group of multidrug-resistant gram-negative bacteria that cause infections among immunocompromised hosts. Bacteremia occurs in patients who are chronically ill and is associated with substantial morbidity and mortality. The aim of this study was to investigate the clinical characteristics and outcomes of *BCC* bacteremic patients without cystic fibrosis.
Methods: We conducted a retrospective study at the National Taiwan University Hospital. Adults with *BCC* bacteremia from January 2015 to May 2019 were enrolled. The primary outcome was 14-day mortality. Multivariable logistic regression was performed for outcome analysis.
Results: One-hundred and ninety-five patients were analyzed and their mean age was 67 years. Over 95% of the *BCC* isolates were susceptible to trimethoprim/sulfomethoxazole (TMP/SXT). Levofloxacin resistance rates were high, with only 25.1% of isolates being susceptible. Pairwise comparisons were made between different definitive regimens including meropenem-monotherapy, ceftazidime-monotherapy, levofloxacin-monotherapy, TMP/SXT-monotherapy, tigecycline-monotherapy as well as combination versus monotherapy. No regimen was significantly associated with survival in our study. Multivariable logistic regression showed that the Pitt bacteremia score (adjust odds ratio [aOR],1.46; 95% confidence interval [CI],1.19–1.79; $p < 0.001$), underlying metastatic cancer (aOR, 2.73; 95% CI, 1.01–7.39; $p = 0.047$), inappropriate definitive treatment independently predicted greater 14-day mortality (aOR, 8.21; 95% CI, 2.49–27.08; $p < 0.001$).

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Conclusions: No single regimen is associated with improved mortality. After adjusting for other potential confounders, our data suggest selection of an appropriate antibiotic provide better clinical outcomes among patients with *BCC* bacteremia.

Introduction

Burkholderia cepacia complex (*BCC*) is a group of catalase producing, non-lactose fermenting gram-negative bacteria consisting of many species.[1,2] They are routinely isolated from the natural environment and usually have low virulence.[3] They are among the most important pathogens in patients afflicted with cystic fibrosis (CF). Among CF-patients, those with *BCC* pulmonary infection appear to have more rapidly deteriorating lung function and decreasing body weight.[4] In addition, *BCC* can also cause fatal infections in other vulnerable populations who do not have CF and lead to substantial mortality.[1,5,6] Invasive pneumonia and septic shock caused by *BCC* have been reported in seemingly immunocompetent hosts.[7] Notably, *Cepacia* syndrome is a fatal and rare combination of rapid respiratory decline with significant radiological changes, multi- organ failure and bacteremia with *B. cepacia*.[3,8,9] According to a large cohort study with a 17-year follow-up period conducted in the United States, most *BCC* bacteremia cases were hospital-acquired.[10] According to prior studies,[11,12] indwelling central lines, presence of renal failure on hemodialysis, multiple bronchoscopic procedures, and recent abdominal surgery are independently associated with the development of *BCC* bacteremia. *BCC* can also spread person-to-person via contact transmission and cause nosocomial outbreaks.[1,11,13–17,19,21–24]

The in-hospital mortality of *BCC* bacteremia is high,[6,10] and presence of underlying malignancies, elderly, high Pitt score,[10] species other than *Burkholderia cenocepacia* and *B. cepacia*,[6] high SOFA (The Sequential Organ Failure Assessment) score, and inappropriate initial empirical antibiotic therapy were identified to be independent risk factors for mortality.[6,18,19]

According to prior studies, significant resistance has been observed.[2,6,10,19] Although the antimicrobial susceptibilities appear to be geographically variable over time, the clinical *BCC* isolates were usually resistant to most antibiotics except ceftazidime, meropenem, and levofloxacin. This antimicrobial resistance profile results in substantial difficulty for treatment, which in turns contributes to mortality.[20] The research on the optimal regimen for *BCC* is still lacking.[21,22]

Therefore, the aim of this study is to explore the epidemiology of the clinical characteristics, susceptibility pattern of the isolates of *BCC*, and outcomes. We hope to provide additional experience of *BCC* bacteremia from a medical center in Taiwan. To our knowledge, this is the largest case number study of BCC bacteremia in Taiwan.[6,19,23] Secondly, we aimed to explore that whether a selected antimicrobial regimen or combination regimen can improve survival. Lastly, we would like to look at the risk factors for mortality in *BCC* bacteremic patients and explore the potential intervention to improve the outcome of *BCC* bacteremia patients.

