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CLINICAL THERAPEUTICS

Multicenter Study of Clinical Features of Breakthrough *Acinetobacter* Bacteremia during Carbapenem Therapy

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ABSTRACT Breakthrough *Acinetobacter* bacteremia during carbapenem therapy is not uncommon, and it creates therapeutic dilemmas for clinicians. This study was conducted to evaluate the clinical and microbiological characteristics of breakthrough *Acinetobacter* bacteremia during carbapenem therapy and to assess the efficacy of various antimicrobial therapies. We analyzed 100 adults who developed breakthrough *Acinetobacter* bacteremia during carbapenem therapy at 4 medical centers over a 6-year period. Their 30-day mortality rate was 57.0%, and the carbapenem resistance rate of their isolates was 87.0%. Among patients with carbapenem-resistant *Acinetobacter* bacteremia, breakthrough bacteremia during carbapenem therapy was associated with a significantly higher 14-day mortality (51.7% versus 37.4%, respectively; $P = 0.025$ by bivariate analysis) and a higher 30-day mortality ($P = 0.037$ by log rank test of survival analysis) than in the nonbreakthrough group. For the treatment of breakthrough *Acinetobacter* bacteremia during carbapenem therapy, tigecycline-based therapy was associated with a significantly higher 30-day mortality (80.0%) than those with continued carbapenem therapy (52.5%) and colistin-based therapy (57.9%) by survival analysis ($P = 0.047$ and 0.045 by log rank test, respectively). Cox regression controlling for confounders, including severity of illness indices, demonstrated that treatment with tigecycline-based therapy for breakthrough *Acinetobacter* bacteremia was an independent predictor of 30-day mortality (hazard ratio, 3.659; 95% confidence interval, 1.794 to 7.465; $P < 0.001$). Patients with breakthrough *Acinetobacter* bacteremia during carbapenem therapy posed a high mortality rate. Tigecycline should be used cautiously for the treatment of breakthrough *Acinetobacter* bacteremia that develops during carbapenem therapy.

KEYWORDS *Acinetobacter*, bacteremia, carbapenem, breakthrough, tigecycline

Acinetobacter species have become major nosocomial pathogens associated with high mortality in immunocompromised hosts (1). Carbapenems, such as imipenem, meropenem, and doripenem, are preferred agents for treating serious *Acinetobacter* infections (2, 3). However, the emergence of carbapenem-resistant *Acinetobacter* spp. threatens the efficacy of these agents for the treatment of health care-associated infections (2,

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4). In addition, carbapenem treatment itself is a risk factor for the development of infections caused by carbapenem-resistant *Acinetobacter* species (2, 5, 6).

Clinical and microbiological features of breakthrough Gram-negative bacteremia during carbapenem therapy have been reported (7), but clinical data specific for *Acinetobacter* spp. are limited. The recommended therapy for carbapenem-resistant *Acinetobacter* spp. was combinations of carbapenem and colistin (2). However, it is unknown whether these regimens or those with other antimicrobials, such as tigecycline, that are active against carbapenem-resistant *Acinetobacter* spp. are appropriate for treating breakthrough *Acinetobacter* bacteremia during carbapenem therapy. Furthermore, the determinants of carbapenem resistance among the causative microorganisms have not yet been elucidated. Therefore, this study was conducted to evaluate the clinical and microbiological features of breakthrough *Acinetobacter* bacteremia during carbapenem therapy and to assess the clinical efficacy of various antimicrobial regimens for breakthrough *Acinetobacter* bacteremia.

RESULTS

We reviewed the charts and medical records of 1,352 patients who had *Acinetobacter* bacteremia during the study period. Of these, 100 patients met the inclusion criteria, after excluding 1,252 patients for various reasons (see Fig. S1 in the supplemental material). The study population included 53 patients who received meropenem, 44 patients who received imipenem, and 3 patients who received doripenem therapy for more than 48 h before the onset of *Acinetobacter* bacteremia and who had a viable first isolate. All patients received carbapenem therapy with a dosage appropriate for end-organ(s) function. The treatment durations with imipenem, meropenem, and doripenem before the onset of *Acinetobacter* bacteremia were 9.8 ± 10.7, 10.2 ± 6.2, and 12.0 ± 6.5 days, respectively ($P = 0.589$). The infections that were treated with carbapenems prior to *Acinetobacter* bacteremia were caused by *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae* and *Enterobacter*, *Citrobacter*, and *Serratia* species, which were all susceptible to carbapenems. None were caused by *Acinetobacter* species. There was no significant difference in 14-day or 30-day mortality after the onset of *Acinetobacter* bacteremia based on the bacterial species that caused infections prior to the *Acinetobacter* bacteremia.

