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ORIGINAL RESEARCH

Clinical Characteristics of Patients Who Acquired Gram-Negative Bacteria During Ceftazidime-Avibactam Therapy

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ABSTRACT

***Introduction*:** Ceftazidime-avibactam (CZA) is recommended to treat infections caused by carbapenem-resistant *Enterobacterales* and *Pseudomonas aeruginosa* with difficult-to-treat resistance. The selective pressure of CZA results in the isolation of multidrug-resistant Gram-negative bacteria (MDR-GNB), causing superinfection or hospital-wide spread. We aimed to study the clinical characteristics of patients who acquired GNB during CZA treatment.

***Methods*:** Adult patients treated with CZA for ≥ 5 days for proven or suspected MDR-GNB were retrospectively enrolled at Taipei Veterans General Hospital between December 2019 and June 2021. GNB acquisition was defined as new GNB species resulting in infection or colonization isolated during the period from 5 days after the initiation of CZA until the end of treatment. Clinical features were compared between patients who acquired GNB from clinical specimen and those who did not. Multivariable analysis was used to explore risk factors for acquisition of GNB and 28-day mortality in patients who acquired GNB.

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Results: Among 321 patients treated with CZA, 68 GNB were identified in 55 patients (17.1%). *Elizabethkingia* species ($n=15$) was the most common GNB, followed by *Acinetobacter* species ($n=13$) and *Burkholderia cenocepacia* ($n=11$). The presence of diabetes mellitus, and mechanical ventilation were independent risk factors for GNB acquisition. There was a statistically nonsignificant trend toward increased 28-day mortality in patients with GNB acquisition compared to those without (38.2% vs. 27.8%, $P=0.105$). Cerebrovascular disease and acquired GNB resulting in infection were associated with 28-day mortality in patients who acquired GNB.
Conclusions: *Elizabethkingia* species, *Acinetobacter* species, and *B. cenocepacia* were the major GNB acquired during CZA treatment. A trend toward increased mortality was observed in patients with GNB acquisition during CZA treatment. Further studies on optimal treatments for these patients were warranted.

Keywords: Ceftazidime-avibactam; Acquisition; Multidrug-resistant organisms; Gram-negative bacteria

Key Summary Points

Why carry out this study?

The selective pressure of ceftazidime-avibactam (CZA) results in the acquisition of multidrug-resistant Gram-negative bacteria (MDR-GNB).

We studied the clinical characteristics of patients who acquired GNB during CZA treatment.

What was learned from the study?

Elizabethkingia species, Acinetobacter species, and *Burkholderia cenocepacia* were commonly acquired GNB during CZA therapy.

A trend toward increased mortality was observed in patients with GNB acquisition during CZA treatment.

INTRODUCTION

Carbapenem-resistant *Enterobacterales* (CRE) has been categorized as critical priorities, and carbapenem-resistant *Pseudomonas aeruginosa* has been listed as high priorities for future research and development of new drugs based on disease burden and the available treatment options [1]. The novel β-lactam/β-lactamase inhibitor, ceftazidime-avibactam (CZA), is recommended as the preferred option for treating infections caused by CRE and *P. aeruginosa* with difficult-to-treat resistance (DTR-*P. aeruginosa*) by international guidelines [2–4]. Avibactam is active against *Klebsiella pneumoniae* carbapenemase (KPC; Ambler Class A), and OXA-48-group carbapenemase (Ambler Class D), but not against metallo-β-lactamase (MBL) enzymes, such as VIM, IMP, and NDM (Ambler Class B). A global surveillance database demonstrated that CZA resistance rate was less than 10% among *Klebsiella pneumoniae*, *Escherichia coli*, and *P. aeruginosa* [5]. A growing body of real-world evidence has demonstrated the superior clinical efficacy of CZA in treating CRE infections, compared with traditional agents [6–12], and good in vitro activity against CRE isolates in Taiwan [13, 14]. Real-world data regarding CZA use in the treatment of DTR-*P. aeruginosa* infections are relatively rare [15, 16].

Emergence of CZA resistance has been reported at a rate of approximately 1.4–13.8% after CZA use for KPC-producing *Enterobacterales* infections in the literature [8, 10, 12, 17, 18]. *P. aeruginosa* isolates have also been reported to develop resistance to CZA during treatment [19–21]. Furthermore, a study from Greece showed that the major carbapenemase in carbapenemase-producing *Klebsiella pneumoniae* bacteremia changed from KPC to VIM after introducing CZA [22]. The selective pressure caused by CZA is alarming, given the common use of this agent in critically ill or immunocompromised patients with CRE or multidrug-resistant (MDR)/DTR-*P. aeruginosa* infections [6–10, 16, 21]. Subsequent isolation of MDR-Gram-negative bacteria (GNB) species during CZA treatment would cause superinfection or hospital-wide MDR-GNB spread. Nevertheless, clinical outcomes and risk factors associated with the acquisition of a new

GNB isolate during CZA treatment have not been reported in the literature.

The aim of this study was to describe the clinical characteristics of patients who acquired GNB during CZA therapy, focusing on risk factors for GNB acquisition during CZA therapy and patient outcomes.