Method

This is a retrospective study conducted at the National Taiwan University Hospital (NTUH), a 2500-bed tertiary-care center in northern Taiwan. The list of patients with blood cultures (Bactec 9240 system, Becton, Dickinson Diagnostic Instrument Systems, Sparks, MD, USA) positive for *BCC* from January 2015 to May 2019 were retrieved from the computerized database of the bacteriology laboratory at NTUH. If a patient had multiple positive blood cultures of BCC, we only count the first episode into analysis in this study.

Patients younger than 18 years were excluded

Blood culture results were obtained from the clinical microbiology laboratory. *BCC* were identified using the Vitek 2 system (bioMerieux, Vitek, Hazelwood,MO, USA) on year 2015—2016, and using MALDI-TOF MS analysis after year 2017.The antimicrobial susceptibility testing was performed using Vitek 2. The MIC breakpoints were based on Clinical and Laboratory Standards Institute's (CLSI) criteria of interpretation.[24]

We obtained the baseline characteristics of patients from the electric medical records. The demographic data, comorbidities, clinical presentations and antimicrobial treatment were recorded. All of our data were ascertained via electronic medical record by manual chart review for each patient. Importantly, ascertainment of dichotomous outcome variables such as 14-day mortality, 30-day mortality, and in-hospital mortality were obtained. Most of the exposure variables are time-fixed variables. And those covariates that are time-varying variables are counted as time-fixed (collected at baseline).

Definitions

The definitions of the underlying diseases were applied according to the comorbid conditions of the Charlson comorbidity index.[25] In brief, the cardiovascular diseases included myocardial infarction, congestive heart failure and peripheral vascular disease. The neurological diseases included cerebrovascular disease, dementia, and hemiplegia. The respiratory diseases included chronic pulmonary diseases (such as chronic obstructive pulmonary disease,

chronic asthma, and pneumoconiosis). The hepatobiliary disease was defined as chronic hepatitis (such as chronic viral hepatitis with persistent or intermittent elevation in serum aminotransferase for >6 months) with or without portal hypertension. The renal diseases included end-stage renal disease and moderate-to-severe renal disease with reduced glomerular filtration rate or kidney damage (<60 ml/min/1.73 m^2 of BSA) for >3 months. Metastatic cancer is cancer that spreads from its site of origin to another part of the body. In our BCC cohort, there is a total of 31 metastatic cancers, the primary sites include: lung cancer (8), colon cancer (2), prostate cancer (2), hepatocellular carcinoma (1), esophageal cancer (2), bladder cancer (1), pancreas cancer (1), head and neck cancers (2), breast cancer (2), urothelial carcinoma (1), thymoma/thymic carcinoma (2), thyroid cancer (1), plasmablastic leukemia (1), diffuse large B cell lymphoma (1), adrenocortical carcinoma (1), uterine sarcoma (1), leiomyosarcoma (1), pancreatic neuroendocrine tumor (1).

The definition of immunosuppression is the presence of active malignancy, organ transplant, or receipt of immunosuppressive therapy.[10] And a patient is considered to have received 'immunosuppressive agent' if he received prednisolone 10 mg/day or its equivalent or greater dose, B-cell–depleting agents, tumor necrosis factor α inhibitors, tyrosine kinase inhibitors, or other cytokine inhibitors within 90 days prior to the onset of bacteremia[10] (based on the admission note of electronic medical record). Of note, we consider a patient to have received steroid if he has received prednisolone 10 mg/d or its equivalent or greater dose (methylprednisolone, hydrocortisone, dexamethasone, betamethasone, cortisone) for a duration of at least 72 h.

Pitt bacteremia score and qSOFA (quick Sequential Organ Failure Assessment) score were used to access the bacteremia severity.