The carbapenem-resistant rate was high (87.0%) among *Acinetobacter* isolates that caused breakthrough bacteremia during carbapenem therapy, and it may have been a confounding factor that influenced patient outcomes (8). Thus, we sought to compare the patients with breakthrough *Acinetobacter* bacteremia during carbapenem therapy caused by carbapenem-resistant strains ($n = 87$) and nonbreakthrough *Acinetobacter* bacteremia caused by carbapenem-resistant strains ($n = 265$) (Table 1). Patients with breakthrough bacteremia were more likely to receive appropriate antimicrobial therapy for their carbapenem-resistant *Acinetobacter* bacteremia than the nonbreakthrough group. They received a carbapenem in combination with colistin or tigecycline as an effective regimen more frequently than the nonbreakthrough group. The Acute Physiology and Chronic Health Evaluation (APACHE) II scores and 14-day mortality rate were significantly higher in the breakthrough group than in the nonbreakthrough group, but there was no significant difference in 30-day mortality rates between the two patient groups by bivariate analysis. Survival analysis revealed that the breakthrough group had a significantly higher 30-day mortality than the nonbreakthrough group ($P = 0.037$, by log rank test; Fig. 1). Breakthrough bacteremia during carbapenem therapy is an independent risk factor for 14-day mortality (Table S1), but not for 30-day mortality (odds ratio [OR], 1.551; 95% confidence interval [CI], 0.864 to 2.783; $P = 0.141$), among patients with carbapenem-resistant *Acinetobacter* bacteremia. Carbapenem-resistant *Acinetobacter* isolates causing breakthrough bacteremia had resistance rates of commonly used antimicrobials similar to those causing nonbreakthrough bacteremia, except for a significantly lower rate of sulbactam resistance, and they were less likely to carry the carbapenemase gene-associated IS*Aba1*-bla_{OXA-23}-like genetic structure (Table 1). The imipenem and meropenem MICs were not significantly different between the 2

TABLE 1 Univariate comparison between patients with breakthrough *Acinetobacter* bacteremia during carbapenem therapy and nonbreakthrough *Acinetobacter* bacteremia caused by carbapenem-resistant strains

Characteristic[a]	Breakthrough carbapenem resistant (n = 87)	Nonbreakthrough carbapenem resistant (n = 265)	P value
Demographic characteristics			
Age (median [IQR]) (yr)	69 (53–80)	72 (58–81)	0.192
Male sex	51 (58.6)	186 (70.2)	0.062
Recent ICU stay	49 (56.3)	124 (46.8)	0.156
Bacteremia acquired in ICU	60 (69.0)	120 (45.3)	<0.001
Length of hospitalization before bacteremia (median [IQR]) (days)	21 (13–34)	22 (10–39)	0.624
Comorbid conditions			
Alcoholism	3 (3.4)	13 (4.9)	0.770
Liver cirrhosis	8 (9.2)	44 (16.6)	0.130
Chronic obstructive pulmonary disease	28 (32.2)	48 (18.1)	0.009
Chronic kidney disease	32 (36.8)	101 (38.1)	0.924
Type 2 diabetes mellitus	31 (35.6)	97 (36.6)	0.972
Hypertension	37 (42.5)	108 (40.8)	0.868
Coronary artery disease	14 (16.1)	31 (11.7)	0.379
Congestive heart failure	21 (24.1)	50 (18.9)	0.363
Cerebrovascular accident	18 (20.7)	51 (19.2)	0.890
Collagen vascular disease	3 (3.4)	8 (3.0)	0.737
Immunosuppressant therapy	11 (12.6)	26 (9.8)	0.585
Solid tumor	13 (14.9)	71 (26.8)	0.035
Hematological malignancy	8 (9.2)	8 (3.0)	0.032
Chemotherapy	7 (8.0)	14 (5.3)	0.494
Neutropenia	7 (8.0)	11 (4.2)	0.165
Trauma	4 (4.6)	9 (3.4)	0.743
Burn	1 (1.1)	5 (1.9)	1.000
Recent surgery	21 (24.1)	57 (21.5)	0.716
Charlson comorbidity index (median [IQR])	4 (2–6)	4 (2–6)	0.919
Invasive procedures			
Arterial catheter	40 (46.0)	108 (40.8)	0.465
Central venous catheter	49 (56.3)	139 (52.5)	0.614
Ventilator use	70 (80.5)	163 (61.5)	0.002
Hemodialysis	18 (20.7)	58 (21.9)	0.932
Thoracic drain	10 (11.5)	18 (6.8)	0.239
Abdominal drain	11 (12.6)	25 (9.4)	0.514
Sources of bacteremia			
Pneumonia	42 (48.3)	99 (37.4)	0.094
Catheter	18 (20.7)	46 (17.4)	0.590
Urinary tract infection	1 (1.1)	10 (3.8)	0.305
Intra-abdominal infection	6 (6.9)	16 (6.0)	0.975
Wound	2 (2.3)	11 (4.2)	0.532
Primary bacteremia	18 (20.7)	83 (31.3)	0.077
Antimicrobial therapy after bacteremia onset			
Appropriate antimicrobial therapy	32 (36.8)	56 (21.1)	0.005
Effective regimens[b]			
Colistin	18 (56.3)	43 (75.4)	0.102
Tigecycline	12 (37.5)	15 (26.3)	0.389
Fluoroquinolone	7 (21.9)	9 (15.8)	0.667
Sulbactam	2 (6.3)	4 (7.0)	1.000
Carbapenem + colistin	16 (50.0)	11 (19.3)	0.005
Carbapenem + tigecycline	6 (18.8)	2 (3.5)	0.023
Carbapenem + sulbactam	2 (6.3)	1 (1.8)	0.293
Colistin + tigecycline	4 (12.5)	12 (21.1)	0.471
Outcome			
Shock	29 (33.3)	89 (33.6)	1.000
APACHE II score (median [IQR])	26 (19–32)	24 (17–30)	0.023
14-day mortality	45 (51.7)	99 (37.4)	0.025
30-day mortality	54 (62.1)	132 (49.8)	0.062

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TABLE 1 (Continued)

