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ORIGINAL ARTICLE

Risk factors for imipenem-nonsusceptible *Acinetobacter nosocomialis* bloodstream infection

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Background: The emergence of imipenem-nonsusceptible (INS) *Acinetobacter baumannii* complex has had a great impact on healthcare systems worldwide. Understanding the risk factors related to INS infection is useful for infection control. The risk factors for INS *A. baumannii* have been well documented; however, the risk factors related to INS *Acinetobacter nosocomialis* infection lack documentation. The purpose of this study was to identify the risk factors associated with INS *A. nosocomialis* bacteremia.
Methods: This retrospective 9-year study included 329 adults with *A. nosocomialis* bacteremia in a tertiary medical center in Taiwan. *Acinetobacter nosocomialis* was identified using a multiplex polymerase chain reaction method and sequence analysis of a 16S—23S intergenic spacer.
Results: Among 329 patients with *A. nosocomialis* bacteremia, 67 had INS isolates (20.4%). Patients with INS isolates tended to have a more severe form of the diseases [with ICU admission and a higher APACHE (Acute Physiology and Chronic Health Evaluation) II score], specific underlying diseases (associated with chronic lung diseases and end-stage renal diseases, but less commonly alcoholism and chemotherapy), multiple invasive procedures, pneumonia as a

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primary focus of infection, and prior antimicrobial use (sulbactam, antipseudomonal penicillins, aminoglycosides, and carbapenems). Multivariable analysis showed that ICU admission, chronic lung diseases, arterial line catheterization, total parenteral nutrition, and prior use of carbapenems were independent risk factors; prior use of carbapenems was found to be the most influential (odds ratio 6.36, 95% confidence interval 2.00—20.21; $p = 0.002$).
Conclusion: To our knowledge, this is the first study describing the risk factors associated with INS *A. nosocomialis* bacteremia. Regulated antibiotic control policy, especially for carbapenem, and infection control measures targeting patients hospitalized in ICU, with chronic lung diseases and multiple invasive procedures, may be helpful in reducing INS *A. nosocomialis* infection.

Introduction

Nosocomial infections have become a serious problem worldwide in recent years. One of the nosocomial pathogens is *Acinetobacter baumannii* complex (ABC), which frequently causes outbreaks of infection with high mortality in hospitalized patients.[1] With the widespread use of broad-spectrum antibiotics and the increasing number of immunocompromised patients, we are now facing the emergence of drug-resistant ABC worldwide.[2] Currently, most ABCs are highly resistant to many of the commonly used antibiotics because of both intrinsic and acquired mechanisms.[3,4] In Europe, the rate of resistance to carbapenems has been reported to be 27%,[5] whereas the SENTRY Surveillance Program found that it was 42.3% in the Asia-Pacific Rim nations.[6] In Taiwan, according to the annual report of the Taiwan Nosocomial Infections Surveillance System, the resistance rate to imipenem had increased to 66.8% in 2010.[7] Studies show that antibiotic resistance significantly prolongs the duration of intensive care unit (ICU) stays and hospitalization,[8,9] leading to increased hospitalization costs. In addition, patients with resistant ABC infection have a higher mortality rate than those infected with bacterial strains susceptible to antibiotics.[8,10,11]

The effective control of drug-resistant ABC outbreaks is, therefore, an important issue requiring knowledge of the infected population so that the dynamics of the spread of endemic and epidemic strains can be investigated and appropriate control measures can be introduced in a timely manner.[12] Numerous clinical studies on the risk factors for imipenem-nonsusceptible (INS) ABC infections, including bacteremia, have been published.[13,14] However, ABC comprises not only *A. baumannii*, but also *Acinetobacter nosocomialis* and *Acinetobacter pittii*, which can only be differentiated by molecular methods.[15,16] Information concerning the risk factors for INS *A. nosocomialis* infection is absent. Therefore, the purpose of this study was to identify the risk factors associated with INS *A. nosocomialis* bacteremia.