The term CABSI, as is used in our study, is interchangeable with CLABSI (central line associated blood stream infection).[26] CLABSI was defined as one of the following in a patient with central line catheter: (1) at least one set of positive blood culture of *BCC*. Together with clinical symptoms/signs (i.e., fever >38 °C, chills, or hypotension). (2) at least two sets of positive blood cultures of *BCC* detected. Repeated positive blood cultures with *BCC* were considered a single episode of CLABSI if the two sets of blood cultures were obtained within 1 week (for bacterial pathogens).[27]

CRBSI is defined as those with clinical signs of infection and the same microorganism grown from at least one percutaneous blood culture and from a culture of the catheter tip (>15 colony-forming units), or a growth of microbes from blood sample drawn from a catheter hub at least 2 h before microbial growth was detected in a blood sample obtained from a peripheral vein.[27]

Persistent bacteremia is defined as at least two positive blood cultures of *BCC* obtained on different calendar days during the same infectious episode.[28] Polymicrobial bacteremia is defined as identification of any bacteria (other than *BCC*) from blood stream within the period starting from 72 h before the onset of *BCC* bacteremia until 72 h after the onset of *BCC* bacteremia. The other bacteria that were isolated and identified from the same specimen include Stenotrophonas maltophilia, Acinetobacter baumanii, *Elizabethkingia meningosepticum*, *Ralstonia mannitolilytica*, MRSA, *Enterococcus faecium*, *Klebsiella pneumoniae* (MDR), *Staphylococcus lugdunensis*, *Bacteroides fragilis*, *Chryseobacterium indologenes*, *Pseudomonas aeruginosa*, *Enterococcus gallinarum*, and *Enterobacter cloacae* complex.

Appropriate treatment was defined as use of any antimicrobial agent that demonstrated *in vitro* susceptibility against the isolated *BCC*. Empiric treatment was defined as the antimicrobial treatment before the results of the blood culture were available. Definitive treatment was defined as the antimicrobial treatment after the results of the blood culture were available. The definitive treatment was classified into fluoroquinolone (levofloxacin)-monotherapy, ceftazidime-based monotherapy, meropenem-monotherapy, trimethoprim/sulfomethoxazole (TMP/SXT)-monotherapy, tigecycline-monotherapy, other monotherapy and combination therapy. TMP/SMX monotherapy is TMP/SMX alone. The combination treatment was defined as receiving greater than or equal to 2 classes of antimicrobials within 7 days of the onset of *BCC* bacteremia and has a duration of combined use for at least 48 h. If the monotherapy or combination agents are not active agents, they will be classified into final inappropriate regimens. The primary outcome is 14-days mortality since onset of *BCC* bacteremia. The secondary outcomes were 30-day mortality and overall in-hospital mortality.

Ethics declaration

This study has been approved by the Institutional Review Board (Ethics Committee) of NTUH (IRB No. 202012286 RIND).

Statistical analysis

Categorical variables were expressed as numbers and percentages, were compared using the chi-square test or Fisher exact test. Continuous variables were expressed as means (standard deviations), and were compared between groups using the Student's *t*-test. All analyses were set at a 2-tailed significance level of 0.05. Logistic regression was used for outcome analysis. Variables included patient's baseline demographic, clinical characteristics, underlying diseases, infection focus, immunosuppression status, severity of bacteremia, and antimicrobial regimens. Those variables with $p \leq 0.1$ were included into multivariable analysis. For multivariable regression, we used stepwise, backward, minimizing Akaike's information criteria (AIC) method.[29] Following the stepwise AIC selection, only variables with a p value of ≤ 0.05 were considered significant and were retained in the final model. Cox proportional hazards models and Kaplan–Meier survival curve analysis were further utilized for survival analysis. All statistics were conducted by Stata software (version 14; StataCorp, College Station, Texas, U.S.A).

Table 1 Baseline demographic and clinical characteristics of patients with Burkholderia cepacian complex bacteremia, divided by 14-day mortality.

