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Original Article

Risk factors of multidrug resistance in nosocomial bacteremia due to *Acinetobacter baumannii*: a case-control study

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Background and Purpose: *Acinetobacter baumannii* is an important nosocomial pathogen. Bacteremia caused by multidrug-resistant *A. baumannii* (MDRAB) leads to higher mortality and medical cost compared with non-MDRAB bacteremia. We aimed to identify risk factors of multidrug resistance in *A. baumannii* bacteremia.

Methods: A matched case-control study was conducted to compare the differences in risk factors of patients with MDRAB and non-MDRAB bacteremia.

Results: Sixty three patients with MDRAB bacteremia and 63 matched patients with non-MDRAB bacteremia were identified from hospital and laboratory records of the period 1996 to 2002. Multivariate logistic regression analysis identified four independent risk factors associated with multidrug resistance in *A. baumannii* bacteremic patients: previous colonization with *A. baumannii* (odds ratio [OR], 7.99; 95% confidence interval [CI], 2.1-30.6; p=0.002), antecedent antimicrobial therapy (OR, 6.10; 95% CI, 1.2-29.9; p=0.026) the number of recently prescribed antibiotics (OR 1.35; 95% CI, 1.0-1.8; p=0.026), and recent invasive procedures (OR, 4.17; 95% CI, 1.6-11.1; p=0.004).

Conclusions: Overall, patients with MDRAB bacteremia had earlier *A. baumannii* colonization, greater previous exposure to antimicrobial agents and recent invasive procedures. The results of this study demonstrate a rationale for the development of effective interventions to minimize the impact of MDRAB.

Key words: *Acinetobacter baumannii*; Anti-bacterial agents; Antibiotic exposure; Bacteremia; Cross infection; Drug resistance, multiple; Risk factors

Introduction

Acinetobacter baumannii strains are becoming increasingly important nosocomial pathogens [1]. This microorganism is difficult both to control and to treat, because of its prolonged environmental survival and ability to develop resistance to many antimicrobial agents [2]. Multidrug-resistant *A. baumannii* (MDRAB) have been rising steadily in recent years [2-7]. *A. baumannii* can result in a wide range of infections, including bacteremia, pneumonia, urinary tract infection, peritonitis, etc. Bacteremia is one of the most significant infections caused by *A. baumannii*, and is characteristically a nosocomial infection, particularly in intensive care units (ICUs) [8]. The clinical course may range from benign transient bacteremia to fulminant septic shock, with a crude mortality rate as high as 52% [9].

Due to the wide distribution and colonizing capability of *A. baumannii*, it does not always act as an infecting pathogen [10-12]. Risk factors may vary between areas with endemic colonization and epidemic outbreaks of infection [10,13]. Our previous study pointed out an increasing incidence of MDRAB in our institution [14]. In contrast to non-MDRAB, MDRAB bacteremia results in a higher morbidity and mortality, as well as increased medical cost [15,16]. The aim of this study was to identify risk factors of multidrug

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resistance in *A. baumannii* bacteremia, and to contrast MDRAB and non-MDRAB bacteremia in this regard.

Methods

Setting and study design

A case-control study was conducted in the National Cheng Kung University Hospital, which is a university-affiliated medical center with approximately 900 beds, including 67 intensive care beds, and serves a population of about two million in southern Taiwan. Patients with *A. baumannii* bacteremia hospitalized between April 1996 and December 2002 were identified from the records of the clinical microbiology laboratory.

Their hospital records and laboratory data were reviewed. Demographic information obtained from the charts included age, gender, hospital service, and dates of admission to hospital and discharge. Medical histories were reviewed for the underlying illness, admission diagnosis, and prior invasive procedures within one week or antimicrobial therapy within four weeks before the development of *A. baumannii* bacteremia. The severity of illness was evaluated at the first day of onset of bacteremia by use of the Simplified Acute Physiology Score II [17], and by the Pittsburgh bacteremic score [18]. Clinical presentations, presumed or documented source of bacteremia, roentgenographic studies, and prescribed antimicrobial agents were also recorded. For patients with more than one episode of *A. baumannii* bacteremia, only the first episode was considered.

Definitions

Multidrug resistance in *A. baumannii* was defined as resistance to at least four classes of commonly available antibiotics (penicillins, cephalosporins, aminoglycosides or fluoroquinolones), but susceptible to carbapenems (imipenem and meropenem), and non-multidrug resistance as being susceptible to at least one class of drugs and to carbapenems.

