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CLINICAL THERAPEUTICS

Multicenter Study of the Relationship between Carbapenem MIC Values and Clinical Outcome of Patients with *Acinetobacter* Bacteremia

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ABSTRACT The Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) offer different recommendations for carbapenem MIC susceptibility breakpoints for *Acinetobacter* species. In addition, the clinical efficacy of the intermediate category remains uncertain. This study was designed to determine the optimal predictive breakpoints based on the survival of patients with *Acinetobacter* bacteremia treated with a carbapenem. We analyzed the 30-day mortality rates of 224 adults who received initial carbapenem monotherapy for the treatment of *Acinetobacter* bacteremia at 4 medical centers over a 5-year period, according to the carbapenem MICs of the initial isolates. The 30-day mortality was about 2-fold greater in patients whose isolates had carbapenem MICs of ≥8 mg/liter than in those with isolates with MICs of ≤4 mg/liter. The differences were significant by bivariate analysis (53.1% [60/113] versus 25.2% [28/111], respectively; $P < 0.001$) and on survival analysis by the log rank test ($P < 0.001$). Classification and regression tree analysis revealed a split between MICs of 4 and 8 mg/liter and predicted the same difference in mortality, with a P value of <0.001. Carbapenem treatment for *Acinetobacter* bacteremia caused by isolates with carbapenem MICs of ≥8 mg/liter was an independent predictor of 30-day mortality (odds ratio, 4.218; 95% confidence interval, 2.213 to 8.039; $P < 0.001$). This study revealed that patients with *Acinetobacter* bacteremia treated with a carbapenem had a more favorable outcome when the carbapenem MICs of their isolates were ≤4 mg/liter than those with MICs of ≥8 mg/liter.

KEYWORDS *Acinetobacter*, carbapenem, MIC, bloodstream infection

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

Breakpoints are useful to define susceptibility and resistance to antimicrobial agents

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(4). However, there are some discrepancies between the carbapenem breakpoints set by the two major organizations, the Clinical and Laboratory Standards Institute (CLSI) (5) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (6). The CLSI resistance breakpoints for the MICs of imipenem and meropenem against *Acinetobacter* spp. are both ≥8 mg/liter (5). The EUCAST breakpoints are both ≥16 mg/liter (6). An MIC of 8 mg/liter indicates resistance according to the CLSI and intermediate susceptibility by the EUCAST guidelines. An MIC of 4 mg/liter is considered intermediate susceptibility by both organizations. An MIC of 4 mg/liter was considered to be susceptible by the CLSI in a previous version of the breakpoints (7). There are no clinical data to support the change from susceptible to intermediate for an MIC of 4 mg/liter.

Susceptibility breakpoints are constructed on the basis of clinical data, MIC distributions, pharmacokinetics/pharmacodynamics (PK/PD) derived from animal exposure-response studies, and Monte Carlo simulations (4, 8). The justification for animal and simulation studies to set carbapenem breakpoints for *Acinetobacter* species has been addressed by investigators (9–12). Clinical correlations that validate the recommended carbapenem breakpoints in patients with *Acinetobacter* infection are limited (13). Outcome data from clinical studies are needed to justify these breakpoints, especially when discrepancies exist between different organizations.

We previously performed a single-center study to provide clinical data to support the carbapenem breakpoints for the *Acinetobacter baumannii* group in patients with bacteremia (13). However, the study was limited by the potential lack of external validity, implausible effect size, and long study period. Therefore, this retrospective chart review study was conducted to evaluate the clinical outcomes of patients with *Acinetobacter* bacteremia treated with carbapenems whose isolates had different carbapenem MICs at multiple centers from 2011 to 2015. The evidence provided in this report should help optimize the current carbapenem breakpoints for *Acinetobacter* species.

RESULTS

We reviewed the charts of 1,104 patients who had *Acinetobacter* bacteremia and their complete medical records during the study period (Fig. 1). Of these, 224 patients met the entry criteria, after the exclusions shown in Fig. 1. The study population included 115 patients who received imipenem and 109 patients who received meropenem monotherapy within 24 h of the onset of bacteremia and had a viable first isolate. The durations of treatment with imipenem and meropenem were 11 ± 8 and 13 ± 8 days, respectively ($P = 0.106$). After initiation of carbapenem monotherapy, 66 of the 224 patients were switched to other antimicrobial agents or treated with another antimicrobial agent in combination with a carbapenem (see Table S1 in the supplemental material). Among the 66 patients, 13 (19.7%) patients started to receive other active drugs 48 to 72 h after the onset of bacteremia, 36 (54.5%) patients started 72 to 96 h after the onset of bacteremia, and 17 (25.8%) patients started 96 to 120 h after the onset of bacteremia. None of the alternative antimicrobial regimens were associated with a significantly higher or lower 30-day mortality. There was no significant difference in survival based on the timing of the additional agents. A total of 147 (65.6%) patients had received antimicrobial agents prior to carbapenem therapy. Most of these patients (128/147 [87.1%]) had received antimicrobial agents that were inactive against *Acinetobacter* species. This group did not have a higher 30-day mortality than those who did not receive prior antimicrobial therapy. There was no significant difference in survival based on the class of antimicrobial agent used prior to carbapenem therapy.