METHODS

Study Design and Patient Population

This retrospective study was conducted between December 2019 and June 2021 at Taipei Veterans General Hospital, a 2900-bed tertiary-care teaching hospital in Taipei, Taiwan. Hospitalized patients aged > 20 years who received CZA for ≥ 5 days for proven or suspected MDR-GNB infection for the first time were enrolled. Patients without cultures obtained from clinical specimens during CZA therapy were excluded. The study protocol was approved by the Institutional Review Board of Taipei Veterans General Hospital, and the need for written informed consent was waived.

Proven MDR-GNB infection was defined as a clinical infection associated with clinical cultures compatible with MDR-GNB. Patients without clinical cultures compatible with MDR-GNB were categorized as having suspected MDR-GNB infection. MDR-*Enterobacterales* or *P. aeruginosa* was defined as species non-susceptibility to at least one agent in three or more antimicrobial categories [23]. The definition of DTR-*P. aeruginosa* was based on previous studies [2]. CZA was administered intravenously at a dose of 2.5 g every 8 h with a 2-h infusion, with dosage adjustments for renal impairment, as recommended by the manufacturers. GNB acquisition was defined as the isolation of new GNB resulting in infection or colonization during the period from 5 days after the starting CZA until the end of treatment, which was not isolated within 1 month prior to the initiation of CZA.

Data Collection and Definition

Electronic medical records were reviewed for age, sex, duration of hospital stay before CZA therapy, duration of CZA therapy, concomitant antibiotic, presence of underlying diseases, type of infection, severity of illness, presence of percutaneous drainage, central venous catheter use, urinary catheter use, nasogastric tube use, the isolated GNB 1 month before, during and after CZA therapy (until 7 days after the completion of CZA therapy), acquisition site, and outcomes. Concomitant antibiotic was defined as antibiotic any for Gram-positive or Gram-negative bacteria used for more than 3 days during CZA therapy before the acquisition of GNB. Patients with neutropenia, with acquired immunodeficiency syndrome, receiving steroid therapy (≥ 20 mg of prednisone or equivalent per day for ≥ 1 month), or receiving other immunosuppressive therapy within the 30 days before CZA initiation were considered to have immunocompromised status. The Acute Physiology and Chronic Health Evaluation (APACHE) II and sequential organ failure assessment (SOFA) scores at CZA treatment initiation and on the day of GNB acquisition (or day 7 of CZA therapy in patients who did not acquire GNB during CZA therapy) were calculated to determine illness severity. For patients who did not acquire GNB, we used day 7 of CZA treatment because the median time from CZA treatment initiation to GNB acquisition was 7 days in patients who acquired GNB. Source control was defined as the removal of necrotic tissue, removal of infected devices or drainage of abscess within the first 7 days of antimicrobial therapy. The outcomes were 28-day mortality rate after GNB acquisition. Regarding outcome analysis in patients who did not acquire GNB, the index day was day 7 of CZA therapy.

Bacterial Identification and Antimicrobial Susceptibility Testing

Bacterial identification was done using a VITEK 2 system (bioMérieux, Marcy-l'Étoile, France) or matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF/MS) (bioMérieux). Minimum inhibitory concentration (MIC) and antimicrobial susceptibility tests were performed using the VITEK 2 system, except for the Etest or broth microdilution, to

determine the MIC of CZA. The breakpoint was interpreted according to the Clinical and Laboratory Standards Institute (CLSI) M100-S32 Performance Standards [24].

Statistical Analyses

The chi-square or Fisher's exact test was used to analyze categorical variables. Two-tailed Student's *t* test or Mann–Whitney *U* test was used to analyze continuous variables based on the distribution of variables. A multivariable logistic regression model was used to explore risk factors for GNB acquisition during and/or 7 days after the completion of CZA treatment. Cox regression analysis was used to identify risk factors for mortality in patients who acquired GNB. All variables statistically significant in the univariate analysis were entered into the multivariable analysis. Odds ratios (ORs), hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for all variables. The results were analyzed using SPSS version 26 (SPSS, Chicago, IL, USA). All P values were two-tailed and considered statistically significant at values < 0.05.

RESULTS

During the study period, 355 patients receiving CZA therapy for ≥ 5 days during hospitalization were identified. In total, 34 patients who did not have any clinical specimens sent for culture during CZA therapy were excluded. Of the remaining 321 patients, 136 patients (42.4%) were admitted to the intensive care unit (ICU), and the overall in-hospital mortality rate was 44.9%. CZA was used for pneumonia [*n* = 158 (49.2%)], followed by bloodstream infections [*n* = 62 (19.3%)], urinary tract infection [*n* = 54 (16.8%)], intra-abdominal infections [*n* = 28 (8.7%)], skin and soft-tissue infections [*n* = 8 (2.5%)] and others [*n* = 11 (3.4%)]. CZA was used to treat 216 patients with CRE infections (mostly *K. pneumoniae*), nine patients with DTR-*P. aeruginosa* infections, and two patients with both CRE and DTR-*P. aeruginosa* infections. ten with MDR-*P. aeruginosa* infections, three with *Burkholderia cenocepacia* infections, and two with MDR-*K. pneumoniae* infections. The remaining 79 patients received CZA for suspected MDR-GNB infections. Fifty-five patients (17.1%) acquired MDR-GNB during CZA therapy, and 11 patients acquired ≥ 2 MDR-GNB species.