Characteristic[a]	Breakthrough carbapenem resistant (n = 87)	Nonbreakthrough carbapenem resistant (n = 265)	P value
Species causing bacteremia			
A. baumannii	52 (59.8)	184 (69.4)	0.125
A. nosocomialis	24 (27.6)	66 (24.9)	0.722
A. pittii	10 (11.5)	8 (3.0)	0.004
A. soli	0 (0.0)	4 (1.5)	0.576
Microbiological characteristics of causative microorganisms			
Nonsusceptibility to:			
Amikacin	46 (52.9)	117 (44.2)	0.196
Ampicillin-sulbactam	52 (59.8)	192 (72.3)	0.036
Cefepime	75 (86.2)	246 (92.9)	0.094
Ceftazidime	78 (89.7)	250 (94.3)	0.208
Piperacillin-tazobactam	83 (95.4)	258 (97.4)	0.475
Ciprofloxacin	67 (77.0)	223 (84.2)	0.176
Levofloxacin	70 (80.5)	221 (83.4)	0.642
Colistin	0 (0.0)	6 (2.3)	0.343
Tigecycline	31 (35.6)	94 (35.5)	1.000
Isolates harboring IS*Aba1*-bla_{OXA-51}-like	20 (23.0)	38 (14.3)	0.085
A. baumannii isolates harboring IS*Aba1*-bla_{OXA-51}-like/total no. of isolates harboring IS*Aba1*-bla_{OXA-51}-like (%)	18/52 (36.7)	32/184 (17.4)	0.013
Isolates harboring IS*Aba1*-bla_{OXA-23}-like	37 (42.5)	168 (63.4)	0.001
A. baumannii isolates harboring IS*Aba1*-bla_{OXA-23}-like/total no. of isolates harboring IS*Aba1*-bla_{OXA-23}-like (%)	21/52 (40.4)	147/184 (79.9)	<0.001
Isolates harboring IS*1008* (or IS*1006*)-ΔIS*Aba3*-bla_{OXA-58}-like	6 (6.9)	8 (3.0)	0.120
Isolates harboring bla_{OXA-24}-like	11 (12.6)	16 (6.0)	0.076
Isolates harboring bla_{IMP}-like	5 (5.7)	5 (1.9)	0.072
Isolates harboring bla_{VIM}-like	3 (3.4)	5 (1.9)	0.414

[a]Data are presented as the number (%), unless otherwise indicated. IQR, interquartile range; ICU, intensive care unit; APACHE II, Acute Physiology and Chronic Health Evaluation II.

[b]Each item denotes the corresponding antimicrobial agent alone or in combination with other antimicrobial agent(s). For example, "colistin" denotes "colistin alone or in combination with other antimicrobial agent(s)." The numbers in parentheses denote the percentage of patients who received the corresponding antimicrobial agent alone or in combination with other antimicrobial agent(s) among the patients who received appropriate antimicrobial therapy.

groups (P = 0.321 and 0.871, respectively). Among carbapenem-resistant isolates of *Acinetobacter baumannii*, the isolates causing breakthrough bacteremia were more likely to carry the IS*Aba1*-bla_{OXA-51}-like structure than those causing nonbreakthrough bacteremia (Table 1). The tigecycline MICs were not significantly different between the 2 groups (P = 0.424). For the treatment of carbapenem-resistant *Acinetobacter* bacteremia, none of the antimicrobial regimens was associated with significantly higher or lower 14-day and 30-day mortality (Table S2), and none of the antimicrobial regimens was an independent risk factor associated with 14-day or 30-day mortality by the logistic regression model (14-day mortality, Table S1; 30-day mortality, data not shown) or Cox regression model (data not shown) in the multivariable analysis. Subgroup analysis among patients with nonbreakthrough carbapenem-resistant *Acinetobacter* bacteremia yielded similar results (data not shown).

The overall 30-day mortality rate of breakthrough *Acinetobacter* bacteremia during carbapenem therapy was 57.0%. The baseline demographics, clinical, and microbiological characteristics of survivors and nonsurvivors at 30 days after breakthrough *Acinetobacter* bacteremia are shown in Table 2. There were no significant differences between survivors and nonsurvivors in terms of comorbid conditions, the regimen and length of carbapenem therapy before bacteremia, and the appropriateness of antimicrobial therapy after the onset of bacteremia. Among the 20 patients with catheter-related infections as the source of bacteremia, early removal of the catheter within 48 h of bacteremia onset was not associated with a lower 30-day mortality (P = 0.921). A Cox proportional regression analysis was performed to see if any regimen was associ-

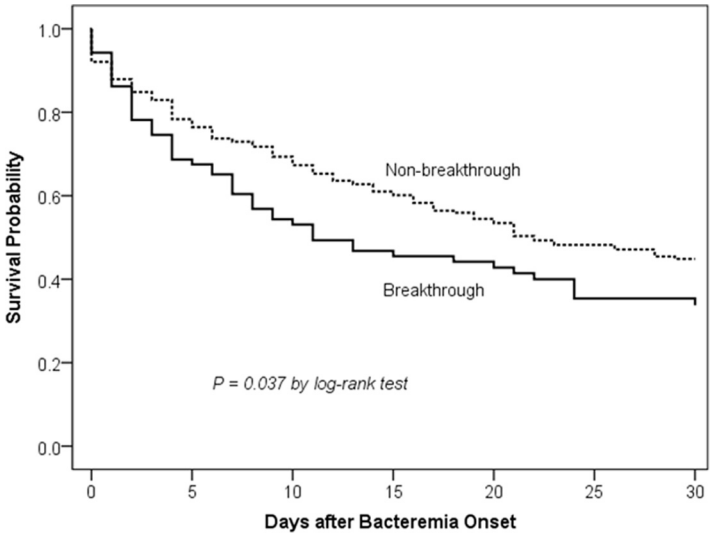

FIG 1 Comparison of Kaplan-Meier survival curves at 30 days among patients with breakthrough and nonbreakthrough carbapenem-resistant *Acinetobacter* bacteremia during carbapenem therapy.