The *Acinetobacter* isolates (one from each patient) were identified as *A. baumannii* (121 isolates, 63 clones), *Acinetobacter pittii* (19 isolates, 12 clones), *Acinetobacter nosocomialis* (73 isolates, 37 clones), *Acinetobacter soli* (2 isolates, 2 clones), and other *Acinetobacter* spp. (9 isolates, 9 clones). The MICs for meropenem or imipenem for the same isolate were not always the same, and there were no significant differences between the MICs for imipenem and those for meropenem ($P = 0.297$). Therefore, only

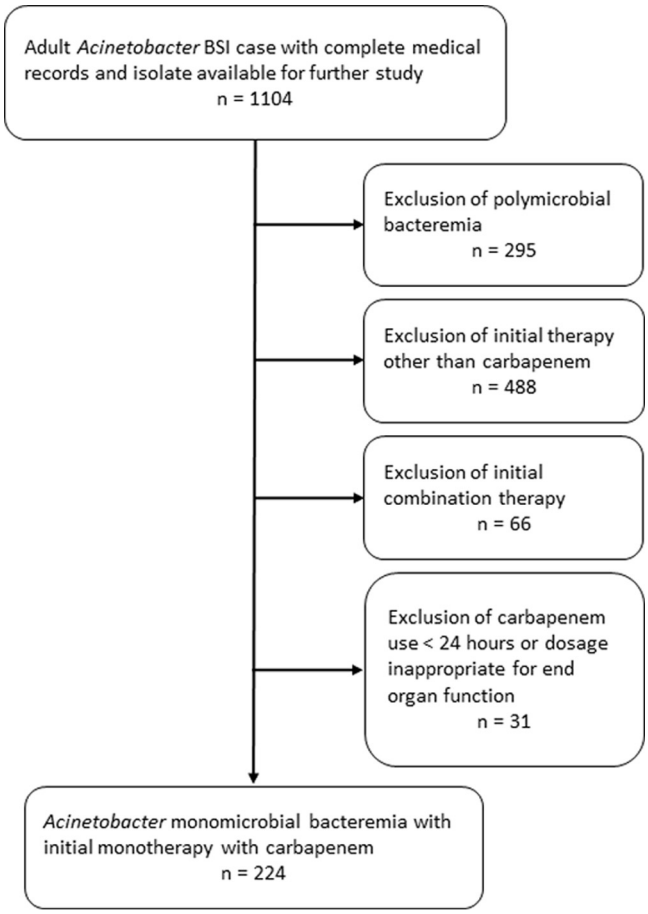

FIG 1 Methodology for application of exclusion criteria. BSI, bloodstream infection.

the MIC of the carbapenem that the patient received was presented in this study. There was no significantly difference in the 30-day mortality rates among patients infected with *A. baumannii*, *A. pittii*, *A. nosocomialis*, and other *Acinetobacter* spp. by survival analysis (Fig. S1). In addition, the 30-day mortality rates between patients receiving either imipenem or meropenem were also not significantly different, as shown by survival analysis (Fig. S2) or by bivariate analysis in different susceptibility categories (including MICs of ≤2, 4, 8 or ≥16 mg/liter). Therefore, we included all of the *Acinetobacter* species and the two carbapenems in our analysis.

The 30-day mortality rates varied in relation to the carbapenem MICs of the *Acinetobacter* isolates (Fig. 2). The mortality rates did not differ significantly between the patients with isolates with MICs of ≤2 and 4 mg/liter (25.5% versus 23.5%, respectively; $P = 1.000$). We then compared the clinical outcomes of patients with isolates with an MIC of 4 mg/liter, which indicated intermediate susceptibility according to the CLSI and EUCAST guidelines, to those with isolates with an MIC of 8 mg/liter, which indicated resistance and intermediate susceptibility according to the CLSI and EUCAST guidelines, respectively. Patients with isolates with an MIC of ≥8 mg/liter had significantly higher 30-day mortality than those with isolates with an MIC of 4 mg/liter (53.1% versus 23.5%, respectively; $P = 0.044$). The 30-day mortality rates of patients with isolates with an MIC of 8 mg/liter did not differ significantly from those with isolates with an MIC of ≥16 mg/liter (42.9% versus 55.4%, respectively; $P = 0.424$). However, those who acquired isolates with an MIC of ≥8 mg/liter had significantly higher 30-day mortality (about 2-fold) than those who acquired isolates with an MIC of ≤4 mg/liter (53.1% versus 25.2%, respectively; $P < 0.001$).

