

Clinical Features and Risk Factors for Development of Breakthrough Gram-Negative Bacteremia during Carbapenem Therapy

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With the increasing use of carbapenems, carbapenem-resistant Gram-negative bacteria have become a major concern in health care-associated infections. The present study was performed to evaluate the clinical and microbiological features of breakthrough Gram-negative bacteremia (GNB) during carbapenem therapy and to assess risk factors for development of breakthrough GNB. A case-control study was performed at a tertiary hospital from 2005 to 2014. Case patients were defined as individuals whose blood cultures grew Gram-negative bacteria while the patients were receiving carbapenems for at least 48 h before breakthrough GNB. Age-, sex-, and date-matched controls were selected from patients who received carbapenem for at least 48 h and did not develop breakthrough GNB during carbapenem treatment. A total of 101 cases of breakthrough GNB were identified and compared to 100 controls. The causative microorganisms for breakthrough GNB were *Stenotrophomonas maltophilia* ($n = 33$), *Acinetobacter baumannii* ($n = 32$), *Pseudomonas aeruginosa* ($n = 21$), and others ($n = 15$). Approximately 90% of *S. maltophilia* isolates were susceptible to levofloxacin and trimethoprim-sulfamethoxazole. The most common infection types were primary bacteremia (38.6%) and respiratory infections (35.6%). More than half of the patients died within a week after bacteremia, and the 30-day mortality rate was 70.3%. In a multivariate analysis, a longer hospital stay, hematologic malignancy, persistent neutropenia, immunosuppressant use, and previous colonization by causative microorganisms were significantly associated with breakthrough GNB. Our data suggest that *S. maltophilia*, *A. baumannii*, and *P. aeruginosa* are the major pathogens of breakthrough GNB during carbapenem therapy, in association with a longer hospital stay, hematologic malignancy, persistent neutropenia, immunosuppressant use, and previous colonization.

Carbapenems, such as meropenem, imipenem, and doripenem, are the currently preferred agents for treating serious bacterial infections caused by multidrug-resistant (MDR) Gram-negative pathogens, such as members of the *Enterobacteriaceae* producing extended-spectrum β -lactamases or AmpC β -lactamase, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* (1). With the increasing use of carbapenems, however, carbapenem-resistant (CR) Gram-negative bacteria have become a major concern in health care-associated infections (2). In the United States, more than 23,000 infections caused by MDR *A. baumannii*, MDR *P. aeruginosa*, or CR *Enterobacteriaceae* are reported annually (3). In the Republic of Korea, the incidence of imipenem-resistant *A. baumannii* infections increased from 43.6% in 2006 to 82.5% in 2010 in intensive care unit (ICU) patients (4).

The term “breakthrough bacteremia” is defined as an episode of continuous or new-onset bacteremia in a patient receiving appropriate antibiotics for the microorganism recovered from blood cultures (5–11). In addition to the use of unsuitable antibiotics—due to either resistance of the microorganism (5, 8, 9, 11) or a suboptimal concentration of active drug at the target organ (5)—a particular type of microorganism (8, 9), inadequate control of the infectious source (5, 7, 8), and host immune status (5–11) may account for breakthrough bacteremia. Some reports have addressed breakthrough bacteremia in patients receiving any antibiotics (5–7), quinolones alone (8–10), or macrolides alone (11). However, little is known regarding breakthrough bacteremia during carbapenem treatment.

Some authors reported that breakthrough bacteremia was associated with poor outcomes compared to those for nonbreakthrough bacteremia (6, 7). Furthermore, because carbapenems

are usually indicated for severe infections caused by MDR Gram-negative pathogens in severely ill or immunocompromised patients, breakthrough Gram-negative bacteremia (GNB) can be fatal. Therefore, this study was performed to evaluate the clinical and microbiologic features of breakthrough GNB during carbapenem therapy and to assess risk factors for development of breakthrough GNB.