Materials and methods

Study population

This retrospective study was conducted between 2000 and 2008 in Taipei Veterans General Hospital, a 2900-bed tertiary care medical center in Taiwan. All adults with *A. nosocomialis* bacteremia and concurrent symptoms and signs of sepsis were included. Patients who were less than 18 years of age or whose medical records were not complete were excluded. The medical records were reviewed and recorded on a standard form. Demographic data, disease severity represented by the Acute Physiology and Chronic Health Evaluation (APACHE) II score, comorbidities, invasive procedures, antimicrobial agents administered within 1 month prior to the onset of bacteremia, and infection foci were recorded for analysis.

Definitions

Chronic lung diseases included chronic obstructive pulmonary diseases, tuberculosis, and asthma. Chronic kidney disease was defined as a glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2, whereas end-stage renal disease was defined as a GFR < 15 mL/min/1.73 m^2 or receipt of permanent renal replacement therapy for more than 3 months. Neutropenia was defined as an absolute neutrophil count <500 cells/mm^3. Immunosuppressant therapy included treatment for neoplastic diseases and organ transplantation, as well as the use of corticosteroids (equivalent to more than 10 mg of prednisolone daily for 5 days) within 4 weeks of the onset of bacteremia. Long-term intravenous access included Hickman catheters, port-A-catheters, and other permanent catheters. The origin of the bacteremia was defined as previously suggested.[17] This study was approved by the institutional review board of Taipei Veterans General Hospital.

Genomic species identification and antimicrobial susceptibility testing

ABC was phenotypically identified by the 32 GN system (bioMérieux, Marcy l'Etoile, France). The bacteria were stored at $-70^{\circ}C$ in trypticase cystine agar (Difco Laboratories, Le Pont de Claix, France) supplemented with 15% glycerol before use. A multiplex polymerase chain reaction[15] was used to identify *A. baumannii*. The non-*baumannii Acinetobacter* species were identified by amplification and sequence analysis of the 16S—23S rRNA intergenic spacer using universal primers.[16] The susceptibility and non-susceptibility of imipenem and other antimicrobial agents were determined by agar dilution methods. The interpretation was performed according to the guidelines of the Clinical and Laboratory Standards Institute.[18] For imipenem, a minimum inhibitory concentration (MIC) ≤ 4 mg/L was considered to reflect susceptibility, whereas an MIC > 4 mg/L was considered to show a nonsusceptible organism.

Table 1 Demographic data and underlying diseases of patients with imipenem-nonsusceptible (INS) and imipenem-susceptible (IS) *Acinetobacter nosocomialis* bacteremia

Characteristics	INS isolates (n = 67)	IS isolates (n = 262)	p
Age, median	76 (64–81)	72 (57–79)	0.132
Sex, male	48 (71.6)	179 (68.3)	0.600
Intensive care unit admission	58 (86.6)	121 (46.2)	<0.001
APACHE II score	26 (19–32)	18 (14–25)	<0.001
Concurrent infections	26 (38.8)	82 (31.3)	0.243
Polymicrobial bacteremia	16 (23.9)	45 (17.2)	0.208
Days of hospitalization prior to bacteremia, median	23 (11–43)	15 (9–26)	0.001
Underlying conditions			
Major operations	32 (47.8)	94 (35.9)	0.074
Hypertension	25 (37.3)	73 (27.9)	0.131
Type 2 diabetes mellitus	21 (31.3)	60 (22.9)	0.152
Chronic lung diseases	20 (29.9)	36 (13.7)	0.002
Solid tumor	20 (29.9)	108 (41.2)	0.088
Cerebrovascular diseases	17 (25.4)	49 (18.7)	0.224
Steroid use	14 (20.9)	56 (21.4)	0.932
Chronic kidney diseases	12 (17.9)	45 (17.2)	0.887
Congestive heart failure	11 (16.4)	26 (9.9)	0.133
Coronary artery diseases	11 (16.4)	45 (17.2)	0.883
Shock during bacteremia	10 (14.9)	25 (9.5)	0.202
Smoking	9 (13.4)	47 (17.9)	0.381
End-stage renal disease	8 (11.9)	10 (3.8)	0.015
Autoimmune diseases	4 (6.0)	15 (5.7)	>0.99
Chemotherapy	3 (4.5)	47 (17.9)	0.006
Use of immunosuppressants	2 (3.0)	11 (4.2)	>0.99
Liver cirrhosis	2 (3.0)	17 (6.5)	0.384
Peripheral arterial occlusive disease	2 (3.0)	4 (1.5)	0.606
Trauma	2 (3.0)	12 (4.6)	0.743
Aortic dissection	1 (1.5)	1 (0.4)	0.297
Burns	1 (1.5)	1 (0.4)	0.297
Hematologic malignancies	1 (1.5)	17 (6.5)	0.138
Neutropenia	1 (1.5)	7 (2.7)	>0.99
Alcoholism	0 (0)	29 (11.1)	0.004
Radiotherapy	0 (0)	2 (0.8)	>0.99