Classification and regression tree (CART) analysis was performed to determine the

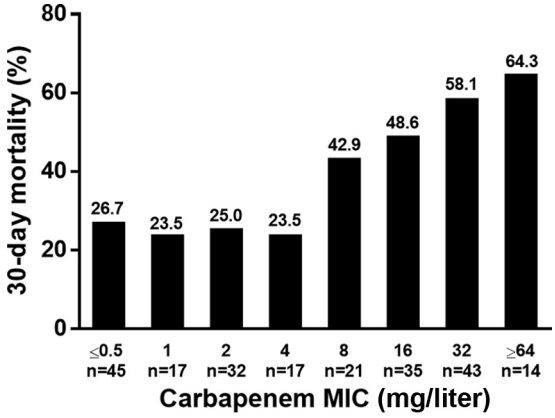

FIG 2 Thirty-day mortality rate of patients with *Acinetobacter* bacteremia in different susceptibility categories. The rate was significantly lower in those with a carbapenem MIC of ≤4 mg/liter than in those with a carbapenem MIC of ≥8 mg/liter.

carbapenem MIC breakpoint that maximized the difference in 30-day mortality. We found a division in the MICs between 4 and 8 mg/liter that predicted a difference in mortality ($P < 0.001$) (Fig. S3). The Kaplan-Meier survival analysis also revealed that the 30-day mortality rate was significantly higher in patients for *Acinetobacter* isolates with carbapenem MICs of ≥8 mg/liter than those with isolates with MICs of ≤4 mg/liter (Fig. 3).

The baseline demographics, clinical characteristics, and microbiologic characteristics of patients, stratified by carbapenem MICs, are shown in Table 1. There were no significant differences in underlying diseases, Charlson comorbidity index values, or Acute Physiology and Chronic Health Evaluation (APACHE) II scores at the onset of bacteremia between patients whose isolates had a carbapenem MIC of ≤4 mg/liter and those with isolates with an MIC of ≥8 mg/liter (Table 1). A multivariate logistic regression analysis was performed to see whether acquisition of isolates with a carbapenem MIC of ≥8 mg/liter was independently associated with 30-day mortality in patients with *Acinetobacter* bloodstream infections (Table 2). It revealed that the acquisition of *Acinetobacter* isolates with a carbapenem MIC of ≥8 mg/liter (odds ratio [OR], 4.218; 95% confidence interval [CI], 2.213 to 8.039; $P < 0.001$), higher APACHE II score at bacteremia onset (OR, 1.055; 95% CI, 1.019 to 1.093; $P < 0.001$), and shock at bacteremia onset (OR, 4.180; 95% CI, 2.173 to 8.040; $P = 0.003$) were independent risk

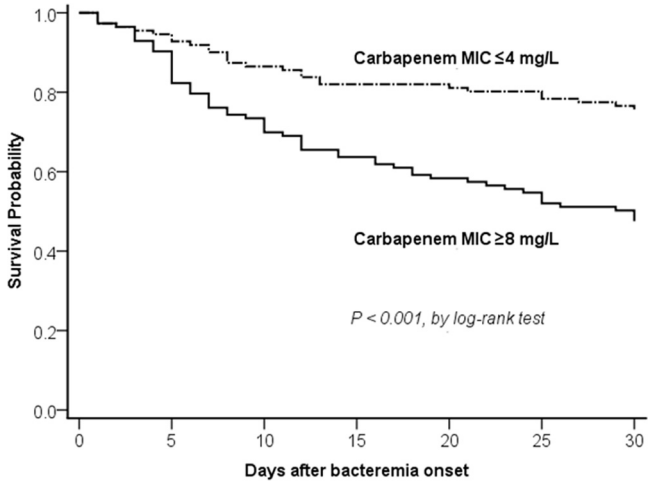

FIG 3 Comparison of Kaplan-Meier survival curves, at 30 days, between patients with *Acinetobacter* bacteremia caused by isolates having MICs of ≤4 mg/liter and ≥8 mg/liter.

TABLE 1 Univariate comparison between patients acquiring *Acinetobacter* isolates with carbapenem MICs ≤4 mg/liter and ≥8 mg/liter