MATERIALS AND METHODS

Study design and patient population. A case-control study was performed at Samsung Medical Center, Seoul, Republic of Korea, a university-affiliated 1,950-bed tertiary care hospital, from September 2005 to July 2014. Patients who were older than 18 years were included in the study. We searched for initial eligible patients who had received a type II carbapenem (e.g., imipenem, meropenem, or doripenem) for at least 48 h and who developed GNB. Case patients were defined as individuals whose blood cultures grew Gram-negative bacteria and who had been receiving a type II carbapenem (e.g., imipenem, meropenem, or doripenem) for at least 48 h before breakthrough bacteremia. Patients who received ertap-

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enem were not included in this study. Patients whose blood cultures yielded the same Gram-negative bacteria as those from a previous infection were excluded.

To establish the control group, we screened adults who received carbapenems for more than 48 h and had no breakthrough bacteremia during carbapenem therapy. The controls were selected and matched to case patients based on age, sex, and date of carbapenem therapy (within 1 month). One control patient was matched to each case patient. This study was performed and described in accordance with the STROBE guidelines for the reporting of cohort studies.

Data collection and definition. Medical records were reviewed for the case and control groups. The following data were collected: age; sex; duration of hospital stay before carbapenem therapy; duration of carbapenem therapy; presence of polymicrobial infection; absolute neutrophil count (ANC); underlying diseases; severity of underlying illness; comorbid conditions; organ transplantation or hematopoietic stem cell transplantation; presence of a central venous catheter (CVC), urinary catheter, nasogastric tube, or percutaneous drainage; acquisition site for causative microorganisms; type of carbapenem used; primary focus of infection; and 7-day, 30-day, infection-related, and in-hospital mortality rates. Microbiological data were obtained from the database at our clinical microbiology laboratory.

The severity of the underlying illness was evaluated on the basis of McCabe and Jackson classification. Charlson's weighted index of comorbidity (WIC) was used to evaluate comorbid conditions (12). Neutropenia was defined as an ANC of <500 cells/mm³ or an ANC that was expected to decrease to <500 cells/mm³ during the next 48 h, according to the clinical practice guidelines of the Infectious Diseases Society of America (13). Clinical diagnosis was assessed by the attending physician, taking into account the clinical situation, laboratory results, and imaging studies. A catheter-related bloodstream infection (CRBSI) was diagnosed when the same organism grew from at least one percutaneous blood culture and from a culture of the catheter tip or when microbes from a blood sample drawn from a catheter hub were grown for at least 2 h before microbes from a blood sample from a peripheral vein (14). The severity of acute illness was assessed at the time of positive blood culture by using the Pitt bacteremia score as described previously (15). Previous colonization by causative microorganisms was defined as the isolation of causative microorganisms from the skin, mucous membranes, open wounds, or discharge in the absence of relevant signs or symptoms in the patients. We defined infection-related mortality as death that could be attributed to breakthrough GNB as the immediate cause. Infection-related death was considered to be related to breakthrough GNB if ≥ 1 of the following criteria were present: (i) blood cultures were positive for GNB at the time of death, (ii) death occurred before resolution of signs and symptoms of GNB, and (iii) death occurred ≤ 14 days after breakthrough GNB, without another explanation.

Microbiologic tests. Blood samples for culture were taken from peripheral veins or central lines. Blood cultures were processed by use of a Bactec-9240 system (Becton Dickinson, Sparks, MD) or a BacT/Alert 3D system (bioMérieux Inc., Marcy l'Etoile, France). To identify microbes and to test their antimicrobial susceptibility, a Vitek II automated system (bioMérieux Inc.) was used with a standard identification card and the modified broth microdilution method. MIC breakpoints and quality control protocols were used according to standards established by the Clinical and Laboratory Standards Institute (CLSI) (16–19).