GNB Acquisition During CZA Therapy

A total of 68 GNB were identified in the 55 patients (Fig. 1). The median time from CZA treatment initiation to GNB acquisition was 7 days (interquartile range: 6–8 days). The most common being *Elizabethkingia* species (*n* = 15, 22.1%): *Elizabethkingia anopheles* (*n* = 11, 73.3%), *Elizabethkingia meningoseptica* (*n* = 3, 20%), and *Elizabethkingia miricola* (*n* = 1, 6.7%); followed by *Acinetobacter* species (*n* = 13, 19.1%): *A. nosocomialis* (*n* = 7, 53.8%), *A. lwoffii* (*n* = 2, 15.4%), *A. baumannii* (*n* = 2, 15.4%), *A. johnsonii* (*n* = 1, 7.7%), and *A. pittii* (*n* = 1, 7.7%); and *B. cenocepacia* (*n* = 11, 16.2%). Other identified GNB included *Serratia marcescens* (*n* = 7, 10.3%), *Stenotrophomonas maltophilia* (*n* = 6, 8.8%), *Chryseobacterium indologenes* (*n* = 5, 7.4%), *Enterobacter hormaechei* (*n* = 2, 2.9%), *Klebsiella oxytoca* (*n* = 1, 1.5%), *K. pneumoniae* (*n* = 1, 1.5%), *K. variicola* (*n* = 1, 1.5%), *Citrobacter freundii* (*n* = 1, 1.5%), *Morganella morganii* (*n* = 1, 1.5%), *P. aeruginosa* (*n* = 1, 1.5%), *Ralstonia insidiosa* (*n* = 1, 1.5%), and *R. mannitolilytica* (*n* = 2, 2.9%). The antimicrobial susceptibility test results for these organisms are shown in Supplementary Table 1. Anatomic sites for clinical cultures that enabled the growth of GNB isolates included 56 respiratory tract (sputum/bronchoalveolar lavage/pleural fluid) (82.4%), four blood (5.9%), four bile (5.9%), two ascites (2.9%), one central venous catheter (1.5%), and one wound (1.5%) specimens. We further determined available isolates for CZA MIC as shown in Supplementary Table 2. *Elizabethkingia* species, *S. maltophilia*, and *C. indologenes* were intrinsically resistant to CZA. Therefore, this GNB acquisition was predictable. However, 10 of 11 *B. cenocepacia* strains were susceptible to ceftazidime, and *P. aeruginosa* was susceptible to CZA. Among seven *Enterobacterales* strains [*S. marcescens* (three strains), *E. hormaechei, C. freundii*, *K. oxytoca*, *K. pneumoniae*]