Characteristic[a]	Results by carbapenem MIC		*P* value
	≤4 mg/liter (*n* = 111)	≥8 mg/liter (*n* = 113)	
Demographic characteristics			
Age (median [IQR]) (yr)	74 (62–82)	75 (58–82)	0.676
Males	80 (72.1)	74 (65.5)	0.358
Length of hospitalization before bacteremia (median [IQR]) (days)	17 (9–34)	24 (12–38)	0.032
Recent stay in ICU	61 (55.0)	68 (60.2)	0.512
Acquired in ICU	53 (47.7)	81 (71.7)	<0.001
Comorbid condition			
Charlson comorbidity index (median [IQR])	3 (2–5)	4 (2–5)	0.584
Type 2 diabetes mellitus	41 (36.9)	33 (29.2)	0.276
Hypertension	43 (38.7)	39 (34.5)	0.605
Cerebrovascular accident	22 (19.8)	29 (25.7)	0.377
Chronic obstructive pulmonary disease	19 (17.1)	29 (25.7)	0.163
Coronary artery disease	17 (15.3)	18 (15.9)	1.000
Congestive heart failure	15 (13.7)	20 (17.7)	0.497
Alcoholism	8 (7.2)	7 (6.2)	0.971
Liver cirrhosis	11 (9.9)	7 (6.2)	0.437
Chronic kidney disease	37 (33.3)	41 (36.3)	0.747
Collagen vascular disease	7 (6.3)	5 (4.4)	0.743
Solid tumor	35 (31.5)	23 (20.4)	0.079
Hematological malignancy	10 (9.0)	8 (7.1)	0.775
Chemotherapy	15 (13.5)	7 (6.2)	0.106
Immunosuppressant therapy	9 (8.1)	10 (8.8)	1.000
Neutropenia	5 (4.5)	3 (2.7)	0.497
Recent surgery	36 (32.4)	36 (31.9)	1.000
Trauma	2 (1.8)	5 (4.4)	0.446
Invasive procedure			
Central venous catheter	58 (52.3)	72 (63.7)	0.109
Endotracheal intubation or tracheostomy	71 (64.0)	91 (80.5)	0.009
Ventilator use	65 (58.6)	84 (74.3)	0.018
Hemodialysis	11 (9.9)	18 (15.9)	0.253
Thoracic drain	7 (6.3)	13 (11.5)	0.259
Abdominal drain	11 (9.9)	12 (10.6)	1.000
Sources of bacteremia			
Pneumonia	62 (55.9)	60 (53.1)	0.779
Catheter	9 (8.1)	20 (17.7)	0.053
Urinary tract infection	6 (5.4)	4 (3.5)	0.537
Intra-abdominal infection	7 (6.3)	5 (4.4)	0.743
Wound	6 (5.4)	4 (3.5)	0.537
Primary bacteremia	24 (21.6)	21 (18.6)	0.689
Previous use of antibiotics	71 (64.0)	76 (67.3)	0.705
Aminoglycoside	13 (11.7)	9 (8.0)	0.473
Penicillin	5 (4.5)	1 (0.9)	0.118
β-lactam–β-lactamase inhibitors	16 (14.4)	8 (7.1)	0.119
Nonantipseudomonal cephalosporins	14 (12.6)	20 (17.7)	0.382
Antipseudomonal cephalosporins	21 (18.9)	22 (19.5)	1.000
Antipseudomonal carbapenems	11 (9.9)	25 (22.1)	0.021
Fluoroquinolone	12 (10.8)	15 (13.3)	0.718
Tigecycline	2 (1.8)	4 (3.5)	0.683
Colistin	1 (0.9)	6 (5.3)	0.119
Macrolide	2 (1.8)	5 (4.4)	0.446
Clindamycin	9 (8.1)	0 (0)	0.002
Vancomycin	2 (1.8)	6 (5.3)	0.280
Teicoplanin	7 (6.3)	13 (11.5)	0.259
Duration of carbapenem therapy (median [IQR]) (days)	13 (7–16)	9 (5.5–15)	0.097
Outcome			
Shock	42 (37.8)	38 (33.6)	0.604
APACHE II score (median [IQR])	24 (17–30)	26 (18.5–31)	0.172
14-day mortality	20 (18.0)	41 (36.3)	0.003
30-day mortality	28 (25.2)	60 (53.1)	<0.001
Length of stay after bacteremia for survivors (median [IQR]) (days)	28 (17–45)	38 (19.75–64.25)	0.196

(Continued on next page)

TABLE 1 (Continued)

Characteristic[a]	Results by carbapenem MIC		*P* value
	≤4 mg/liter (*n* = 111)	≥8 mg/liter (*n* = 113)	
Species causative of bacteremia			
A. baumannii	50 (45.0)	71 (62.8)	0.011
A. nosocomialis	37 (33.3)	36 (31.9)	0.813
A. pittii	13 (11.7)	6 (5.3)	0.139
Microbiological characteristics of causative microorganisms			
Multidrug resistance	47 (42.3)	92 (81.4)	<0.001
Isolates harboring genetic structure:			
IS*Aba1*-bla_{OXA-51}-like	16 (14.4)	27 (23.9)	0.103
IS*Aba1*-bla_{OXA-23}-like	1 (0.9)	38 (33.6)	<0.001
IS*1008* (or IS*1006*)-ΔIS*Aba3*-bla_{OXA-58}-like	1 (0.9)	12 (10.6)	0.005
bla_{OXA-24}-like	1 (0.9)	8 (7.1)	0.035
bla_{IMP}-like	0 (0)	5 (4.4)	0.060
bla_{VIM}-like	1 (0.9)	8 (7.1)	0.035

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

factors associated with 30-day mortality. The above-mentioned analyses were performed in the same manner using all-cause 14-day mortality as the endpoint, and the results were similar to those of analysis using all-cause 30-day mortality as the primary outcome measure (date not shown).