	Total (N = 195)	14-day Survivor (N = 154)	14-day Non-Survivor (N = 41)	p
Age, mean (sd)	67.27 (16.14)	67.55 (15.76)	66.24 (17.64)	0.65
Men, n (%)	112 (57.4%)	89 (57.8%)	23 (56.1%)	0.85
BMI, mean (sd)	23.00 (5.06)	23.09 (5.34)	22.71 (4.05)	0.70
Underlying disease				
Cardiovascular disease	92(47.2%)	74(48.1%)	18 (43.9%)	0.64
Pulmonary disease	92 (47.2%)	72 (46.8%)	20 (48.8%)	0.82
Stroke	20 (10.3%)	18 (11.7%)	2 (4.9%)	0.20
Cirrhosis	10 (5.1%)	9 (5.8%)	1 (2.4%)	0.38
DM	59 (30.3%)	46 (29.9%)	13 (31.7%)	0.82
Autoimmune disease	28 (14.4%)	20 (13.0%)	8 (19.5%)	0.29
RRT	31 (15.9%)	26 (16.9%)	5 (12.2%)	0.47
SOT	10 (5.1%)	8 (5.2%)	2 (4.9%)	0.94
Solid tumor	56 (28.7%)	41 (26.6%)	15 (36.6%)	0.21
Metastatic cancer	31 (15.9%)	21 (13.6%)	10 (24.4%)	0.09
HIV infection	1 (0.5%)	1 (0.7%)	0 (0%)	0.61
Immunosuppression	151 (77.4%)	115 (74.7%)	36 (87.8%)	0.074
Type of Infection				
CLABSI	161 (82.6%)	127 (82.5%)	34 (82.9%)	0.95
Pneumonia	134 (68.7%)	106 (68.8%)	28 (68.3%)	0.95
Clinical Parameters				
ICU-onset	150 (76.9%)	116 (75.3%)	34 (82.9%)	0.31
Pitt score	5.28 (2.11)	4.98 (1.94)	6.50 (2.34)	<0.001
qSOFA	1.55 (0.83)	1.47 (0.81)	1.89 (0.85)	0.006
persistent bacteremia	65 (33.3%)	53 (34.4%)	12 (29.3%)	0.53
polymicrobial bacteremia	30 (15.5%)	24 (15.7%)	6 (14.6%)	0.87
C-Reactive Protein (mg/dL)	9.19 (7.24)	8.46 (6.81)	12.02 (8.23)	0.01
Treatment				
Inappropriate definitive Abx	18 (9.2%)	8 (5.2%)	10 (24.4%)	<0.001
Monotherapy	12 (66.7%)	4 (50%)	8 (80%)	0.32
No therapy	6 (33.3%)	4 (50%)	2 (20%)	0.32
Appropriate definitive therapy	177 (90.8%)	146 (94.8%)	31 (75.6%)	<0.001
Monotherapy	111	92 (63.0%)	19 (61.3%)	0.86
FQ-monotherapy	11 (5.6%)	8 (5.2%)	3 (7.3%)	0.60
TMP/SXT-monotherapy	9 (4.6%)	8 (5.2%)	1 (2.4%)	0.46
CAZ-monotherapy	35 (18.0%)	29 (18.8%)	6 (14.6%)	0.53
MEM-monotherapy	57 (29.2%)	44 (28.6%)	13 (31.7%)	0.70
TGC-monotherapy	2 (1.0%)	1 (0.7%)	1 (2.4%)	0.31
Other monotherapy	9 (4.6%)	6 (3.9%)	3 (7.3%)	0.35
Combination	66 (34.6%)	54 (35.5%)	12 (30.8%)	0.58
Dual combination	39 (20%)	31 (20.1%)	8 (19.5%)	0.93
Triple combination	23 (11.8%)	19 (12.3%)	4 (9.8%)	0.65
Quadruple combination	4 (2.1%)	4 (2.6%)	0 (0%)	0.30

Abbreviations: Abx = antibiotic, BMI = body mass index, CABSI = catheter-associated blood stream infection. CLABSI = central-line associated blood stream infection, CAZ = ceftazidime, DM = diabetes mellitus, FQ = fluoroquinolone, ICU = intensive care unit, MEM = meropenem, qSOFA = Quick Sequential Organ Failure Assessment, RRT = renal replacement therapy, SOT = solid organ transplant, TGC = tigecycline, TMP/SXT = trimethoprim/sulfamethoxazole.

Results

Clinical characteristics of patients with bacteremia due to BCC

During the study period, a total of 195 BCC bacteremic patients were identified (Table 1). The mean (SD) age was 67.27 (16.14), and 112 (57.4%) were male. The mean (SD) Pitt bacteremia score was 5.28 (2.11). Of the included *BCC* strains, 187 (95.9%) were susceptible to TMP/SXT, 49 (25.1%) to fluoroquinolones (FQs), 147 (75.4%) to meropenem, and 145 (74.4%) to ceftazidime. Overall, the proportion of patients who received FQ-monotherapy, TMP-SXT-monotherapy, ceftazidime-monotherapy, meropenem-

monotherapy, and tigecycline-monotherapy are 18%, 6.7%, 25.1%, 36.9%, and 5.1%.