Statistical analysis. Student's *t* test and the Mann-Whitney test were used to compare continuous variables, and the chi-square test and Fisher's exact test were used for comparison of categorical variables. To identify risk factors for breakthrough GNB, a logistic regression model was used to control for confounding variables. All *P* values were two-tailed, and *P* values of <0.05 were considered to be statistically significant. Variables that were statistically significant in the univariate analyses were candidates for multivariate analysis, in addition to the main variable of interest. SPSS

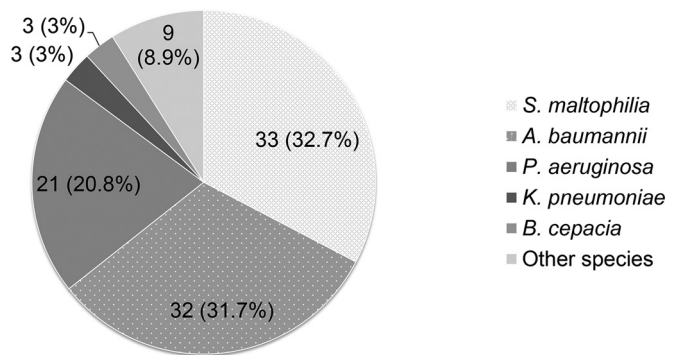


FIG 1 Distribution of pathogens of breakthrough Gram-negative bacteremia during carbapenem therapy.

for Windows/PASW, version 22.0 (IBM, Armonk, NY), was used for analysis.

RESULTS

Causative microorganisms for breakthrough GNB. A total of 1,955 GNB episodes were initially identified. Among these episodes, 101 episodes were consistent with the definition of breakthrough GNB (5.2% [101/1,955 episodes]). The causative pathogens for breakthrough GNB are presented in Fig. 1. *Stenotrophomonas maltophilia* ($n = 33$; 32.7%) was the most common pathogen, followed by *Acinetobacter baumannii* ($n = 32$; 31.7%), *Pseudomonas aeruginosa* ($n = 21$; 20.8%), and others ($n = 15$; 14.9%). Among the 32 *A. baumannii* and 21 *P. aeruginosa* isolates, 27 (84.4%) and 17 (81.0%), respectively, were not susceptible to carbapenems. None of the *A. baumannii* and *P. aeruginosa* isolates were colistin resistant. Approximately 90% of *S. maltophilia* isolates were susceptible to levofloxacin and trimethoprim-sulfamethoxazole (Table 1).

Clinical outcomes for patients with breakthrough GNB. Variables related to the clinical presentation of breakthrough GNB were analyzed and are presented in Table 2. Primary bacteremia and respiratory infections accounted for more than half of the cases of breakthrough GNB. None of the cases of breakthrough GNB resulted from urinary tract or central nervous system infection. Although primary bacteremia was the most common infection overall, respiratory infections were most common in patients with *A. baumannii* bacteremia. The outcomes of breakthrough GNB were poor, and more than half of the patients died within a week after bacteremia. The mortality rate was highest for *A. baumannii* infections, followed by infections with *P. aeruginosa*, *S. maltophilia*, and others. Mortality rates did not differ significantly between patients who received appropriate empirical antibiotics and those who did not (7-day mortality rates, 51.5% versus 61.8%, respectively; $P > 0.05$).

Risk factor analysis for development of breakthrough GNB. The baseline characteristics of patients with breakthrough GNB and of the control group are presented in Table 3. Both groups were predominantly male, and the prevalences of underlying diseases, including diabetes mellitus and cardiovascular, liver, pulmonary, renal, and neurologic diseases, were similar. The total durations of hospital stay were also similar. However, patients with breakthrough GNB had significantly longer hospital stays before carbapenem treatment ($P < 0.001$). Larger proportions of patients in the case group had hematologic malignancy, under-

TABLE 1 Antimicrobial susceptibility results for causative microorganisms of breakthrough Gram-negative bacteremia^a