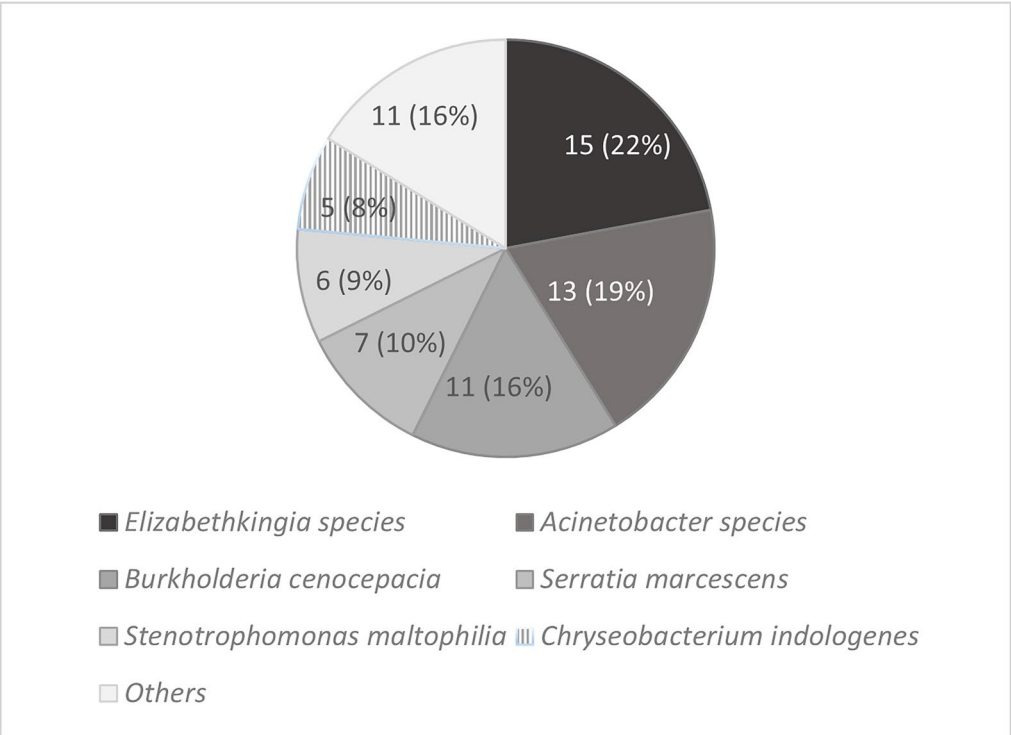

Fig. 1 Distribution of acquisition of Gram-negative bacteria during ceftazidime-avibactam therapy. The most common being *Elizabethkingia* species ($n=15$), followed by *Acinetobacter* species ($n=13$), and *Burkholderia cenocepacia* ($n=11$). Others included *Enterobacter hormaechei* ($n=2$), *Klebsiella oxytoca* ($n=1$), *K. pneumoniae* ($n=1$), *K. varicola* ($n=1$), *Citrobacter freundii* ($n=1$), *Morganella morganii* ($n=1$), *Pseudomonas aeruginosa* ($n=1$), *Ralstonia insidiosa* ($n=1$), and *R. mannitolilytica* ($n=2$)

which were available for testing CZA susceptibility, only *E. hormaechei* was susceptible to CZA.

GNB Acquisition After the Completion of CZA Therapy

During the 7 days following the discontinuation of CZA, 33 GNB were identified in 30 patients (Supplementary Table 2), including *S. maltophilia* ($n=7$, 21.2%), *Acinetobacter* species ($n=6$, 18.2%), *P. aeruginosa* ($n=4$, 12.1%), *C. indologenes* ($n=3$, 9.1%), *E. anopheles* ($n=2$, 6.1%), *Burkholderia* species ($n=2$, 6.1%), *Enterobacterales* ($n=7$, 21.2%) (two *E. cloacae*, one *E. hormaechei*, one *K. pneumoniae*, one *K. oxytoca*, one *S. marcescens*, and one *C. freundii*), *Achromobacter* species ($n=1$, 3.0%), and *R. mannitolilytica* ($n=1$, 3.0%). Among 30 patients who acquired GNB after the completion of CZA therapy, 8 patients also acquired GNB during CZA therapy. The available susceptibility results of CZA among these GNB are shown in Supplementary Table 2.

Risk Factors for Acquisition of GNB During CZA Therapy and/or After the Completion of CZA Therapy

The clinical characteristics of the patients who acquired GNB and those who did not during CZA therapy are shown in Table 1. Higher proportions of patients who acquired GNB had bloodstream infections (30.9% vs. 16.9%, $P=0.017$), had ICU admission (69.1% vs. 36.8%, $P<0.001$), had diabetes mellitus (49.1% vs. 33.5%, $P=0.028$), used central venous catheter (78.2% vs. 56.8%, $P=0.003$), used nasogastric tube (87.3% vs. 73.3%, $P=0.028$), required mechanical ventilation (83.6% vs. 40.8%,

Table 1 Demographic and clinical characteristics of patients who acquired Gram-negative bacteria and those who did not acquire Gram-negative bacteria during ceftazidime-avibactam therapy

Variable	Patients who acquired GNB ($n = 55$)	Patients who did not acquire GNB ($n = 266$)	*P* value
Age, years, median (IQR)	74 (66–83)	75 (63–88)	0.997
Male sex	34 (61.8%)	177 (66.5%)	0.502
LOS, days, median (IQR)	79 (51–117)	58 (35–108)	0.489
LOS before CZA use, days, median (IQR)	29 (14–53)	23 (10–42)	0.671
Duration of CZA use, days, median (IQR)	13 (8–16)	12 (9–15)	0.748
Type of infection			
Pneumonia	31 (56.4%)	127 (47.7%)	0.244
Bloodstream infections	17 (30.9%)	45 (16.9%)	0.017
Urinary tract infections	2 (3.6%)	52 (19.5%)	0.004
Intra-abdominal infections	4 (7.3%)	24 (9.0%)	0.675
Skin and soft-tissue infections	1 (1.8%)	7 (2.6%)	0.725
Others	0 (0%)	11 (4.1%)[a]	0.125
Concomitant use of other antibiotics			
Colistin	4 (7.3%)	13 (4.9%)	0.472
Tigecycline	8 (14.5%)	49 (18.4%)	0.494
Fluoroquinolone	8 (14.5%)	32 (12.0%)	0.607
Aminoglycosides	2 (3.6%)	11 (4.1%)	0.864
Carbapenem	1 (1.8%)	11 (4.1%)	0.410
Piperacillin-tazobactam	1 (1.8%)	6 (2.3%)	0.840
Glycopeptide, daptomycin, and linezolid	21 (38.2%)	95 (35.7%)	0.729
Previous hospitalization[b]	27 (49.1%)	141 (53.0%)	0.597
Transfer of hospitals	10 (18.2%)	42 (15.8%)	0.661
ICU stay	38 (69.1%)	98 (36.8%)	< 0.001
Pathogens			
Proven MDR-GNB	46 (83.6%)	196 (73.7%)	0.119
CRE	41 (74.5%)	175 (65.8%)	
DTR-*P. aeruginosa*	1 (1.8%)	8 (3.0%)	
CRE + DTR-*P. aeruginosa*	1 (1.8%)	1 (0.4%)	
MDR-*P. aeruginosa*	3 (5.5%)	7 (2.6%)	
Burkholderia cenocepacia	0 (0%)	3 (1.1%)	