The outcome variable 14-day mortality was counted from the date of first positive blood culture reported. There were 41 deaths (21%) at Day 14 (primary outcome). The overall in-hospital mortality in our cohort is 47.69% (93/195) and the median length of stay is 66 days (interquartile range; IQR, 38–117 days).

The majority of *BCC* bacteremic episodes of our study were ICU-onset (74.79%). Most of our patients with *BCC* bacteremia were hospital-acquired (94.12%), only 5.88% were non-hospital-acquired, including community and healthcare-associated infections. We did not collect the source of our study populations, that is whether they are nursing home residents or long-term care residents. Furthermore, among the 161 episodes of CLABSI in our *BCC* cohort, there is a total of 25 BCC bacteremic episodes which met the IDSA definition for CRBSI. Of note, there were substantial concurrent infections with pneumonia and CLABSI caused by BCC (n = 116) in our cohort (59.5%). Among pneumonia cases, BCC species were isolated from the respiratory specimens.

Ultimately, 177 (90.77%) versus 18 (9.23%) patients received appropriate versus inappropriate definitive therapy. The 14-day mortality for appropriate therapy versus inappropriate therapy are 17.51% versus 55.56% respectively ($p < 0.001$). There were only 18 patients who received inappropriate therapy. Of these 18 patients who had inappropriate antibiotics, 12 received monotherapy while 6 patients did not receive any antimicrobial therapy at that time.The antibiotics used in the inappropriate therapy group includes ceftazidime (n = 1), cefepime (2), piperacillin-tazobactam (2), imipenem (2), meropenem (3), colistin (2). Of the 177 patients who had final appropriate antibiotics, 111 patients received monotherapy and 66 patients received combination regimens. The latter can be further categorized into dual combination therapy (n = 39), triple combination therapy (23), and quadruple combination therapy (4). The characteristics of 14-day survivors and 14-day non-survivors were shown in Table 1.

In addition, there is no statistically significant 14-day mortality (18.46% versus 22.31%, p = 0.53), 30-day mortality (36.92% versus 34.62%, p = 0.75), and all-cause mortality differences (52.31% versus 45.38%, p = 0.36) when comparing the persistent bacteremia group versus the non-persistent bacteremic group. However, disease severity on presentation (such as Pitt score and qSOFA), C-reactive protein level, and final adequate antibiotic therapy were significantly different between the two groups. Compared with those who survived at Day 14, those who died at Day 14 had higher Pitt scores (6.50 [2.34] versus 4.98 [1.94], $p < 0.001$), higher qSOFA scores (1.89 [0.85] versus 1.47 [0.81], p = 0.006), higher C-reactive protein levels (12.02 [8.23] versus 8.46 [6.81], p = 0.01), and a greater proportion of final inappropriate definitive antibiotics (24.4% versus 5.2%, $p < 0.001$) (Table 1).

Antimicrobial susceptibilities of the isolates

The distribution of the four *BCC*-active antimicrobials among the 195 isolates of *BCC* and susceptibility categories (susceptible versus non-susceptible) of the *BCC* isolates as stratified by the survivor status at Day 14 are shown in Table 2. Overall, TMP/SXT appears to be the most active antibiotic with 95.9% of the 195 BCC isolates being susceptible *in vitro*, followed by meropenem and ceftazidime (75.4% and 74.4% susceptibility respectively). Levofloxacin was found to be less active against the isolates in our study, with only 25.1% of isolates being susceptible.

Independent risk factor for 14-day mortality

Univariable analysis showed that final inappropriate treatment (odds ratio [OR], 5.89; 95% confidence interval [CI], 2.15–16.12, $p < 0.001$), C-reactive protein (OR, 1.06; 95% CI, 1.01–1.12, p = 0.01), and Pitt bacteremia score (OR, 1.46; 95% CI, 1.19–1.79, $p < 0.001$) were associated with greater rate of 14-day mortality (Table 3). We compared pairs of different definitive regimens: meropenem-monotherapy, ceftazidime-monotherapy, tige cycline-monotherapy, levofloxacin-monotherapy, TMP/SXT-monotherapy, as well as combination versus monotherapy. No single regimen was significantly associated with improved survival in our study.