ated with a better or worse outcome (Table 3). It revealed that tigecycline-based therapy (hazard ratio [HR], 3.659; 95% CI, 1.794 to 7.465; $P < 0.001$), higher APACHE II score at bacteremia onset (HR, 1.049; 95% CI, 1.020 to 1.080; $P = 0.001$), and catheter-related infection as a source of bacteremia (HR, 1.984; 95% CI, 1.075 to 3.660; $P = 0.028$) were independent risk factors associated with 30-day mortality. Patients receiving colistin and tigecycline combination therapy with or without other antimicrobial(s) were excluded from the following analysis that compared tigecycline-based and colistin-based therapies. The Kaplan-Meier survival analysis revealed that the 30-day mortality rate was significantly higher in patients receiving tigecycline-based therapy than in those continuing carbapenem therapy without any concomitant antimicrobial(s) ($P = 0.047$, by log rank test) and those receiving colistin-based therapy ($P = 0.045$, by log rank test) (Fig. 2). The APACHE II scores were not significantly different among patients receiving tigecycline-based therapy, continued carbapenem therapy, and colistin-based therapy ($P = 0.828$ in a comparison of 3 therapies; tigecycline-based therapy versus continued carbapenem therapy, $P = 0.554$; tigecycline-based therapy versus colistin-based therapy, $P = 0.861$) (Table S3). In the tigecycline-based therapy group, most patients (11/15) received concomitant antimicrobial(s) with tigecycline. Among 100 *Acinetobacter* isolates causing breakthrough bacteremia, 40.0% were inhibited at 1 mg/liter and 71.0% at 2 mg/liter tigecycline (MIC_{50}, 2 mg/liter; MIC_{90}, 4 mg/liter). The case patients were treated continuously with a carbapenem without combination with other antimicrobial agent(s) after the onset of breakthrough *Acinetobacter* bacteremia due to the following reasons. First, some of the causative *Acinetobacter* isolates of breakthrough *Acinetobacter* bacteremia were susceptible to carbapenems. Second, the case patients may have been treated continuously with a carbapenem before the blood culture reported carbapenem-resistant *Acinetobacter* spp. Third, the case patients may have been treated continuously with a carbapenem even though the blood culture reported carbapenem-resistant *Acinetobacter* spp. because they improved after receiving carbapenem therapy. There was no significant difference in patient outcomes based on the reasons for continuous treatment with carbapenem monotherapy after the onset of breakthrough *Acinetobacter* bacteremia.

Tigecycline-based therapy was independently associated with a poor outcome in patients with breakthrough *Acinetobacter* bacteremia during carbapenem therapy but not in patients with carbapenem-resistant *Acinetobacter* bacteremia or nonbreakthrough carbapenem-resistant *Acinetobacter* bacteremia. Among patients with carbapenem-resistant *Acinetobacter* bacteremia who were treated with tigecycline-based therapy,

TABLE 2 Univariate comparison between 30-day survivors and nonsurvivors in patients with breakthrough *Acinetobacter* bacteremia during carbapenem therapy