Colonizations and nosocomial infections were defined according to the definition of the Centers for Disease Control and Prevention (Atlanta, GA, USA) [19]. Polymicrobial infection was defined as the isolation of two or more microorganisms during an infectious episode, excluding contamination. Immunosuppression was defined as the receipt of corticosteroid (10 mg per day or equivalent dosage) for more than two weeks, or antineoplastic chemotherapy or antirejection medication within the month prior to bacteremia onset. Prior antibiotic therapy was defined as the receipt of a systemic antimicrobial agent for at least 72 h within the preceding four weeks. Recent invasive procedures was defined as receipt of procedures such as arterial catheters, central venous catheters, pulmonary artery catheters, urinary indwelling catheters, or endotracheal tubes within 48 h before the onset of bacteremia.

Matching and selection of control patients

Controls were selected from patients with bacteremia caused by *A. baumannii* without multidrug resistance, hospitalized in the same unit and during the same period (3 days before or after the date of bacteremia onset) as the matched cases, i.e., patients with MDRAB bacteremia. Only adults (≥18 years old) were included in the study. Controls were matched with cases at a ratio of 1:1.

Microbiological analysis

All blood cultures were processed by the clinical microbiology laboratory using the BACTEC 9240 system (Becton Dickinson and Company, Franklin Lakes, NJ, USA). *A. baumannii* complex, referred to as *A. baumannii* in this study, was identified by both standard microbiological techniques [20] and the VITEK system (bioMérieux, Marcy l'Etoile, France). Antimicrobial susceptibility testing was determined by disk diffusion technique, according to the criteria established by the National Committee for Clinical Laboratory Standards [21].

Statistical analysis

Continuous variables were expressed as mean values ± standard deviation, and categorical variables as a proportion of the total number of patients. Univariate analysis was conducted by the chi-squared test for categorical variables and the Student's *t* test or Mann-Whitney *U* test for continuous variables, as indicated. Factors were considered to be significant at a p value of <0.05. All p values are two tailed. Risk factors associated with multidrug resistance in patients with *A. baumannii* bacteremia were identified by stepwise logistic regression analysis of variables selected by the univariate analysis, with a limit of a p value of 0.05 for entering and removing variables.

Results

From 1996 to 2002, a total of 430 episodes of *A. baumannii* bacteremia was recorded. Among them, we identified 63 patients (14.6%) with MDRAB bacteremia.

Another 63 patients with non-MDRAB were chosen as the control cohort. At the onset of MDRAB bacteremia, 41 cases (65.1%) were treated in ICUs, 16 (25.4%) at medical wards, and 6 (9.5%) at surgical wards.

The two groups did not differ in baseline characteristics such as age, gender and underlying diseases or comorbidities. Also, there was no significant difference in the portals of entry of bacteremia, places of acquisition, and proportion of polymicrobial bacteremia (Table 1). Patients with MDRAB bacteremia had a longer hospitalization period before the onset of bacteremia compared to those with non-MDRAB bacteremia (33.0 ± 30.3 vs 21.9 ± 18.6 days).

Risk factors associated with multidrug resistance

Risk factors related to multidrug resistance in patients with *A. baumannii* bacteremia are shown in Table 2, along with the results of univariate analysis. Cases were significantly more likely to receive antimicrobial therapy than controls (92.1% vs 69.8%, p=0.012). Cases were significantly more likely than controls to receive more antibiotic agents within 4 weeks before bacteremia (2.6 ± 1.5 vs 1.8 ± 1.7, p=0.008). Prior to the onset of bacteremia, however, no specific antimicrobial agent was prescribed more often than others.

Prior to the onset of bacteremia, seventeen cases (27.0%), in contrast to 3 controls (4.7%), had been colonized with an *A. baumannii* isolate exhibiting the same resistant phenotype (p=0.01). At the onset of bacteremia, 57 cases (90.5%) and 53 controls (84.1%) had at least one invasive device in place. More cases (n = 24, 38.1%) than controls (8, 12.7%) [p=0.02] had received invasive procedures within 48 h before the onset of bacteremia. Multivariate logistic regression analysis identified four independent risk factors associated with multidrug resistance in *A. baumannii* bacteremia patients: previous colonization with *A. baumannii* (odds ratio [OR], 7.99; 95% confidence interval [CI], 2.1-30.6; p=0.002), antecedent antimicrobial therapy

Table 1. Clinical characteristics of patients with multidrug-resistant *Acinetobacter baumannii* (MDRAB) bacteremia and non-MDRAB