Multivariable logistic regression confirmed that the Pitt bacteremia score (adjusted OR [aOR], 1.46; 95% CI, 1.18–1.80, p = 0.001), underlying metastatic cancer (aOR, 2.73; 95% CI, 1.01–7.39, p = 0.047), inappropriate definitive treatment predicted greater 14-day mortality (aOR, 8.21; 95% CI, 2.49–27.08, p = 0.001). There were only 24 patients (12.3%) who had delayed removal of catheter (i.e. ≥3 days after onset of bacteremia). Among those who had delayed removal catheters (i.e. >3 days after onset of *BCC* bacteremia), inappropriate antibiotic therapy perfectly predicts 14-day mortality. After accounting for all the other confounding factors (including delayed catheter removal),

Table 2 Susceptibilities Distribution stratified by survival status at 14 days.

	Total (N = 195)		14-day Survivor (N = 154)		14-day Non-Survivor (N = 41)		P
	S	NS	S	NS	S	NS	
Ceftazidime	74.4%	25.6%	74%	26%	75.6%	24.4%	0.84
Levofloxacin	25.1%	74.9%	25.3%	74.7%	24.4%	75.6%	0.90
Meropenem	75.4%	24.6%	76.0%	24%	73.2%	26.8%	0.71
Trimethoprim/sulfamethoxazole	95.9%	4.1%	96.8%	3.2%	92.7%	7.3%	0.24

Abbreviations: NS = non-susceptible; S = susceptible.

inappropriate antibiotic is still a significant risk factor for 14-day mortality (aOR, 276.8; 95% CI, 4.54—16867.9, p = 0.007). Cox regression and survival curve analysis similarly confirmed that disease severity (indicated by Pitt bacteremia score), inappropriate definite treatment predicted rapid mortality (adjust hazard ratio [aHR], 4.32; 95% CI, 1.92—9.69, p < 0.001) (Fig. 1).

In the secondary outcomes, overall mortality rate was 47.7%, and 30-day mortality rate was 35.4% (Supplementary Table 1). Similar risk factors are also associated with 30-day mortality. Pitt bacteremia score (aOR, 1.41; 95% CI, 1.18—1.69; p < 0.001) and inappropriate definite treatment independently predicted 30-days mortality (aOR, 3.22; 95% CI, 1.19—8.75, p = 0.02) Remarkably, immunosuppression predicts 30-day mortality (Supplementary Table 2). However, inappropriate definite treatment didn't predict in-hospital mortality (aOR, 1.59; 95% CI, 0.49—5.23; p = 0.44) independent to Pitt bacteremia score (aOR, 1.32; 95% CI, 1.09—1.60; p = 0.005), and metastatic cancer (aOR, 2.84; 95% CI, 1.10—7.35; p = 0.03).

Table 3 Multivariable logistic regression analysis of prognostic factors associated with 14-day mortality in patients with *Burkholderia cepacia* complex (BCC) bacteremia.

	Univariable analysis			Multivariable analysis		
	OR	95% CI	p	aOR	95% CI	p
Age, per 1-year increase	1.00	0.97—1.02	0.65			
Men	0.93	0.47—1.87	0.85			
BMI	0.98	0.91—1.06	0.70			
Underlying diseases						
Cardiovascular disease	0.85	0.42—1.69	0.64			
Pulmonary disease	1.08	0.54—2.16	0.82			
Stroke	0.39	0.09—1.74	0.22			
Cirrhosis	0.40	0.05—3.27	0.40			
DM	1.09	0.52—2.29	0.82			
Autoimmune disease	1.62	0.66—4.01	0.29			
Renal replacement therapy	0.68	0.25—1.91	0.47			
Solid organ transplant	0.94	0.19—4.59	0.94			
Solid tumor	1.59	0.77—3.30	0.21			
Metastatic cancer	2.04	0.87—4.77	0.10	2.73	1.01—7.39	0.047
Immunosuppression	2.44	0.90—6.66	0.08			
Type of Infection						
CLABSI	1.03	0.41—2.57	0.95			
Pneumonia	0.98	0.46—2.05	0.95			
Clinical Parameters						
ICU-onset	1.59	0.65—3.88	0.31			
Pitt score	1.46	1.19—1.79	<0.001	1.46	1.18—1.80	<0.001
qSOFA	1.89	1.19—3.02	0.007			
Persistent bacteremia	0.79	0.37—1.67	0.54			
Polymicrobial bacteremia	0.92	0.35—2.43	0.87			
C-Reactive Protein (mg/dL)	1.06	1.01—1.12	0.01			
Treatment						
Inappropriate definitive Abx	5.89	2.15—16.12	0.001	8.21	2.49—27.08	0.001
Monotherapy	1.27	0.59—2.70	0.54			
FQ-monotherapy	1.44	0.36—5.69	0.60			
TMP/SXT-monotherapy	0.46	0.06—3.76	0.47			
CAZ-monotherapy	0.74	0.28—1.92	0.54			
MEM-monotherapy	1.16	0.55—2.44	0.70			
TGC-monotherapy	3.83	0.23—62.50	0.35			
Other monotherapy	1.95	0.47—8.15	0.36			
Combination	0.81	0.38—1.72	0.58			
Dual combination	0.96	0.40—2.29	0.93			
Triple combination	0.77	0.25—2.40	0.65			
Quadruple combination	NA[a]	NA[a]	NA[a]			
No therapy	1.92	0.34—10.89	0.46			