Characteristic[a]	All (n = 100)	Survivors (n = 43)	Nonsurvivors (n = 57)	P value
Demographical characteristics				
Age (median [IQR]) (yr)	70.5 (53.25–80.75)	75 (55–83)	66 (52–79.5)	0.215
Male sex	62 (62.0)	22 (51.2)	40 (70.2)	0.083
Recent ICU stay	58 (58.0)	26 (60.5)	32 (56.1)	0.819
Bacteremia acquired in ICU	66 (66.0)	27 (62.8)	39 (68.4)	0.707
Length of hospitalization before bacteremia (median [IQR]) (days)	21.5 (13.25–36.5)	25 (15–37)	21 (11.5–36)	0.477
Comorbid conditions				
Alcoholism	4 (4.0)	0 (0.0)	4 (7.0)	0.132
Liver cirrhosis	9 (9.0)	4 (9.3)	5 (8.8)	1.000
Chronic obstructive pulmonary disease	32 (32.0)	12 (27.9)	20 (35.1)	0.585
Chronic kidney disease	38 (38.0)	18 (41.9)	20 (35.1)	0.629
Type 2 diabetes mellitus	34 (34.0)	14 (32.6)	20 (35.1)	0.959
Hypertension	42 (42.0)	19 (44.2)	23 (40.4)	0.857
Coronary artery disease	17 (17.0)	10 (23.3)	7 (12.3)	0.239
Congestive heart failure	24 (24.0)	12 (27.9)	12 (21.1)	0.577
Cerebrovascular accident	19 (19.0)	11 (25.6)	8 (14.0)	0.230
Collagen vascular disease	4 (4.0)	3 (7.0)	1 (1.8)	0.312
Immunosuppressant therapy	12 (12.0)	3 (7.0)	9 (15.8)	0.302
Solid tumor	16 (16.0)	8 (18.6)	8 (14.0)	0.733
Hematological malignancy	10 (10.0)	4 (9.3)	6 (10.5)	1.000
Chemotherapy	8 (8.0)	4 (9.3)	4 (7.0)	0.722
Neutropenia	8 (8.0)	2 (4.7)	6 (10.5)	0.460
Trauma	4 (4.0)	3 (7.0)	1 (1.8)	0.312
Burn	1 (1.0)	1 (2.3)	0 (0.0)	0.430
Recent surgery	25 (25.0)	14 (32.6)	11 (19.3)	0.200
Charlson comorbidity index (median [IQR])	4 (2–5.75)	4 (2–6)	4 (2–5)	0.816
Invasive procedures				
Arterial catheter	43 (43.0)	19 (44.2)	24 (42.1)	0.997
Central venous catheter	55 (55.0)	26 (60.5)	29 (50.9)	0.453
Ventilator use	76 (76.0)	30 (69.8)	46 (80.7)	0.303
Hemodialysis	20 (20.0)	9 (20.9)	11 (19.3)	1.000
Thoracic drain	11 (11.0)	2 (4.7)	9 (15.8)	0.109
Abdominal drain	14 (14.0)	8 (18.6)	6 (10.5)	0.389
Sources of bacteremia				
Pneumonia	49 (49.0)	21 (48.8)	28 (49.1)	1.000
Catheter	20 (20.0)	6 (14.0)	14 (24.6)	0.289
Urinary tract infection	1 (1.0)	1 (2.3)	0 (0.0)	0.430
Intra-abdominal infection	6 (6.0)	2 (4.7)	4 (7.0)	0.697
Wound	2 (2.0)	2 (4.7)	0 (0.0)	0.182
Primary bacteremia	22 (22.0)	11 (25.6)	11 (19.3)	0.612
Carbapenem therapy before bacteremia				
Imipenem	44 (44.0)	23 (53.5)	21 (36.8)	0.145
Meropenem	53 (53.0)	18 (41.9)	35 (61.4)	0.083
Doripenem	3 (3.0)	2 (4.7)	1 (1.8)	0.576
Length of carbapenem therapy before bacteremia (median [IQR]) (days)	9 (5–13)	9 (4–13)	9 (5–14)	0.829
Antimicrobial therapy after bacteremia onset[b]				
Appropriate antimicrobial therapy	44 (44.0)	23 (53.5)	22 (38.6)	0.201
Continued carbapenem monotherapy	59 (59.0)	28 (65.1)	31 (54.4)	0.382
Colistin-based therapy[c]	19 (19.0)	8 (18.6)	11 (19.3)	1.000
Tigecycline-based therapy	15 (15.0)	3 (7.0)	12 (21.1)	0.095
Fluoroquinolone-based therapy	9 (9.0)	3 (7.0)	6 (10.5)	0.728
Sulbactam-based therapy	5 (5.0)	3 (7.0)	2 (3.5)	0.649
Carbapenem- and colistin-based therapy[c]	17 (17.0)	7 (16.3)	10 (17.5)	1.000
Outcome				
Shock	34 (34.0)	11 (25.6)	23 (40.4)	0.183
APACHE II score (median [IQR])	26 (18–31.75)	22 (17–29)	28 (21–33)	0.014

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TABLE 2 (Continued)

Characteristic[a]	All (n = 100)	Survivors (n = 43)	Nonsurvivors (n = 57)	P value
Species causing bacteremia				
A. baumannii	53 (53.0)	17 (39.5)	36 (63.2)	0.032
A. nosocomialis	30 (30.0)	15 (34.9)	15 (26.3)	0.481
A. pittii	13 (13.0)	9 (20.9)	4 (7.0)	0.080
A. soli	2 (2.0)	1 (2.3)	1 (1.8)	1.000
Microbiological characteristics of causative microorganisms				
Isolates harboring IS*Aba1*-bla_{OXA-51}-like	22 (22.0)	8 (18.6)	13 (22.8)	0.793
Isolates harboring IS*Aba1*-bla_{OXA-23}-like	37 (37.0)	11 (25.6)	26 (45.6)	0.065
Isolates harboring IS*1008* (or IS*1006*)-ΔIS*Aba3*-bla_{OXA-58}-like	6 (6.0)	0 (0.0)	6 (10.5)	0.036
Isolates harboring bla_{OXA-24}-like	11 (11.0)	6 (14.0)	5 (8.8)	0.523
Isolates harboring bla_{IMP}-like	5 (5.0)	4 (9.3)	1 (1.8)	0.162
Isolates harboring bla_{VIM}-like	4 (4.0)	2 (4.7)	2 (3.5)	1.000

[a]Data are presented as the number (%), unless otherwise indicated. IQR, interquartile range; ICU, intensive care unit; APACHE II, Acute Physiology and Chronic Health Evaluation II.
[b]An antimicrobial agent (or antimicrobial agents)-based therapy denotes the corresponding antimicrobial agent(s) alone or in combination with other antimicrobial agent(s).
[c]Only intravenous colistin was included. Inhaled colistin was not included.

the breakthrough group had a significantly higher 14-day mortality (78.6% [11/14] versus 36.4% [12/33], respectively; $P = 0.020$) and a higher 30-day mortality but without reaching statistical significance (78.6% [11/14] versus 42.4% [14/33], respectively; $P = 0.051$) than the nonbreakthrough group. There were no significant differences in demographic characteristics, underlying diseases, Charlson comorbidity index ($P = 0.831$), invasive procedures, sources of bacteremia, including pneumonia (50.0% [7/14] versus 51.5% [17/33]; $P = 1.000$), APACHE II scores ($P = 0.369$), bacterial species and tigecycline MICs ($P = 0.654$) of causative pathogens, or the percentage and regimens of combination therapy between the 2 groups.