Table 1 continued

Variable	Patients who acquired GNB ($n = 55$)	Patients who did not acquire GNB ($n = 266$)	*P* value
MDR-*K. pneumoniae*	0 (0%)	2 (0.8%)	
Suspected MDR-GNB	9 (16.4%)	70 (26.3%)	0.119
Renal dose adjustment of CZA	37 (67.3%)	182 (68.4%)	0.868
Comorbidities			
Bedridden status	25 (45.5%)	97 (36.5%)	0.211
Dementia	5 (9.1%)	31 (11.7%)	0.583
Diabetes mellitus	27 (49.1%)	89 (33.5%)	0.028
PAOD	2 (3.6%)	18 (6.8%)	0.382
Hypertension	30 (54.5%)	143 (53.8%)	0.915
Coronary artery disease	15 (27.3%)	54 (20.3%)	0.252
COPD	5 (9.1%)	21 (7.9%)	0.767
Congestive heart failure	13 (23.6%)	60 (22.6%)	0.862
Cerebrovascular disease	14 (25.5%)	56 (21.1%)	0.472
Chronic kidney disease	38 (69.1%)	176 (66.2%)	0.675
Liver cirrhosis	3 (5.5%)	16 (6.0%)	0.873
Rheumatology disease	6 (10.9%)	17 (6.4%)	0.237
Malignancy	24 (43.6%)	114 (42.9%)	0.915
Hematologic malignancy	7 (12.7%)	36 (13.5%)	0.873
Solid tumor	17 (30.9%)	80 (30.1%)	0.902
Immunocompromised state	32 (58.2%)	138 (51.9%)	0.394
Steroid use	25 (45.5%)	98 (36.8%)	0.232
Immune modulator	7 (12.7%)	42 (15.8%)	0.565
Charlson Comorbidity Index, median (IQR)	4 (3–6)	4 (2–6)	0.284
Invasive procedure			
Central venous catheter	43 (78.2%)	151 (56.8%)	0.003
Indwelling urinary catheter	43 (78.2%)	192 (72.2%)	0.360
NG tube	48 (87.3%)	195 (73.3%)	0.028
Abdominal drain	10 (18.2%)	37 (13.9%)	0.415
Thoracic drain	11 (20.0%)	44 (16.5%)	0.535
Mechanically ventilation	46 (83.6%)	108 (40.8%)	< 0.001
Renal replacement therapy	19 (34.5%)	75 (28.3%)	0.355

Table 1 continued

Variable	Patients who acquired GNB (*n* = 55)	Patients who did not acquire GNB (*n* = 266)	*P* value
Previous surgery[c]	35 (63.6%)	109 (41.0%)	0.002
SOFA score, median (IQR)	8 (6–11)	6 (4–10)	0.036
APACHE II score, median (IQR)	24 (21–28)	21 (14–26)	< 0.001
Clinical outcomes			
28-day mortality	21 (38.2%)	74 (27.8%)[d]	0.105
In hospital mortality	32 (58.2%)	112 (42.1%)	0.029
LOS since use of CZA	42 (26–67)	29 (15–56)	0.252

Data are expressed as No. (%) unless otherwise specified

GNB Gram-negative bacteria, *IQR* interquartile range, *LOS* length of hospital stay, *CZA* ceftazidime-avibactam, *ICU* intensive care unit, *MDR-GNB* multidrug-resistant Gram-negative bacteria, *CRE* carbapenem-resistant *Enterobacterales*, *DTR* difficult-to-treat resistance, *PAOD* peripheral arterial occlusion disease, *COPD* chronic obstruction pulmonary disease, *SOFA* Sequential Organ Failure Assessment, *APACHE* Acute Physiology and Chronic Health Evaluation

[a]Includes catheter-associated infections (*n* = 4), neutropenic fever (*n* = 3), meningitis (*n* = 1), osteomyelitis (*n* = 1), sepsis of unknown origin (*n* = 2)

[b]During the 3 months preceding the day of admission

[c]During the 3 months preceding CZA therapy

[d]For patients who did not acquire GNB, the index day was the day 7 of CZA therapy

P < 0.001), and had previous surgery (63.6% vs. 41.0%, *P* = 0.002). A lower proportion of patients who acquired GNB had urinary tract infections (3.6% vs. 19.5%, *P* = 0.004). The distribution of concomitant antibiotics was similar between the two groups. Patients who acquired GNB had a higher APACHE II score than those who did not acquire GNB during CZA therapy (24 vs. 21, *P* < 0.001). Urinary tract infections, bloodstream infections, ICU stay, diabetes mellitus, central venous catheter, NG tube, mechanical ventilation, previous surgery, and APACHE II score were analyzed in a multivariable logistic regression model, and the result showed that diabetes mellitus (OR, 2.14; 95% CI, 1.11–4.11; *P* = 0.023) and use of mechanical ventilation (OR, 6.06; 95% CI, 2.03 to 18.12; *P* = 0.001) were independent risk factors associated with GNB acquisition during CZA therapy (Table 2).