Patients who acquired isolates with an MIC of ≥8 mg/liter were more likely to have acquired the isolate in the intensive care unit (ICU), had a longer length of hospitalization prior to bacteremia, had endotracheal intubation or tracheostomy and ventilator use at the onset of bacteremia, and had prior use of antipseudomonal carbapenems in the univariate analysis (Table 1). The risk factors that independently predicted the acquisition of *Acinetobacter* isolates with a carbapenem MIC of ≥8 mg/liter included the acquisition of an *Acinetobacter* isolate in an ICU (OR, 2.305; 95% CI, 1.295 to 4.103; $P = 0.005$), bacteremia caused by *A. baumannii* (OR, 2.194; 95% CI, 1.243 to 3.873; $P = 0.007$), and previous use of antipseudomonal carbapenems (OR, 2.331; 95% CI, 1.027 to 5.290; $P = 0.043$) (Table 3).

Bloodstream isolates with a carbapenem MIC of ≥8 mg/liter had a significantly higher rate of multidrug resistance than those with a carbapenem MIC of ≤4 mg/liter and were more likely to carry the carbapenemase gene-associated genetic structures, such as the IS*Aba1*-bla_{OXA-23}-like, IS*1008* (or IS*1006*)-ΔIS*Aba3*-bla_{OXA-58}-like, bla_{IMP}-like, and bla_{VIM}-like structures (Table 1). Among the 113 isolates with a carbapenem MIC of ≥8 mg/liter, the carbapenemase genes (and associated insertion sequences) associated with carbapenem resistance were detected in 98 (86.0%) isolates (Table 1). Fourteen isolates with a carbapenem MIC of ≥8 mg/liter carried either a bla_{OXA-23}-like gene without upstream IS*Aba1* or bla_{OXA-58}-like gene with upstream IS*Aba3* without IS*1008* or IS*1006* truncation. Only one isolate with a carbapenem MIC of ≥8 mg/liter did not carry any currently known carbapenemase gene. Carbapenemase genes and associated

TABLE 2 Logistic regression analysis of prognostic factors associated with 30-day mortality among patients treated with carbapenem for *Acinetobacter* bacteremia

Variable	Survivors (*n* = 136)	Nonsurvivors (*n* = 88)	Univariate analysis		Multivariate analysis	
			OR (95% CI)[a]	*P*	OR (95% CI)[a]	*P*
Bacteremia due to *A. baumannii* (no. [%])	66 (48.5)	55 (62.5)	1.768 (1.023–3.055)	0.041		
Shock (no. [%])	32 (23.5)	48 (54.5)	3.900 (2.190–6.945)	<0.001	4.180 (2.173–8.040)	0.003
APACHE II score (median [IQR])[b]	23 (17–28)	27.5 (21–34)	1.071 (1.036–1.107)	<0.001	1.055 (1.019–1.093)	<0.001
Acquisition of isolates with MIC of ≥8 mg/liter (no. [%])	53 (39.0)	60 (68.2)	3.356 (1.906–5.908)	<0.001	4.218 (2.213–8.039)	<0.001

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

TABLE 3 Risk factors associated with acquisition of *Acinetobacter* isolates with carbapenem MIC of ≥8 mg/liter

Variable[a]	Univariate analysis		Multivariate analysis	
	OR (95% CI)[b]	*P*	OR (95% CI)[b]	*P*
Acquired in ICU	2.770 (1.593–4.817)	<0.001	2.305 (1.295–4.103)	0.005
Previous use of antipseudomonal carbapenems	2.583 (1.202–5.549)	0.015	2.331 (1.027–5.290)	0.043
Solid tumor	0.555 (0.302–1.020)	0.058		
Presence of endotracheal tube or tracheostomy	2.330 (1.272–4.271)	0.006		
Ventilator use	2.050 (1.163–3.612)	0.013		
Catheter as source of bacteremia	2.437 (1.057–5.620)	0.037		
Bacteremia caused by *A. baumannii*	2.062 (1.209–3.519)	0.008	2.194 (1.243–3.873)	0.007

[a]ICU, intensive care unit.
[b]OR, odds ratio; CI, confidence interval.