DISCUSSION

This multicenter study was designed to assess the clinical features of breakthrough *Acinetobacter* bacteremia during carbapenem therapy and to evaluate the clinical outcomes among patient groups receiving different antimicrobial therapies. Breakthrough *Acinetobacter* bacteremia during carbapenem therapy was associated with a high mortality rate and high carbapenem resistance rate. Among patients with carbapenem-resistant *Acinetobacter* bacteremia, the breakthrough group was associated with significantly higher 14-day mortality than the nonbreakthrough group, even though the breakthrough group was more likely to receive appropriate antimicrobial therapy. For the treatment of patients with breakthrough bacteremia, tigecycline-based therapy was independently associated with a poor outcome.

Breakthrough *Acinetobacter* bacteremia during carbapenem therapy is not uncommon in patients. However, its clinical impact has not yet been determined. In addition,

TABLE 3 Cox regression analyses of prognostic factors associated with 30-day mortality among patients with breakthrough *Acinetobacter* bacteremia during carbapenem therapy

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)[a]	P	HR (95% CI)[a]	P
APACHE II score[b]	1.044 (1.015–1.074)	0.003	1.049 (1.020–1.080)	0.001
Recent surgery	0.508 (0.262–0.983)	0.044		
Catheter-related infection	1.842 (1.003–3.384)	0.049	1.984 (1.075–3.660)	0.028
Bacteremia due to *A. baumannii*	1.866 (1.086–3.205)	0.024		
Bacteremia due to *A. pittii*	0.422 (0.153–1.167)	0.097		
Tigecycline-based therapy	2.142 (1.124–4.082)	0.021	3.659 (1.794–7.465)	<0.001
Appropriate therapy	0.637 (0.373–1.088)	0.099		

[a]HR, hazard ratio; CI, confidence interval.
[b]APACHE II, Acute Physiology and Chronic Health Evaluation II.

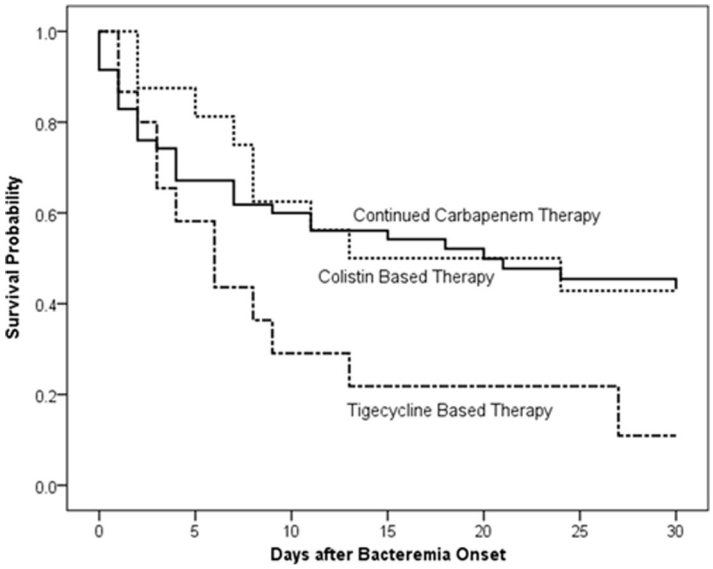

FIG 2 Comparison of Kaplan-Meier survival curves at 30 days among patients who received continued carbapenem therapy, colistin-based therapy, and tigecycline-based therapy for their breakthrough *Acinetobacter* bacteremia (tigecycline-based therapy versus continued carbapenem therapy, $P = 0.047$ by log rank test; tigecycline-based therapy versus colistin-based therapy, $P = 0.045$ by log rank test).

patients with breakthrough bacteremia during carbapenem therapy are sometimes excluded from the study population of carbapenem-resistant *Acinetobacter* bloodstream infections in outcome analysis (9), despite the high prevalence of carbapenem resistance among their *Acinetobacter* isolates. This study provides the first data on the clinical significance of breakthrough *Acinetobacter* bacteremia during carbapenem therapy. We found that in the carbapenem-resistant subgroup, breakthrough bacteremia was associated with a higher 14-day mortality than with nonbreakthrough bacteremia. For 30-day mortality, survival analysis revealed that the breakthrough group had a higher mortality rate. Overall, the breakthrough group was associated with a poorer outcome than the nonbreakthrough group in carbapenem-resistant *Acinetobacter* bacteremia. The unfavorable outcome is not a result of inappropriate antimicrobial therapy, because patients with breakthrough bacteremia are more likely to receive appropriate antimicrobial therapy for their carbapenem-resistant *Acinetobacter* bacteremia than those in the nonbreakthrough group, such as a carbapenem in combination with colistin or tigecycline. Since they had already received a carbapenem, it was reasonable to add colistin or tigecycline when symptoms/signs of bacteremia occurred.

Tigecycline is often used for the treatment of carbapenem-resistant *Acinetobacter* infections or as a salvage therapy for *Acinetobacter* infections with carbapenem treatment failure. However, our results do not support the use of a tigecycline-based regimen for the treatment of breakthrough *Acinetobacter* bacteremia during carbapenem therapy. The similarity of APACHE II scores among patient groups receiving different regimens and the finding that tigecycline-based therapy remains an independent mortality risk factor after controlling for severity of illness indices exclude disease severity as a confounder to explain the difference in mortality. Possible explanations include the bacteriostatic property of tigecycline, the relatively high MICs of tigecycline of our study isolates that were unachievable by the currently approved dose of tigecycline in serum (10), a low AUC/MIC ratio when the currently approved dose is used (11–16), and a high prevalence of hospital-acquired pneumonia as a source of bacteremia in breakthrough *Acinetobacter* bacteremia during carbapenem therapy (14, 17). Since there were no differences in patient characteristics, tigecycline MICs, and the percentage of pneumonia between breakthrough and nonbreakthrough groups of carbapenem-resistant *Acinetobacter* bacteremia, the reasons for the association of

tigecycline-based therapy with more unfavorable outcomes in the breakthrough group require further investigation.