Abbreviations: Abx = antibiotic, BMI = body mass index, CABSI = catheter-associated blood stream infection. CLABSI = central-line associated blood stream infection, CAZ = ceftazidime, DM = diabetes mellitus, FQ = fluoroquinolone, ICU = intensive care unit, MEM = meropenem, NA = not applicable, qSOFA = Quick Sequential Organ Failure Assessment, RRT = renal replacement therapy, SOT = solid organ transplant, TGC = tigecycline, TMP/SXT = trimethoprim/sulfamethoxazole.
NA[a] = tigecycline-based combination predict 14-day mortality perfectly.

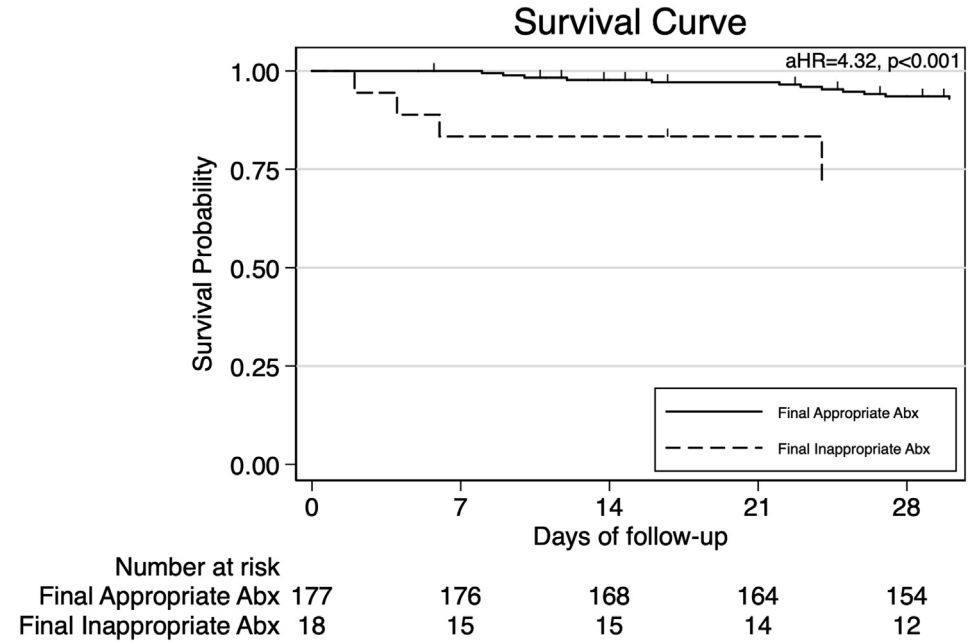

Figure 1. Survival curve by Cox regression analysis between patients finally received appropriate definite therapy and inappropriate definite therapy.

Discussion

In this study, we reviewed 195 non-cystic fibrosis patients with *BCC* bacteremia at a single institution over the last 4.4 years. Most of the *BCC* bacteremic patients in our cohort were immunocompromised and had underlying cancers. After accounting for disease severity and underlying metastatic cancer, inappropriate definitive treatment was still significantly associated with 14-day mortality. No universal regimen was associated with better outcomes following *BCC* bacteremia.