We then added patients with GNB isolation after completion of CZA therapy for risk analysis of GNB acquisition. A total of 77 patients acquired GNB during CZA therapy and/or after completion of CZA treatment were identified. ICU stay (OR, 2.41; 95% CI, 1.20–4.82; *P* = 0.013), presence of diabetes mellitus (OR, 2.26; 95% CI, 1.26–4.03; *P* = 0.006), use of mechanical ventilation (OR, 5.14; 95% CI, 2.21–11.95; *P* < 0.001) and bacteremia (OR, 2.10; 95% CI, 1.08–4.07; *P* = 0.028) were independent risk factors for GNB acquisition during CZA therapy and/or after completion of CZA treatment (Supplementary Table 3).

Clinical Outcomes of Patients Who Acquired GNB During CZA Therapy

To compare clinical outcomes between patients with and without GNB acquisition, the index day for patients who did not acquire GNB was set as day 7 of CZA therapy. There was a statistically nonsignificant trend toward increased 28-day mortality in patients with GNB acquisition compared to those without (38.2% vs. 27.8%, *P* = 0.105) (Table 1).

Table 2 Univariate and multivariable logistic regression analysis of risk factors of Gram-negative bacteria acquisition

Variable	Univariate		Multivariable	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Urinary tract infections	0.16 (0.04–0.66)	0.011		
Bloodstream infections	2.20 (1.14–4.23)	0.019		
ICU stay	3.83 (2.05–7.15)	< 0.001		
Diabetes mellitus	1.92 (1.07–3.45)	0.030	2.14 (1.11–4.11)	0.023
Central venous catheter	2.73 (1.38–5.41)	0.004		
NG tube	2.50 (1.08–5.77)	0.032		
Mechanically ventilation	7.43 (3.49–15.81)	< 0.001	6.06 (2.03–18.12)	0.001
Previous surgery	2.52 (1.38–4.60)	0.003		
APACHE II score	1.07 (1.03–1.12)	0.001		

ICU intensive care unit, *APACHE* Acute Physiology and Chronic Health Evaluation

Thirty-nine of 55 patients (70.9%) acquired GNB during CZA therapy, which resulted in infection. The remaining 16 patients acquired GNB resulting in colonization. The 28-day and in-hospital mortality rates in these 39 patients were 51.3% and 71.8%, respectively. Notably, four patients developed breakthrough bacteremia (three *S. marcescens* and one *Acinetobacter lwoffii* strains). Two patients with carbapenem-resistant and CZA-resistant *S. marcescens* bacteremia died within 2 days of these bacteremia episodes. One patient with ertapenem-susceptible *S. marcescens* bacteremia recovered well after treatment with meropenem. One patient with *A. lwoffii* bacteremia recovered after cefoperazone-sulbactam treatment.

We further analyzed risk factors for mortality among the 55 patients who acquired GNB during CZA therapy (Table 3). We selected cerebrovascular disease, acquired GNB resulting in infection, SOFA score and APACHE II score at acquisition into multivariable Cox regression analysis, and the results showed cerebrovascular disease (HR, 3.10; 95% CI = 1.22–7.83; *P* = 0.017) and acquired GNB resulting in infection (HR, 9.22; 95% CI = 1.22–69.84; *P* = 0.032) were associated with 28-day mortality (Table 4).

DISCUSSION

The present study showed that 17.1% of patients acquired GNB during CZA therapy, with *Elizabethkingia* species, *Acinetobacter* species, and *B. cenocepacia* being the most common species acquired during CZA therapy. The 28-day mortality and in-hospital mortality among patients who acquired GNB were 38.2% and 58.2%, respectively. The presence of diabetes mellitus and use of mechanical ventilation were independent risk factors for GNB acquisition during CZA therapy.

Our study included hospitalized patients receiving CZA for ≥ 5 days for any indication. Most patients received CZA for CRE infections in this study (67.3%), consistent with the findings of current real-world studies that also included patients treated with CZA [25, 26]. However, our in-hospital mortality was higher than that reported in the literature (44.9% vs. 16.7–23.1%), possibly because our patients were older (75 years vs. 62 years old) [25, 26], had a higher proportion of those with immunocompromised status (53% vs. 10.8–47.1%), and had a higher disease severity (SOFA score) [25].