Pathogen and antibiotic(s)	No. of susceptible isolates/ total no. of isolates (%)
<i>Stenotrophomonas maltophilia</i>	
Levofloxacin	30/33 (90.9)
Trimethoprim-sulfamethoxazole	30/33 (90.9)
Ticarcillin-clavulanate	6/12 (50.0)
Minocycline	21/21 (100)
<i>Acinetobacter baumannii</i>	
Levofloxacin	1/14 (7.1)
Amikacin	9/32 (28.1)
Tigecycline	0/3 (0.0)
Minocycline	26/29 (89.7)
Colistin	30/30 (100)
Trimethoprim-sulfamethoxazole	5/29 (17.2)
<i>Pseudomonas aeruginosa</i>	
Levofloxacin	6/13 (46.2)
Amikacin	14/21 (66.7)
Colistin	21/21 (100)
Ciprofloxacin	12/21 (57.1)
Ceftazidime	9/21 (42.9)
Cefepime	11/21 (52.4)
Piperacillin-tazobactam	8/21 (38.1)
Aztreonam	5/21 (23.8)

^a A Vitek II automated system (bioMérieux Inc.) was used with a standard identification card and the modified broth microdilution method to identify microbes and to test their susceptibility to antimicrobials, including colistin. MIC breakpoints and quality control protocols were used according to standards established by the Clinical and Laboratory Standards Institute (from 2005 to 2008, document M100-S13 [16]; from 2009 to January 2011, document M100-S18 [17]; from February 2011 to April 2012, document M100-S20 [18]; and from May 2012 to July 2014, document M100-S24 [19]).

went hematopoietic stem cell transplantation ($P < 0.05$), and were in a neutropenic state during carbapenem therapy ($P < 0.05$). McCabe and Jackson scores were higher for the case group than for the control group ($P < 0.05$). Risk factors for development of breakthrough GNB are presented in Table 4. In the multivariate analysis using a logistic regression model, a longer hospital stay, hematologic malignancy, persistent neutropenia during carbapenem treatment, immunosuppressant use, and previous colonization by causative microorganisms were independent risk factors associated with breakthrough GNB during carbapenem therapy.

DISCUSSION

This study demonstrated that *S. maltophilia* may be the main pathogen for breakthrough GNB during carbapenem therapy, along with MDR *A. baumannii*, MDR *P. aeruginosa*, and CR *Enterobacteriaceae*. Breakthrough GNB was independently associated with a prolonged hospital stay before carbapenem treatment, hematologic malignancy, persistent neutropenia during carbapenem treatment, and previous colonization with causative microorganisms. Although *Escherichia coli* and *P. aeruginosa* were the most common Gram-negative bacteria in breakthrough GNB in previous studies (5–8, 10), *S. maltophilia* was the most common pathogen in breakthrough GNB during carbapenem therapy in our study.

S. maltophilia is an important nosocomial pathogen with intrinsic multidrug resistance (20). Neutropenia, underlying malig-

TABLE 2 Clinical features and outcomes for 101 patients with breakthrough Gram-negative bacteremia during carbapenem therapy

Variable ^a	No. (%) of patients ^b
Type of infection	
Primary bacteremia	39 (38.6)
Catheter-related infection	12 (11.9)
Respiratory infection	36 (35.6)
Urinary tract infection	0 (0.0)
Hepatobiliary infection	4 (4.0)
Intra-abdominal infection	7 (6.9)
Skin and soft tissue infection	2 (2.0)
Deep neck infection	2 (2.0)
Severity of illness	
Pitt bacteremia score (median [IQR])	4.0 (2, 12)
ICU care	70 (69.3)
Acute renal failure	51 (50.5)
LOH after event (median [IQR])	7.0 (3.0, 23.0)
Duration of ICU care (days) (median [IQR])	3.0 (1.0, 7.0)
Mortality	
7-day mortality	55 (54.5)
30-day mortality	71 (70.3)
In-hospital mortality	78 (77.2)
Infection-related mortality	60 (59.4)
Time to death (days) (median [IQR])	5.0 (2.0, 18.5)

^a Abbreviations: GNB, Gram-negative bacteremia; IQR, interquartile range; ICU, intensive care unit; LOH, length of hospital stay.