Although all the study isolates were susceptible to colistin, colistin alone or in combination with other antimicrobial agents was still associated with a high mortality rate. It is suggested that susceptibility to colistin cannot ensure successful treatment. The current colistin susceptibility breakpoint of 2 mg/liter may not be adequate, based on its pharmacokinetic properties, such as inadequate plasma levels and potential for development of resistance (2). Whether colistin is effective for certain subgroups of patients and whether colistin combined with other antimicrobials, such as rifampin, can improve patient outcomes are yet to be determined. In addition, only patients who received the standard dose of carbapenem therapy were included in the current study. Maximizing carbapenem dosing or prolonging infusion may be associated with better patient outcomes, since these strategies have improved the probability of attaining pharmacodynamic targets (3, 18). Further studies are needed to evaluate if these strategies can prevent or treat breakthrough *Acinetobacter* bacteremia during carbapenem therapy.

Among the mechanisms of carbapenem resistance in *Acinetobacter* spp., the most notable is the expression of class D carbapenemases (1, 2). Although carbapenem-resistant *Acinetobacter* isolates causing breakthrough bacteremia during carbapenem therapy were less likely to carry the IS*Aba1-bla*$_{\text{OXA-23}}$-like structure than the nonbreakthrough group, the IS*Aba1-bla*$_{\text{OXA-23}}$-like structure was still the most prevalent carbapenem resistance determinant in both groups. The IS*Aba1-bla*$_{\text{OXA-23}}$-like genetic structure was often contained in transposons which were carried by conjugative plasmids, facilitating its widespread in *Acinetobacter* isolates in recent years (19, 20). Of greater interest is that the carbapenem-resistant *A. baumannii* isolates causing breakthrough bacteremia are more likely to carry the IS*Aba1-bla*$_{\text{OXA-51}}$-like structure. It has been suggested that carbapenem therapy may be a risk factor for rapid acquisition of *A. baumannii* isolates harboring the IS*Aba1-bla*$_{\text{OXA-51}}$-like structure. The universal chromosomal location of *bla*$_{\text{OXA-51}}$-like genes in *A. baumannii* (21) and the wide distribution of the insertion sequence IS*Aba1* in the *A. baumannii* genome (22) may facilitate the transposition of IS*Aba1* upstream of *bla*$_{\text{OXA-51}}$-like genes to confer a high level of carbapenem resistance (23).

The major limitations of this study are its retrospective design and intrinsic selection bias. The strengths of this study are the inclusion of a large number of patients from multiple medical centers located in representative regions of Taiwan using stringent inclusion criteria, recent isolates, and detailed characterization of resistance markers among breakthrough and nonbreakthrough carbapenem-resistant isolates. Our findings provide clinicians with outcome data of breakthrough *Acinetobacter* bacteremia during carbapenem therapy.

In conclusion, patients with breakthrough *Acinetobacter* bacteremia during carbapenem therapy posed a high mortality rate. Compared to continued carbapenem- or colistin-based therapy, tigecycline-based therapy was associated with higher mortality. Further studies are required to determine the optimal treatment of breakthrough *Acinetobacter* bacteremia during carbapenem therapy.

MATERIALS AND METHODS

Hospital setting and study population. This retrospective study was conducted from January 2010 to December 2015 at 4 medical centers in Taiwan: Changhua Christian Hospital (CCH; 1,676 beds) in central Taiwan, Mackay Memorial Hospital (MMH; 2,055 beds) in northern Taiwan, Taipei Veterans General Hospital (TVGH; 2,900 beds) in northern Taiwan, and Tri-Service General Hospital (TSGH; 1,712 beds) of the National Defense Medical Center in northern Taiwan. Patients with at least one positive blood culture for *Acinetobacter* spp. who had symptoms and signs of infection were recruited into the study. For patients with $\geq$2 positive blood cultures, only the first blood culture was included. Patients $<$20 years of age and those with incomplete medical records were excluded. Case patients were defined as individuals whose blood cultures grew *Acinetobacter* spp. and who had been receiving a type II carbapenem (e.g., imipenem, meropenem, or doripenem) as monotherapy for at least 48 h before breakthrough bacteremia. The case patients were treated with a carbapenem before the onset of breakthrough *Acinetobacter* bacteremia as definite antimicrobial treatment for infections which were not caused by *Acinetobacter* spp. and were caused by carbapenem-susceptible microorganisms, such as

pneumonia caused by carbapenem-susceptible *Pseudomonas aeruginosa*, or urosepsis caused by extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae*. Patients who received ertapenem and those whose blood cultures yielded the same *Acinetobacter* spp. prior to breakthrough bacteremia were excluded. Among the patients with carbapenem-resistant *Acinetobacter* bacteremia, the nonbreakthrough group was defined as those who did not receive any type II carbapenem therapy within 48 h before the onset of bacteremia. All patients who fulfilled the criteria were included in the study. The protocol was approved by the hospitals' institutional review boards (IRB) (CCH, IRB no. 140514; MMH, IRB no. 14MMHIS125; TVGH, IRB no. 2014-07-006CC; and TSGH, IRB no. 1-103-05-100).