Table 3 Characteristics of 55 patients who acquired Gram-negative bacteria (GNB) during ceftazidime-avibactam therapy

Variable	Survivors ($n = 34$)	Non-survivors ($n = 21$)	*P* value
Age, years, median (IQR)	75 (66–84)	74 (63–84)	0.609
Male sex	21 (61.8%)	13 (61.9%)	0.992
Time to GNB acquisition, days, median (IQR)	7 (6–8)	7 (6–10)	0.186
ICU stay	23 (67.6%)	15 (71.4%)	0.768
Comorbidities			
Bedridden status	13 (38.2%)	12 (57.1%)	0.171
Dementia	4 (11.8%)	1 (4.8%)	0.639
Diabetes mellitus	16 (47.1%)	11 (52.4%)	0.701
PAOD	1 (2.9%)	1 (4.8%)	1.000
Hypertension	19 (55.9%)	11 (52.4%)	0.800
Coronary artery disease	9 (26.5%)	6 (28.6%)	0.865
COPD	4 (11.8%)	1 (4.8%)	0.639
Congestive heart failure	7 (20.6%)	6 (28.6%)	0.498
Cerebrovascular disease	5 (14.7%)	9 (42.9%)	0.020
Chronic kidney disease	22 (64.7%)	16 (76.2%)	0.371
Liver cirrhosis	3 (8.8%)	0 (0%)	0.279
Rheumatology disease	4 (11.8%)	2 (9.5%)	1.000
Malignancy	13 (38.2%)	11 (52.4%)	0.304
Hematologic malignancy	3 (8.8%)	4 (19.0%)	0.408
Solid tumor	10 (29.4%)	7 (33.3%)	0.760
Immunocompromised state	20 (58.8%)	12 (57.1%)	0.902
Steroid use	15 (44.1%)	10 (47.6%)	0.800
Immune modulator	5 (14.7%)	2 (9.5%)	0.696
Charlson Comorbidity Index, median (IQR)	4 (3–6)	5 (4–7)	0.264
Invasive procedure			
Central venous catheter	27 (79.4%)	16 (76.2%)	0.779
Indwelling urinary catheter	26 (76.5%)	17 (81.0%)	0.696
NG tube	29 (85.3%)	19 (90.5%)	0.696
Abdominal drain	7 (20.6%)	3 (14.3%)	0.556
Thoracic drain	7 (20.6%)	4 (19.0%)	0.890
Mechanically ventilation	28 (82.4%)	18 (85.7%)	0.743

Table 3 continued

Variable	Survivors ($n = 34$)	Non-survivors ($n = 21$)	*P* value
Renal replacement therapy	13 (38.2%)	6 (28.6%)	0.464
Previous surgery[a]	24 (70.6%)	11 (52.4%)	0.173
SOFA score at acquisition, median (IQR)	7 (4–10)	9 (6–14)	0.013
APACHE II score at acquisition, median (IQR)	24 (21–27)	25 (24–31)	0.021
Acquired GNB resulting in infection	19 (55.9%)	20 (95.2%)	0.002

Data are expressed as No. (%) unless otherwise specified

GNB Gram-negative bacteria, *IQR* interquartile range, *LOS* length of hospital stay, *CZA* ceftazidime-avibactam, *ICU* intensive care unit, *PAOD* peripheral arterial occlusion disease, *COPD* chronic obstruction pulmonary disease, *SOFA* Sequential Organ Failure Assessment, *APACHE* Acute Physiology and Chronic Health Evaluation

[a]During the 3 months preceding GNB acquisition

Table 4 Univariate and multivariable Cox regression analysis of risk factors of 28-day mortality in patients acquired GNB

Variable	Univariate		Multivariable	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Cerebrovascular disease	2.87 (1.20–6.82)	0.018	3.10 (1.22–7.83)	0.017
Acquired GNB resulting in infection	9.47 (1.27–70.62)	0.028	9.22 (1.22–69.84)	0.032
SOFA score at acquisition	1.20 (1.08–1.35)	0.001		
APACHE II score at acquisition	1.13 (1.03–1.23)	0.007		

GNB Gram-negative bacteria, *SOFA* sequential organ failure assessment, *APACHE* Acute Physiology and Chronic Health Evaluation

The efficacy and safety of CZA for CRE and DTR-*P. aeruginosa* infections have been discussed in many studies [6–12, 15, 16, 21]. However, the potential problems associated with the use of CZA have rarely been addressed. The emergence of CZA-resistant CRE or *P. aeruginosa* isolates after the use of CZA has been reported [8, 10, 12, 17–21, 27–29]. In addition, a change in the epidemiology of carbapenemase, characterized by the replacement of KPC with MBL-producing isolates, was observed in a Greek ICU after the introduction of CZA [22]. In the present study, we reported subsequent GNB acquisition owing to the selective pressure of CZA.