upstream insertion sequences carried by *Acinetobacter* isolates with different carbapenem MICs are shown in Table 4. Nine (9/32 [28.1%]) and 7 (7/17 [41.2%]) isolates with carbapenem MICs of 2 and 4 mg/liter carried carbapenem resistance-associated genetic structures, respectively. These genetic structures were observed in 16 (16/21 [76.2%]) and 32 (32/35 [91.4%]) isolates with carbapenem MICs of 8 and 16 mg/liter, respectively. The 20 patients who acquired isolates that exhibited carbapenem MICs of ≤4 mg/liter and harbored a carbapenem resistance-associated carbapenemase gene had 30-day mortality similar to that of the 91 patients who acquired isolates that exhibited carbapenem MICs of ≤4 mg/liter and did not harbor carbapenem resistance-associated carbapenemase genes (25.0% [5/20] versus 24.2% [22/91], respectively; $P = 1.000$); however, the group of 20 patients had significantly lower 30-day mortality than the 113 patients who acquired isolates with carbapenem MICs of ≥8 mg/liter (25.0% [5/20] versus 53.1% [60/113], respectively; $P = 0.038$).

To ensure that the results of this study were not driven by the results of the previous single-center study (13), we carried out a sensitivity analysis that excluded the 31 overlapping patients between the two studies. The clinical data of the 193 patients finally included in the sensitivity analysis were analyzed in the same manner as the above-mentioned analysis. The results were similar to the original results (data not shown). In addition, we performed a subgroup analysis of patients with *A. baumannii* bacteremia (121 patients). The 30-day mortality was significantly higher in patients who had isolates of *A. baumannii* with carbapenem MICs of ≥8 mg/liter than in those who had isolates with carbapenem MICs of ≤4 mg/liter, as shown by bivariate analysis (54.9% [39/71] versus 32.0% [16/50], respectively; $P = 0.021$) and survival analysis by the log rank test ($P = 0.019$). Carbapenem treatment for *A. baumannii* bacteremia caused by isolates with carbapenem MICs of ≥8 mg/liter was an independent predictor of 30-day mortality (OR, 4.468; 95% CI, 1.783 to 11.198; $P = 0.001$).

TABLE 4 Carbapenemase genes and associated insertion sequences carried by *Acinetobacter* isolates with different carbapenem MICs

Genetic structure harbored by isolates	*n*	30-day mortality (%)	No. of isolates with carbapenem MIC (mg/liter):							
			≤0.5	1	2	4	8	16	32	≥64
IS*Aba1*-bla_{OXA-51}-like	43	37.2	0	2	8	6	5	5	12	5
IS*Aba1*-bla_{OXA-23}-like	39	59.0	1	0	0	0	3	15	17	3
IS*1008* (or IS*1006*)-ΔIS*Aba3*-bla_{OXA-58}-like	13	69.2	1	0	0	0	7	5	0	0
bla_{OXA-24}-like	9	55.6	0	0	1	0	0	2	3	3
bla_{IMP}-like	5	40.0	0	0	0	0	0	3	2	0
bla_{VIM}-like	9	44.4	0	0	0	1	1	2	4	1
Total	118	50.0	2	2	9	7	16	32	38	12

DISCUSSION

This multicenter center study was designed to assess the different carbapenem breakpoints for *Acinetobacter* spp. set by CLSI and EUCAST and the potential clinical efficacy of the intermediate category of an MIC of 4 mg/liter. We included patients who received carbapenem monotherapy for the treatment of *Acinetobacter* bacteremia and evaluated the clinical outcomes among patient groups acquiring isolates with different carbapenem MICs. We found that patients with *Acinetobacter* bacteremia had a more favorable outcome when the carbapenem MICs of their isolates were ≤4 mg/liter than those with isolates with MICs of ≥8 mg/liter when treated with a carbapenem. Isolates with carbapenem MICs of ≥8 mg/liter were independently associated with a poor outcome in patients treated with carbapenems for *Acinetobacter* bacteremia.

The CLSI and EUCAST guidelines classify an MIC of imipenem or meropenem of 8 mg/liter as resistant and intermediate susceptible, respectively. In the current study, we found that the mortality rate did not differ significantly between the patients who acquired *Acinetobacter* isolates with carbapenem MICs 8 mg/liter and ≥16 mg/liter. Patients who acquired isolates with carbapenem MICs of ≥8 mg/liter had a significantly higher 30-day mortality than those with isolates with MICs of ≤4 mg/liter. After controlling for confounders, including severity of illness indices, acquisition of isolates with an MIC of ≥8 mg/liter remained an independent risk factor associated with 30-day mortality. In addition, most *Acinetobacter* isolates carrying carbapenem resistance-associated genetic structures exhibit carbapenem MICs of ≥8 mg/liter. These results provide clinical data and genetic resistance mechanisms to support the use of an MIC of ≥8 mg/liter as carbapenem resistant.