^b Unless specified otherwise.

nancy, prolonged hospitalization, previous antibiotic use, steroid use, mechanical ventilator support, and indwelling central venous catheters have been reported as major risk factors for *S. maltophilia* bacteremia (20–23). Our study also showed that hematologic malignancy, persistent neutropenia, and prolonged hospitalization were risk factors for breakthrough GNB. However, only 4 patients (12%) with breakthrough *S. maltophilia* bacteremia had CRBSI in our study. Rather, respiratory infection and primary bacteremia were the main types of infection. Note, though, that more than half of patients with breakthrough GNB were in a neutropenic state, and it may be difficult to accurately distinguish between primary bacteremia and catheter-related infection in such patients. Micozzi et al. reported that more than 50% of *S. maltophilia* bacteremia cases presented as breakthrough infection, although no breakthrough bacteremia developed during carbapenem treatment (21). However, our study showed that *S. maltophilia* was the most common pathogen of breakthrough GNB during carbapenem treatment. This difference can be explained by the different study periods (1986 to 1996 versus 2005 to 2014) and by increased carbapenem use more recently. A previous study reported that increased carbapenem use was associated with an increased number of *S. maltophilia* isolates (24).

As expected, *A. baumannii* and *P. aeruginosa* were also major pathogens of breakthrough GNB during carbapenem treatment. Because the isolates were not available for further analysis, the mechanisms of carbapenem resistance in *A. baumannii* and *P. aeruginosa* isolates could not be evaluated. Prolonged hospitalization (25–27), previous carbapenem use (1, 25–30), ICU care (25, 27, 29), and the presence of medical devices (26–28) are considered risk factors for CR *A. baumannii* and CR *P. aeruginosa* colonization. The risk factors for CRGNB were similar to the risk fac-