Interestingly, we found that besides Pitt bacteremia score and inappropriate definitive antibiotic, immunosuppression also independently predicts 30-day mortality. Immunosuppression, as defined in our study, is a partially modifiable risk factor as it includes the use of steroid or immunosuppressive. With a rapidly ageing population, growing number of cancer patients, and an ever increasing and liberal use of steroids and immunosuppressants, this finding not only reminds us of the increasing number of immunocompromised hosts, but also informs us on the potential role physicians have in prescribing steroids or immunosuppressants judiciously.

Prior studies have suggested that *BCC* bacteremia occurring in the non-CF patients is mostly hospital-acquired.[10,30] It usually affects patients who are chronically or severely ill or have malignancy.[6,19,23] The mortality in this group is high and significant drug resistance has been observed.[10,30] In the current study, we attempt to address some of the unresolved issues regarding *BCC* bacteremia further, such as the optimal antibiotic regimen or the potential benefits of combination regimen.

Previous studies have shown age,[10] *BCC* species other than *B.cenocepacia* and *B.cepacia*,[6] high SOFA score,[6] Pitt score[10] to be predictive of 30-day mortality. Although Chien et al. did not identify inappropriate antimicrobial to be an independent risk factor for 14-day mortality,[6] inappropriate definitive antimicrobials were associated with increased risk for 14-day mortality in their univariable regression analysis. Some possible explanation for the different results might include the differences in the study populations (their study population was more critically ill, with more resistant *BCC* isolates), the difference in methodology (Chien's group used agar dilution method while we used the Vitek 2 system to define susceptibilities), and sample size (the sample size of Chien's study was 54, which is significantly smaller than ours). Importantly, our study has identified a potentially modifiable factor, the final appropriate antimicrobial, that may influence short-term mortality of patients with *BCC* bacteremia.

Similar to the large cohort study with 17-year follow-up,[10] we also found that no single antimicrobial regimen was significantly associated with better outcomes. There were no significant differences in 14-day and 30-day mortality when comparing the monotherapy versus the combination therapy group. In fact, there appears to higher all-cause mortality when comparing the combination therapy group versus the monotherapy group (65.52% versus 40.34%, $p = 0.002$), which might be due to selection bias, as patients in the combination group were generally sicker. And combination therapy was not associated with improved outcomes. Our study results are in line with one of the largest multi-center retrospective studies conducted in South Korea which also showed that the outcome did not differ according to the type of antibiotics used.[30] The reason why no single regimen impacted the outcome might be due to the multiple comorbidities and high disease severity of the *BCC* bacteremia patients,

or the heterogeneity of the patient population and the microbial species and susceptibility patterns.

Our study has several important limitations. First, as with most observational studies, selection bias and confounding by indications are inevitable. Although we attempt to adjust for potential confounders via multivariate logistic regression models, we cannot adjust for unmeasured confounders and thus residual confounding is possible. Secondly, as with most retrospective studies, the data is less granular compared to prospective studies and randomized control trials. As mentioned before, the heterogeneity in the combination subgroup is substantial, and due to the retrospective nature of the study, it is difficult to establish causality. Thirdly, we did not perform genospecies identification, thus we cannot explore the potential causal association between genospecies and mortality. Fourth, we did not report the susceptibility results of piperacillin/tazobactam by MIC interpretative breakpoint for *P. aeruginosa*. The latest CLSI Guideline on Performance Standards for Antimicrobial Susceptibility Testing, 31st edition does not specifically include piperacillin-tazobactam for routine, selective, or supplemental reporting regarding *BCC*. Our microbiology lab did not routinely report MIC of piperacillin/tazobactam of BCC. Lastly, although some studies have reported the possible benefits for ceftazidime-avibactam in patients with *BCC* bacteremia,[31,32] we were not able to assess its potential effects on mortality outcomes as no patient received ceftazidime-avibactam.

Conclusion

Our study suggests that after controlling for other potential confounders, no single regimen appears to be significantly associated with improved survival and use of combination regimens is not associated with decreased mortality. Notably, after adjusting for all the potential confounders, including Pitt bacteremia score and metastatic cancer, appropriate definitive antimicrobial was still associated with improved short-term mortality.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2021.09.009.