Data collection and definitions. The medical records of the patients were reviewed retrospectively and analyzed. Patients were assessed for demographic characteristics, duration of hospitalization, stay in the intensive care unit (ICU), comorbidities, invasive procedures at the time of bacteremia onset, and time of receipt, dose, and route of therapy with individual antimicrobial drugs. Recent stay in the ICU was defined as being within 2 weeks of the first positive blood culture. Episodes of bloodstream infection were considered to be acquired in the ICU if they appeared beyond 48 h after ICU admission. Immunosuppressive therapy was defined as use of immunosuppressive agents within 2 weeks or use of corticosteroids at a dosage equivalent to or higher than 15 mg of prednisolone daily for 1 week within 4 weeks before the onset of bacteremia. Chemotherapy was defined as administration of cytotoxic agents within 6 weeks before onset of bacteremia. Recent surgery was defined as operations performed within 4 weeks before the onset of bacteremia. The source of bacteremia was determined according to the definitions of the U.S. Centers for Disease Control and Prevention (24). The severity of infection was evaluated using the Acute Physiology and Chronic Health Evaluation (APACHE) II score within 24 h before the onset of bacteremia. Appropriate antimicrobial therapy was defined as administration of at least one antimicrobial agent to which the causative pathogen was susceptible *in vitro* within 24 h after the onset of bacteremia for a minimum of 24 h, with an approved route and dosage appropriate for end-organ(s) function. Antimicrobial therapy that did not meet this definition was considered inappropriate. Monotherapy with an aminoglycoside was not considered an appropriate therapy. An antimicrobial agent (or antimicrobial agents)-based therapy was defined as treatment with the antimicrobial agent(s) alone or in combination with another antimicrobial agent(s). Continued carbapenem therapy was defined as maintaining treatment with the carbapenem that the patient had received before the onset of breakthrough *Acinetobacter* bacteremia without any concomitant antimicrobial agent(s). The dose of colistin was 5 mg/kg colistin base activity loading, followed by 5 mg/kg/day colistin base activity divided over 8 or 12 h in patients with normal renal function. For those with impaired renal function, the dosage was adjusted according to renal function, as previously described (25, 26). The loading dose of tigecycline was 100 mg, followed by a maintenance dose of 50 mg every 12 h. The all-cause 14-day and 30-day mortality rates were used as the endpoints and were defined as death occurring within 14 and 30 days after the date of bacteremia onset, respectively. For patients who were discharged before the 30-day limit, the status was determined by a review of outpatient records or by contacting the patient directly.

Bacterial identification, clonal study, antimicrobial susceptibility testing, and detection of carbapenem resistance determinants. The initial isolate was used for the microbiological studies. The bacteria were phenotypically identified as *Acinetobacter* spp. using the Vitek 2 system (bioMérieux, Marcy l'Étoile, France). *Acinetobacter baumannii* was identified by a multiplex PCR method (10). Isolates identified as non-*baumannii Acinetobacter* spp. were further identified to the genomic species level by 16S-23S ribosomal DNA intergenic spacer sequence analysis, as previously described (27). The MICs of carbapenems, tigecycline, and colistin and the antimicrobial susceptibilities of other agents were determined by agar dilution according to the Clinical and Laboratory Standards Institute (CLSI) (28). Multidrug resistance (MDR) was defined as resistance to any one agent in at least 3 of the following classes of antimicrobials: aminoglycosides, carbapenems, antipseudomonal cephalosporins, β-lactam–β-lactamase inhibitor combinations, and fluoroquinolones.

Multiplex PCR assays were performed to detect the carbapenem-hydrolyzing class D β-lactamase (CHDL) genes (bla_{OXA-23}-like, bla_{OXA-24}-like, bla_{OXA-51}-like, bla_{OXA-58}-like, and $bla_{OXA-143}$-like) (29). Metallo-β-lactamases were detected by phenotypic methods and PCR assays, including the multiplex PCR with primers specific for the bla_{IMP}, bla_{VIM}, bla_{SIM}, bla_{SPM}, and bla_{GIM-1} genes (30), and the PCR assay detecting the presence of bla_{NDM-1} (31). The upstream locations of insertion sequences (ISs) IS*Aba1* of the bla_{OXA-51}-like or bla_{OXA-23}-like gene and IS*1008* or IS*1006* upstream of the bla_{OXA-58}-like gene were analyzed by PCR mapping (23, 30, 32–34).

Statistical analysis. PASW for Windows version 18 (SPSS, Chicago, IL, USA) was used for all data analyses. The χ^2 test with Yates correction or Fisher's exact test was used to compare categorical data. Continuous variables were analyzed using the Mann-Whitney *U* test or two-sample *t* test. The Wilcoxon signed-rank test was used to determine statistically significant differences between paired samples. The time to mortality, defined as the interval between the onset of bacteremia and death, was analyzed using the Kaplan-Meier survival analysis, and the log rank test was used to compare univariable survival distributions between different groups of patients. A logistic regression model was used to explore independent prognostic factors associated with 14-day and 30-day mortality of patients with *Acinetobacter* bacteremia caused by carbapenem-resistant strains. A Cox proportional hazard regression model was used to explore independent prognostic factors associated with the 30-day mortality of patients with breakthrough *Acinetobacter* bacteremia during carbapenem therapy. Univariable analyses were performed separately for each risk factor to ascertain the odds ratio (OR) or hazard ratio (HR) and 95% confidence interval (CI). All biologically plausible variables with a *P* value of <0.10 in the univariable analysis were considered for inclusion in the logistic regression model or Cox regression model in the multivariable analysis. A *P* value of <0.05 was considered statistically significant.

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at https://doi.org/10.1128/AAC.00931-17.

SUPPLEMENTAL FILE 1, PDF file, 0.6 MB.

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