CZA-resistant *Enterobacterales*, *Elizabethkingia* species, carbapenem-resistant *Acinetobacter* species, *B. cenocepacia*, *S. maltophilia*, and *C. indologenes* were the most common GNB acquired during CZA therapy. *Elizabethkingia* species, *S. maltophilia*, and *C. indologenes* are intrinsically resistant to CZA because of the chromosomally mediated MBL production [30]. Notably, *S. maltophilia*, *C. indologenes*, *Elizabethkingia* species have recently been reported as the third, seventh, and ninth most common species found in patients with pneumonia in the ICU in a recent surveillance data from Taiwan [31]. However, these three non-fermenting Gram-negative bacteria (NFGNB) have not been extensively studied. In the present study, most patients who acquired GNB were admitted to the ICU (69.1%) and received mechanical ventilation (83.6%), and most GNB were isolated from the respiratory tract (82.4%). Therefore, the acquisition of *Elizabethkingia* species, *S. maltophilia*, and *C. indologenes* during CZA treatment emphasizes

that NFGNB other than *Pseudomonas* and *Acinetobacter* species could emerge as a threat in the future. A recent study found that this kind of NFGNB usually caused catheter-associated infections or respiratory tract infections and were associated with higher mortality in patients with longer hospitalization and chronic organ disease [32]. Contrastingly, in the present study, 10 of 11 *B. cenocepacia* strains were susceptible to ceftazidime. Adding avibactam to ceftazidime has been reported to result in the reduction of the MIC of ceftazidime [33]. In addition, some successful experiences with CZA for *B. cepacia* complex infections have been reported [34, 35]. Thus, in the present study, the acquisition of *B. cenocepacia* during CZA treatment was unexpected, and the strains were not available for further MIC testing. A possible explanation for this finding is the unreliable results of ceftazidime susceptibility tests in *Burkholderia* species owing to the poor performance of automated antibiotic susceptibility testing methods and critical illness characteristics [36]. The distribution of GNB isolated within 7 days of CZA therapy completion was similar to the distribution of those acquired during CZA therapy. These results suggest that the selective pressure caused by CZA might persist after the completion of CZA therapy, and further studies regarding its long-term effects are necessary.

Risk factors for NFGNB acquisition have been well defined in the literature [37], including prolonged hospital stay, ICU admission, exposure to broad-spectrum antibiotics, presence of comorbidities, use of mechanical ventilation, and application of invasive procedure. Our study focused on risk factors for GNB acquisition during and/or after CZA therapy and found that use of mechanical ventilation was the most significant risk factor. More attention should be paid to patients receiving antibiotics with high selective pressure, and essential infection control measures are necessary to prevent further dissemination of multidrug-resistant organisms.

In this study, the acquired GNB during CZA use can result in infection or colonization, and both conditions were included in the analysis. There was a statistically nonsignificant trend toward increased 28-day mortality in patients with GNB acquisition compared with those without (38.2% vs. 27.8%, $P=0.105$). Previous studies have demonstrated that colonization with multidrug-resistant organisms was still associated with increased risk of mortality in immunocompromised patients [38, 39]. Our previous studies also demonstrated that positive culture for carbapenem-nonsusceptible *K. pneumoniae* from clinical samples was associated with high in-hospital mortality, regardless of colonization or infection status [40]. The colonization with drug-resistant GNB is usually representative of poor general condition in hosts or heavy antibiotic exposure [40], which are associated with poor outcomes. Therefore, we should pay attention to GNB acquisition in patients with CZA therapy. Among patients who acquired GNB during CZA treatments, GNB resulting in infection was associated with a higher risk of 28-day mortality (HR, 9.22; 95% CI = 1.22–69.84; $P=0.032$). Novel agents for these MDR-GNB, such as cefiderocol, were not available during the study period, suggesting the need for new drugs in the current era to combat emerging MDR-GNB.

Our study has several limitations. First, this was a single-center study, limiting its generalizability. The distribution of acquired GNB may vary based on local epidemiology. Second, owing to the retrospective study design, the time of culture collection was not standardized, and the results may not reflect the actual acquisition time and incidence. Third, it was difficult to determine whether GNB acquired during CZA therapy was responsible for the infection in clinical practice. This poor outcome may not be directly associated with the acquired GNB itself. Despite these limitations, to our knowledge, this is the first study to elucidate the clinical presentation and risk factors for GNB acquisition during CZA treatment. These results provide insights into patients treated with CZA, given the wide use of this agent for CRE and DTR-*P. aeruginosa*.

CONCLUSIONS

About 17% of patients acquired GNB during CZA treatment, with *Elizabethkingia* species,

Acinetobacter species, *B. cenocepacia, S. maltophilia*, and carbapenem-resistant *Enterobacterales* being the common GNB identified. Some species acquired during or after CZA treatment were intrinsically CZA resistant. There was a statistically nonsignificant trend toward increased 28-day mortality in patients with GNB acquisition compared to those without, and more attention should be paid to them. Further studies regarding the optimal management of these patients are necessary.

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Data Availability. Due to the sensitive nature of the questions asked in this study, survey respondents were assured that raw data would remain confidential and not be shared.

Declarations

Conflict of interest. Chien Chuang, Tzu-Chi Kao, Chih-Han Juan, Sheng-Hua Chou, Yu-Chien Ho, Szu-Yu Liu, Yi-Ru Huang, Hsiang-Ling Ho, and Yi-Tsung Lin have nothing to disclose.

Ethical Approval. The study was approved by the Institution Review Board of Taipei Veterans General Hospital (Taipei, Taiwan) (registration no. 2021–12-015CC). Informed consent was waived due to the retrospective study design.

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