Characteristic	MDRAB (n = 63) No. (%)	Non-MDRAB (n = 63) No. (%)	*p*
Age (years; mean ± SD)	63.4 ± 17.8	59.1 ± 17.8	0.18
Length of hospital stay before acquisition of *Acinetobacter baumannii* (days; mean ± SD)	33.0 ± 30.3	21.9 ± 18.6	0.015
Gender (female)	21 (33.3)	23 (36.5)	0.3
Pittsburgh bacteremic score (mean ± SD)	4.67 ± 2.92	3.84 ± 2.57	0.095
SAPS II score (mean ± SD)	47.95 ± 18.07	42.11 ± 16.79	0.062
Comorbidity			
Diabetes mellitus	26 (41.3)	25 (39.7)	1.0
Malignancy	24 (38.1)	25 (39.7)	1.0
Solid tumor	17 (26.9)	21 (33.3)	0.6
Hematological malignancy	7 (11.1)	4 (6.3)	0.5
Chronic renal disease	9 (14.3)	8 (12.7)	1.0
Heart failure	5 (7.9)	10 (15.9)	0.3
Neutropenia	5 (7.9)	1 (1.6)	0.2
Immunosuppression	5 (7.9)	10 (15.9)	0.3
Liver cirrhosis	4 (6.3)	12 (19.0)	0.06
Chronic obstructive pulmonary disease	4 (6.3)	0 (0)	0.1
None	8 (12.7)	8 (12.7)	1.0
Portal of entry			
Low respiratory tract infection	28 (44.4)	23 (36.5)	0.5
Primary bacteremia	25 (39.7)	26 (41.3)	1.0
Catheter-related infection	5 (7.9)	11 (17.5)	0.2
Urinary tract infection	2 (3.2)	1 (1.6)	1.0
Peritonitis	2 (3.2)	0 (0)	0.5
Soft tissue infection	1 (1.6)	1 (1.6)	1.0
Polymicrobial bacteremia	25 (39.7)	16 (25.4)	0.1

Abbreviations: SD = standard deviation; SAPS = Simplified Acute Physiology Score

Table 2. Risk factors for acquisition of multidrug-resistant *Acinetobacter baumannii* (MDRAB) bacteremia

Risk factor	MDRAB (n = 63) No. (%)	Non-MDRAB (n = 63) No. (%)	*p*
Prior colonization	17 (27.0)	3 (4.7)	0.01
Prior antimicrobial therapy	58 (92.1)	44 (69.8)	0.012
Cephalosporin	43 (68.2)	32 (50.8)	0.1
Broad-spectrum penicillin	24 (38.1)	15 (23.8)	0.20
Fluoroquinolone	21 (33.3)	14 (22.2)	0.2
Glycopeptide	19 (30.2)	11 (17.5)	0.6
Aminoglycoside	11 (17.5)	12 (19.0)	0.8
Carbapenem	11 (17.5)	5 (7.9)	1.0
Metronidazole	5 (7.9)	4 (6.3)	1.0
Duration of antimicrobial therapy before bacteremia (mean ± SD)	13.3 ± 10.4	10.7 ± 9.4	0.2
Number of prescribed systemic antibiotics (mean ± SD)	2.6 ± 1.5	1.8 ± 1.7	0.008
Recent invasive procedure	24 (38.1)	8 (12.7)	0.02
Presence of invasive device	57 (90.5)	53 (84.1)	0.4
Central venous catheter	47 (74.6)	41 (65.1)	0.3
Arterial catheter	41 (65.1)	30 (47.6)	0.07
Endotracheal tube	38 (60.3)	35 (55.6)	0.7
Urinary indwelling catheter	32 (50.8)	23 (36.5)	0.2
Pulmonary artery catheter	1 (1.5)	4 (6.3)	0.4
Total number of invasive devices (mean ± SD)	2.8 ± 1.6	2.5 ± 1.8	0.3
Prior surgical procedures[a]	9 (19.6)	17 (37.0)	0.1
Prior admission to intensive care unit[b]	35 (55.5)	32 (50.8)	0.7

Abbreviation: SD = standard deviation

[a]Surgical procedures required general anesthesia within 2 weeks prior to the onset of bacteremia.

[b]Admission to an intensive care unit within 4 weeks prior to the onset of bacteremia.

(OR, 6.10; 95% CI, 1.2-29.9; p=0.026), recent invasive procedure (OR, 4.17; 95% CI, 1.6-11.1; p=0.004), and the number of recently prescribed antibiotics (OR 1.35; 95% CI, 1.0-1.8; p=0.026) [Table 3].

Discussion

A. baumannii is emerging as an important pathogen in the hospital setting [1]. A previous study demonstrated that patients with MDRAB strains have longer lengths of stay in both the hospital and ICU than patients with drug-susceptible *Acinetobacter* [22]. MDRAB bacteremia also had a higher mortality rate and greater medical cost compared with non-MDRAB bacteremia [15,22].