TABLE 3 Clinical characteristics of the case and control groups^a

Characteristic	Value		P value
	Cases (n = 101)	Controls (n = 100)	
Age (yr) (mean ± SD)	50.5 ± 14.9	50.2 ± 14.6	0.900
No. (%) of males	65 (64.4)	66 (66.0)	0.800
No. of HD (median [IQR])	50.0 (23.0, 86.0)	43.5 (29.0, 80.0)	0.419
No. of HD until carbapenem treatment (median [IQR])	28.0 (18.0, 61.5)	16.7 (10.7, 26.4)	<0.001
No. (%) of patients receiving carbapenem			
Meropenem	85 (14.2)	85 (85.0)	1.000
Imipenem	12 (11.9)	12 (12.0)	1.000
Doripenem	4 (4.0)	3 (3.0)	0.712
Duration of carbapenem treatment (days) (median [IQR])	8.0 (5.0, 12.0)	11.0 (8.0, 14.0)	<0.001
No. (%) of patients with underlying disease			
Diabetes mellitus	17 (16.8)	19 (19.0)	0.689
Heart failure	4 (4.5)	14 (14.0)	0.014
Myocardial infarction	3 (3.0)	7 (7.0)	0.214
Cerebrovascular disease	4 (4.0)	5 (5.0)	0.748
Liver disease	13 (12.9)	13 (13.0)	0.978
Renal disease	6 (5.9)	5 (5.0)	0.769
Pulmonary disease	13 (12.9)	15 (15.0)	0.663
Solid tumor	20 (19.8)	25 (25.0)	0.337
Leukemia	45 (44.6)	33 (33.0)	0.093
Lymphoma	19 (18.8)	9 (9.0)	0.045
HSCT	14 (13.9)	5 (5.0)	0.032
SOT	8 (7.9)	12 (12.0)	0.334
Charlson's score (median [IQR])	2.0 (2.0, 3.0)	3.9 (2.0, 5.0)	0.172
McCabe score (median [IQR])	3.0 (2.0, 3.0)	2.0 (2.0, 3.0)	0.006
No. (%) of patients receiving ICU care	52 (51.5)	40 (40.0)	0.102
APACHE II score (median [IQR])	28.5 (24.0, 36.0)	24.0 (20.0, 29.0)	0.001
No. (%) of patients with:			
Mechanical ventilation	36 (35.6)	34 (34.0)	0.807
Renal replacement treatment	23 (22.8)	15 (15.0)	0.159
Neutropenia	67 (66.3)	43 (43.0)	0.001
Profound neutropenia	27 (26.7)	39 (39.0)	0.064
Prolonged neutropenia	22 (21.8)	34 (34.0)	0.053
Recovery from neutropenia during carbapenem treatment	4 (4.0)	30 (30.0)	<0.001
Severe mucositis ^b	16 (51.6)	15 (32.6)	0.095
Cytotoxic chemotherapy	63 (62.4)	47 (47.0)	0.029
Corticosteroid use	28 (27.7)	24 (24.0)	0.547
Immunosuppressant use	55 (54.5)	18 (18.0)	<0.001
Recent operation	15 (14.9)	27 (27.0)	0.034
Indwelling catheter			
Urinary catheter	58 (57.4)	54 (54.0)	0.625
CVC	93 (92.1)	88 (88.0)	0.334
Nasogastric tube	52 (51.5)	42 (42.0)	0.178
Percutaneous drainage	19 (18.8)	26 (26.0)	0.222
Prior invasive procedure	13 (12.9)	22 (22.0)	0.088
Previous colonization by Gram-negative bacteria	29 (28.7)	17 (17.0)	0.048

^a Abbreviations: SD, standard deviation; IQR, interquartile range; HD, hospital days; HSCT, hematopoietic stem cell transplant; SOT, solid organ transplant; APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit; CVC, central venous catheter.

^b Oral or gastrointestinal mucositis that interferes with swallowing or causes severe diarrhea during neutropenic period.

tors for CR *A. baumannii* and CR *P. aeruginosa* colonization. In addition, prior colonization by CR *A. baumannii* was a risk factor for the development of GNB (26). In this study, prolonged hospitalization before carbapenem treatment and prior carriage of CR Gram-negative bacteria were risk factors for breakthrough GNB. However, the proportions of patients with ICU care, mechanical

ventilation, indwelling catheters, and invasive procedures did not differ significantly between the case and control groups. Factors that affect host immunity, such as hematologic malignancies and neutropenia during carbapenem treatment, may play an important role in the development of GNB in patients previously colonized by MDR Gram-negative pathogens.

TABLE 4 Risk factors associated with development of breakthrough Gram-negative bacteremia^a

Factor	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Prolonged hospital stay ^b	3.43 (1.86–6.34)	<0.001	2.84 (1.33–6.05)	0.007
Hematologic malignancy	2.44 (1.41–4.40)	0.002	6.65 (2.90–15.25)	<0.001
HSCT	3.06 (1.06–8.84)	0.04	2.27 (0.46–11.29)	0.32
Persistent neutropenia ^c	10.39 (3.50–30.84)	<0.001	24.83 (6.33–97.45)	<0.001
Immunosuppressant use	5.45 (2.86–10.36)	<0.001	2.75 (1.23–6.12)	0.01
Previous colonization by causative microorganisms	1.97 (1.00–3.87)	0.05	2.74 (1.18–6.38)	0.02

^a Abbreviations: CI, confidence interval; HSCT, hematopoietic stem cell transplant.

^b More than 28 days prior to carbapenem treatment.

^c During carbapenem treatment.