An MIC of 4 mg/liter for imipenem or meropenem is considered intermediate susceptibility by both organizations, but the clinical efficacy in this cutoff remains uncertain. A PK/PD simulation from healthy volunteers and PK/PD data from animal models proposed that the susceptibility breakpoints for both imipenem and meropenem for *A. baumannii* are ≤4 mg/liter (9, 10). PK/PD data from other groups in both critically ill (14) and healthy patients (15) suggested that standard dosing of carbapenems might be suboptimal when the MIC is over 2 mg/liter. Discrepancies between these PK/PD breakpoints may have resulted from variation in patient populations. An MIC of 4 mg/liter was categorized as susceptible in the previous CLSI version. Clinical studies that include significant numbers of cases, wherein the infectious pathogen has an MIC on either side of the epidemiological and PK/PD cutoff values, are valuable to assist in the clinical validation of final breakpoints (4). In the current study, the mortality rate did not differ significantly between the patients who acquired *Acinetobacter* isolates with carbapenem MICs of ≤2 and 4 mg/liter. Patients who acquired isolates with carbapenem MICs of ≥8 mg/liter and received the standard dose of carbapenem therapy had a significantly higher 30-day mortality than those who acquired isolates with an MIC of 4 mg/liter or ≤4 mg/liter. These findings support the concept that MICs of ≤4 mg/liter should be considered carbapenem susceptible.

In addition to susceptibility testing, PK/PD, and clinical outcome data, resistance markers are also required for the establishment of appropriate breakpoints (4). Among the mechanisms of carbapenem resistance in *Acinetobacter* spp., the most notable contribution comes from the expression of class D carbapenemases (1, 2). In the current study, we found that PCR detection of the IS*Aba1*-$bla_{\text{OXA-23}}$-like, IS*1008* (or IS*1006*)-ΔIS*Aba3*-$bla_{\text{OXA-58}}$-like, bla_{IMP}-like, and bla_{VIM}-like genetic structures can be used as a tool to predict higher carbapenem MIC in an *Acinetobacter* isolate. However, the *Acinetobacter* isolates carrying the IS*Aba1*-$bla_{\text{OXA-51}}$-like genetic structure exhibit carbapenem MICs ranging from 1 to ≥64 mg/liter. A possible explanation for this phenomenon is that clinical variants of OXA-51 enzymes exhibit different hydrolytic activities against carbapenems (16, 17). In addition, the contribution of the IS*Aba1*-$bla_{\text{OXA-51}}$-like structure on carbapenem resistance varied, depending on its plasmid or chromosome location (18). The findings that the outcomes of the patients who acquired isolates with carbapenem MICs of ≤4 mg/liter and with a carbapenemase

gene were more similar to those who acquired isolates with carbapenem MICs of ≤4 mg/liter and without a carbapenemase gene than those who acquired isolates with carbapenem MICs of ≥8 mg/liter suggest that a high carbapenem MIC, rather than the presence of carbapenemase gene, is associated with an unfavorable outcome in patients with *Acinetobacter* bacteremia treated with carbapenems.

Early identification of patients who acquired isolates with a carbapenem MIC of ≥8 mg/liter is important, because carbapenem therapy at standard doses is likely to fail. In addition to PCR detection of the genetic structures associated with carbapenem resistance, the multiplex PCR assay that identifies *A. baumannii* (19) can also be used as a tool to predict higher carbapenem MICs. Medical centers that are unable to perform PCR for *Acinetobacter* can use acquisition in an ICU and prior use of antipseudomonal carbapenems as independent risk factors to consider these isolates to have carbapenem MICs of ≥8 mg/liter.

In the current study, we included only those patients with *Acinetobacter* bacteremia who received the standard dose of carbapenem therapy. 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, 20, 21). Further studies are needed to evaluate the effect of various carbapenem dosing strategies on the clinical outcome of patients with *Acinetobacter* infections.

The major limitations of this study are its retrospective design, intrinsic selection bias, and strict inclusion criteria. The strengths of this study are the inclusion of a large number of patients from multiple medical centers located in representative regions of Taiwan, recent isolates, and detailed characterization of resistance markers among isolates with various carbapenem susceptibilities. Our findings are consistent with the major findings of a previous study (13). The sensitivity analysis excluding the overlapping cases between the previous single-center study and the current multicenter study yielded similar results, which adds credence to the robustness of our results.

In conclusion, patients with *Acinetobacter* bacteremia and treated with a carbapenem had a more favorable outcome when the carbapenem MICs of the isolates were ≤4 mg/liter than those with an isolate with an MIC of ≥8 mg/liter.