Our results demonstrate that prior colonization, previous antimicrobial therapy, the number of recently prescribed antibiotics, and recent invasive procedures were independently related to the development of multidrug resistance in *A. baumannii* bacteremia. Selective pressure exerted by antibiotics plays a crucial role in the emergence and dissemination of these pathogens. In general, antibiotic exposure is not thought to directly induce resistance mechanisms, but promotes proliferation of antibiotic-resistant bacilli and inhibition of competing microflora [23]. In a meta-analysis study, prior use of carbapenems, third-generation cephalosporins and/or fluoroquinolones was an independent risk factor for acquisition of MDRAB [24]. However,

Table 3. Independent risk factors associated with multidrug resistance among patients with *Acinetobacter baumannii* bacteremia by multivariate logistic regression analysis

Risk factor	Odds ratio (95% confidence interval)	*p*
Length of hospital stay before acquisition of *Acinetobacter baumannii*	1.01 (0.99-1.03)	0.293
Prior colonization of isolates with an identical antibiogram	7.99 (2.1-30.6)	0.002
Number of recently prescribed antibiotics	1.35 (1.0-1.8)	0.026
Prior antimicrobial therapy	6.10 (1.2-29.9)	0.026
Recent invasive procedures	4.17 (1.6-11.1)	0.004

in our study, the prior prescription of carbapenems, third-generation cephalosporins or fluoroquinolones did not show a higher OR for acquisition of MDRAB compared to other kinds of antibiotics. This variation may be explained by the concept of Harris et al [25], who suggested that the selection of individuals infected with antibiotic-susceptible organisms as controls will lead the false identification of certain antibiotics and overestimation of the OR of the resistance-defining antibiotic. In our study, the number of antibiotics prescribed before bacteremia was also a significant independent risk factor for MDRAB acquisition.

Multiple invasive procedures and reservoirs have been related to a higher incidence of *A. baumannii* acquisition in an outbreak [10]. Invasive devices may not be intrinsically related factors, but they probably reflect the severity of the illness. Our study revealed that recent invasive procedures were associated with an increasing risk of resistance to multiple classes of drugs in *A. baumannii* bacteremia, by at least four-fold. This could be related to the presence of more critical conditions, inadequate implementation of infection control measures in urgent conditions, or a higher degree of acute organ dysfunction, leading to more invasive management. More importantly, transmission can occur as a result of contact between patients via the contaminated hands of health care staff during invasive procedures. Although the direct relationship between the procedures and MDRAB infections was not evident in the study, an earlier observation of high carriage rates of *A. baumannii* in health care workers and persistence in the hospital environments, supported the possibility of horizontal transmission in hospitals [1]. The appropriate adherence to standard infection control measures may reduce the risk of nosocomial acquisition of antimicrobial-resistant *A. baumannii*.

A. baumannii has been found to be able to colonize the human intestinal tract [23]. Therefore, the prevalence of colonized patients was likely to be an important determinant of MDRAB acquisition. Several studies have shown that intestinal colonization by Gram-negative bacilli, including *A. baumannii*, often precedes the onset of infection [26-29]. This is in agreement with the finding in the present study that 27% of patients with MDRAB bacteremia had been colonized by strains with an identical antibiogram. Colonization density, i.e., the proportion of body sites colonized with MDRAB, was also a significant risk factor for MDRAB infections [30]. Likewise, colonizations or infections with MDRAB have been independent risk factors for mortality [16]. Although some factors, such as illness severity and length of stay, have been associated with *A. baumannii* acquisition, these were often not amenable to modification [30]. These findings support the implementation of aggressive control measures to limit the transmission or acquisition of MDRAB, and subsequent MDRAB infections in hospitals.

In this study, not only prior exposures to antibiotics, but also variables related to hospitalization, were risk factors for nosocomial acquisition of antibiotic-resistant microorgansms. Some studies identified stay in the hospital or ICU, and the length of ICU stay, as risk factors for MDRAB acquisition [24]. In our study, the length of hospital stay before bacteremia was associated with multidrug resistance in the univariate analysis, but did not show significance in the multivariate analysis. This factor may be confounded by other factors.

In conclusion, recent antimicrobial therapy, the number of recently prescribed antibiotics, prior colonization of *A. baumannii*, and recent invasive procedures were identified as independent risk factors for multidrug resistance in *A. baumannii* bacteremia. The development of innovative control strategies is necessary to decrease the prevalence of antimicrobial-resistant *A. baumannii* infections and their ensuing morbidity or mortality.

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