In previous studies of breakthrough bacteremia, the presence of CVCs was identified as an independent risk factor (5, 7, 8). However, the proportions of individuals with CVCs in this study did not differ significantly between the case and control groups. Patients with persistent bacteremia with the same pathogen were excluded because we intended to evaluate risk factors for bacteremia caused by a new pathogen during carbapenem therapy, with an appropriate source control for previous infection. The traditional definition may be suitable for studying breakthrough bacteremia during all antibiotic treatments for any pathogen (i.e., Gram-positive and -negative bacteria and fungi). Given the limited therapeutic options for uncontrolled Gram-negative bacterial infection during carbapenem treatment, physicians do their best to locate an uncontrolled source of infection or to administer appropriate antimicrobial therapy in cases of persistent GNB. Although we did not find the presence of a CVC to be an independent risk factor for breakthrough GNB, CVCs might be an important source. CRBSI was the third most common type of infection for breakthrough GNB.

We showed that previous colonization by MDR Gram-negative bacteria (mostly in the respiratory tract) was an independent risk factor for breakthrough GNB. Prolonged impairment of host immunity, including prolonged neutropenia and immunosuppressant use, as well as the selective antibiotic effect of carbapenems, may favor the development of breakthrough GNB in such patients.

According to the antibiotic susceptibility results in this study, there is no single antibacterial agent which is active against all three of the major pathogens for breakthrough GNB. As combination therapy, levofloxacin, trimethoprim-sulfamethoxazole, or minocycline with colistin may be an option for the selection of empirical antimicrobial therapy in patients who develop symptoms and signs of sepsis while receiving carbapenem therapy, particularly for patients at high risk of breakthrough GNB. The outcomes of breakthrough GNB were poor regardless of the use of appropriate antimicrobial therapy. Fatal underlying conditions, such as hematologic malignancy and prolonged neutropenia, as well as limited therapeutic options, may result in high mortality. Strategies to reduce colonization by MDR pathogens, such as proper infection control practices, antibiotic stewardship, environmental precautions, and routine screening cultures, should be applied to the care of patients at high risk for breakthrough GNB during carbapenem treatment (31). Further studies are necessary to find appropriate prophylactic methods for high-risk patients colonized by MDR pathogens. We also found that the duration of carbapenem therapy was longer for the control group. There may

be several reasons for this, e.g., case patients died earlier regardless of appropriate therapy (the median time to death for the case group was 5 days) or there were earlier changes of carbapenem to other antibacterial agents once a carbapenem-resistant isolate was identified.

This study has several limitations. First, due to the retrospective study design, there might have been bias during data collection. Given that this study was an exploratory research study without an exact calculation of the sample size in a statistical manner, the study may have been underpowered to detect weaker but potentially clinically significant effects. Second, because we matched the control groups by age and sex, we could not evaluate the effects of age and sex as risk factors associated with development of breakthrough GNB. Third, while the study was conducted at a single medical center, the distribution of pathogens for breakthrough GNB may differ according to local epidemiology, especially in areas where carbapenemase-producing *Enterobacteriaceae* are highly prevalent. Further multicenter studies are needed to overcome this limitation. Finally, as this study was performed with the design of a case-control study, we could assess only the cumulative incidence of breakthrough GNB. A further study regarding this issue and including the incidence per day of carbapenem therapy may be warranted. Despite these limitations, this study may be the first and largest to evaluate the clinical presentation and risk factors of breakthrough GNB during carbapenem treatment, and we believe that the findings may provide useful information for clinicians who are caring for critically ill patients with carbapenem treatment.

Conclusions. Our data suggest that the most likely pathogens are *S. maltophilia*, *CR A. baumannii*, and *CR P. aeruginosa* when breakthrough GNB occurs during carbapenem therapy. The independent risk factors associated with breakthrough GNB were a longer hospital stay before carbapenem administration, hematologic malignancy, persistent neutropenia during carbapenem treatment, immunosuppressant use, and previous colonization by causative microorganisms.

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