MATERIALS AND METHODS

Study design and patient population. This retrospective cohort study was conducted at 4 medical centers located in different parts of Taiwan, including (in alphabetical order): 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. Adult patients age >20 years with *Acinetobacter* bacteremia between January 2011 and December 2015 were identified from microbiological records. Patients who had monomicrobial growth of *Acinetobacter* spp. in blood cultures and had received either imipenem or meropenem as initial monotherapy within 24 h of the onset bacteremia for a minimum of 24 h were included in the study. For patients with creatinine clearance (CL_{CR}) of >50 ml/min/1.73 m^2, 500 mg of imipenem was administered intravenously every 6 h, and 1 g of meropenem was administered every 8 h. For patients with CL_{CR} of 10 to 50 ml/min/1.73 m^2, 250 mg of imipenem was administered every 8 h. For patients with CL_{CR} of 10 to 25 or 25 to 50 ml/min/1.73 m^2, 500 mg or 1 g of meropenem was administered every 12 h, respectively. For patients with CL_{CR} of <10 ml/min/1.73 m^2, 250 mg of imipenem was administered every 12 h, and 500 mg of meropenem was administered every 24 h. Imipenem/meropenem was normally infused for 30 to 60 min, and a uniform dose/infusion strategy was used across all sites. Patients who received inappropriate dosages of carbapenem for end organ function, and those with incomplete medical records were excluded. The institutional review board (IRB) of each hospital approved the protocol (CCH, IRB no. 140514; MMH, IRB no. 14MMHIS125; TVGH, IRB no. 2014-07-006CC; TSGH, IRB no. 1-103-05-100).

Data collection and definition. The medical records of the patients were retrospectively reviewed and analyzed. Patients were assessed for demographic characteristics, duration of hospital and ICU stays, comorbidities, the presence of tubes, lines, and drainage catheters at the time of bacteremia onset, and time of receipt, dose, and route of therapy with individual antimicrobial drugs. An episode of *Acinetobacter* bacteremia was defined as isolation of an *Acinetobacter* sp. from a blood culture on 1 or more occasions and clinical manifestations compatible with sepsis syndrome. The onset of bacteremia was defined as the day the blood culture was obtained that eventually yielded *Acinetobacter* species. Recent stay in an ICU was defined as within 2 weeks of the first positive blood culture. Episodes of bloodstream infection were considered acquired in the ICU if they occurred 48 h after ICU admission. Chemotherapy

was defined as receipt of cytotoxic agents within 6 weeks before the onset of bacteremia. Immunosuppressive therapy was defined as receipt of an immunosuppressive agent within 2 weeks or corticosteroid use at a dosage equivalent to or higher than 15 mg of prednisolone daily for 1 week within 4 weeks prior to the onset of bacteremia. Recent surgery was defined as an operation 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 (22). Prior use of antimicrobial agents was defined as treatment with these drugs within 30 days prior to the date of onset of bacteremia. The severity of the infection was evaluated using the Acute Physiology and Chronic Health Evaluation (APACHE) II score within 24 h before the onset of bacteremia. The all-cause 30-day mortality rate was used as the endpoint; it was defined as death occurring within 30 days after the date of onset of bacteremia. No follow-up was done after hospital discharge unless the discharge occurred before the 30-day time limit. For those who were discharged before the 30-day limit, their status was determined by directly contacting the patient or by review of their outpatient records; no patients in this group were lost to follow-up.

Laboratory investigations. 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'Etoile, France). *Acinetobacter baumannii* was identified by a multiplex PCR method (19). Isolates recognized as non-*baumannii Acinetobacter* spp. were identified to the genomic species level by 16S-23S ribosomal DNA intergenic spacer sequence analysis, as previously described (23). The clonality was determined by pulsed-field gel electrophoresis, as previously described (24). MICs of carbapenems and antimicrobial susceptibilities of other agents were determined by agar dilution, in accordance with the recommendations of the CLSI (5). Multidrug resistance (MDR) was defined as resistance to any agent in at least three of the following classes of antimicrobials: aminoglycosides, antipseudomonal 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 ($bla_{\text{OXA-23}}$-like, $bla_{\text{OXA-24}}$-like, $bla_{\text{OXA-51}}$-like, $bla_{\text{OXA-58}}$-like, and $bla_{\text{OXA-143}}$-like genes) and metallo-β-lactamase genes (25). The upstream locations of insertion sequences (ISs) IS*Aba1* of the $bla_{\text{OXA-51}}$-like or $bla_{\text{OXA-23}}$-like gene and the IS*1008* or IS*1006* upstream of the $bla_{\text{OXA-58}}$-like gene were determined by PCR mapping (18, 25–28).

Statistical analysis. Data were analyzed using the SPSS software for Windows, version 22.0. A χ^2 test or Fisher's exact test was used to compare categorical differences. Continuous variables were analyzed using the Mann-Whitney *U* test or two-sample *t* test. The time to mortality was analyzed using the Kaplan-Meier curve and log rank test. Logistic regression models were used to explore independent predictors for mortality. Variables with a *P* value of <0.10, as determined using univariate analysis, were included in a multiple conditional logistic regression analysis. Classification and regression tree (CART) modeling was utilized to define a split in the carbapenem MIC distribution that maximized the difference in mortality. 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.00661-17.

SUPPLEMENTAL FILE 1, PDF file, 0.7 MB.

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We declare no relevant conflicts of interest related to this article.

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