Data represent the median value (interquartile range) for continuous variables and the number of cases (%) for categorical variables.
APACHE II = Acute Physiology and Chronic Health Evaluation II.

Statistical analysis

All statistical analyses were performed using SPSS software (version 18.00; SPSS, Chicago, IL, USA). A value of p <0.05 was considered to be statistically significant. Fisher's exact test or the Chi-square test was used to compare categorical variables, whereas the Student t test or Mann–Whitney U test was used to compare the continuous ones. A logistic regression model was used to determine the independent risk factors associated with INS *A. nosocomialis* bacteremia. All variables with statistical significance in univariable analyses were entered into multivariable analyses to assess their association with imipenem nonsusceptibility.

Results

Among 329 patients with *A. nosocomialis* bacteremia, 67 (20.4%) patients had INS isolates and the remaining 262 (79.6%) patients had imipenem-susceptible (IS) isolates.

Demographic data and the underlying diseases of patients with INS and IS *A. nosocomialis* are shown in Table 1. Compared with patients with IS *A. nosocomialis*, those who had INS isolates were admitted to ICU more often (86.6% vs. 46.2%; $p < 0.001$), had higher APACHE II scores (26 vs. 18; $p < 0.001$), had a longer duration of hospitalization prior to the onset of bacteremia (23 vs. 15 days; $p < 0.001$), had more chronic lung diseases (29.9% vs. 13.7%; $p = 0.002$), and suffered from end stage renal disease more commonly (11.9% vs. 3.8%; $p = 0.015$). In contrast, patients with INS isolates were less likely to have a history of chemotherapy or alcoholism (4.5% vs. 17.9%, $p = 0.006$, and 0.0% vs. 11.1%, $p = 0.004$, for chemotherapy and alcoholism, respectively).

With respect to previous invasive procedures (Table 2), INS isolates were more commonly recovered from patients who had undergone multiple invasive procedures (5 vs. 1; $p < 0.001$) such as use of a nasogastric tube (82.1% vs. 43.1%; $p < 0.001$), foley catheterization (77.6% vs. 42.4%; $p < 0.001$), central venous catheterization (76.1% vs. 38.2%; $p < 0.001$), mechanical ventilation (74.6% vs. 32.4%;

Table 2 Previous use of invasive procedures in patients with imipenem-nonsusceptible (INS) and imipenem-susceptible (IS) *Acinetobacter nosocomialis* bacteremia

Characteristics	INS isolates ($n = 67$)	IS isolates ($n = 262$)	p
Total number of invasive procedures, median	5 (3–6)	1 (0–4)	<0.001
Nasogastric tube	55 (82.1)	113 (43.1)	<0.001
Foley catheterization	52 (77.6)	111 (42.4)	<0.001
Central venous catheter	51 (76.1)	100 (38.2)	<0.001
Mechanical ventilation	50 (74.6)	85 (32.4)	<0.001
Arterial line catheter	33 (49.3)	35 (13.4)	<0.001
Pulmonary arterial catheter	15 (22.4)	28 (10.7)	0.011
Tracheostomy	12 (17.9)	23 (8.8)	0.031
Total parenteral nutrition	10 (14.9)	10 (3.8)	0.002
Abdominal drainage	9 (13.4)	26 (9.9)	0.406
Thoracic drainage	9 (13.4)	16 (6.1)	0.043
Extraventricular drainage	3 (4.5)	7 (2.7)	0.431
Long-term intravenous access	2 (3.0)	14 (5.3)	0.541
Arteriovenous fistula or shunt	1 (1.5)	3 (1.1)	>0.99

Data represent the median value (interquartile range) for continuous variables and the number of cases (%) for categorical variables.

$p < 0.001$), arterial catheterization (49.3% vs. 13.4%; $p < 0.001$), a pulmonary arterial line (22.4% vs. 10.7%; $p = 0.011$), tracheostomy (17.9% vs. 8.8%; $p = 0.031$), total parenteral nutrition (14.9% vs. 3.8%; $p = 0.002$), and thoracic drainage (13.4% vs. 6.1%; $p = 0.043$).

The difference in antimicrobial susceptibility between INS and IS isolates is given in Table 3. Compared to IS isolates, INS isolates were more resistant to piperacillin/tazobactam, ampicillin/sulbactam, colistin, amikacin and gentamicin. The antimicrobial agents that had high activity against INS isolates were ciprofloxacin (92.5%), ceftazidime (77.6%), cefepime (80.6%), and sulfamethoxazole/trimethoprim (76.1%). Patients with INS isolates more frequently received antibiotics prior to the onset of bacteremia (77.6% vs. 51.1%, $p < 0.001$) than those with IS isolates. Further analysis, as shown in Table 4, revealed that the use of antipseudomonal penicillins, aminoglycosides, carbapenems, and sulbactam was associated with the recovery of INS isolates (all $p < 0.05$). Pneumonia was the most common source of *A. nosocomialis* bacteremia in both the IS and INS groups (Table 4). Patients with INS isolates tended to have pneumonia as a source of infection (71.6% vs. 40.8%; $p < 0.001$), with the infection less commonly caused by primary bacteremia (10.4% vs. 29.8%; $p = 0.001$), compared with those with IS isolates.

After multivariable analysis (Table 5), the independent risk factors for harboring INS isolates included admission to ICU, chronic lung diseases, previous arterial line catheterization, total parenteral nutrition, and previous use of carbapenems. Previous use of carbapenems was the most influential risk factor (odds ratio 6.36, 95% confidence interval 2.00–20.21; $p = 0.002$).

Discussion

INS ABC has emerged in recent years because of the increasing number of susceptible patients and the widespread use of broad-spectrum antimicrobials.[2] Although most studies have delineated the risk factors for INS ABC infections, this is the first study targeting patients with INS *A. nosocomialis* bacteremia. Using multivariable analysis, our study, spanning 9 years and including 329 patients, revealed the independent risk factors for acquiring INS

Table 3 The antimicrobial susceptibility of imipenem-nonsusceptible (INS) and imipenem-susceptible (IS) *Acinetobacter nosocomialis*

Antibiotics	INS isolates ($n = 67$)	IS isolates ($n = 262$)	p
Ceftriaxone	17 (25.4)	74 (28.2)	0.752
Ceftazidime	52 (77.6)	220 (84.0)	0.297
Cefepime	54 (80.6)	229 (87.4)	0.216
Ciprofloxacin	62 (92.5)	243 (92.7)	0.842
Piperacillin/tazobactam	21 (31.3)	229 (87.4)	<0.001
Ampicillin/sulbactam	38 (56.7)	216 (82.4)	<0.001
Colistin	37 (55.2)	220 (84.0)	<0.001
Amikacin	32 (47.8)	201 (76.7)	<0.001
Gentamicin	8 (11.9)	183 (69.8)	<0.001
Sulfamethoxazole/trimethoprim	51 (76.1)	175 (66.8)	0.186

Data presented as number of cases (%).

Table 4 Previous use of antimicrobial agents and infection sources of patients with imipenem-nonsusceptible (INS) and imipenem-susceptible (IS) *Acinetobacter nosocomialis* bacteremia

Characteristics	INS isolates ($n = 67$)	IS isolates ($n = 262$)	p
Previous use of antimicrobial agents			
Antipseudomonal penicillins	19 (28.4)	19 (7.3)	<0.001
Aminoglycosides	17 (25.4)	34 (13.0)	0.012
Carbapenems	13 (19.4)	6 (2.3)	<0.001
Antipseudomonal cephalosporins	9 (13.4)	33 (12.6)	0.855
Sulbactam or ampicillin/sulbactam	5 (7.5)	5 (1.9)	0.033
Fluoroquinolones	4 (6.0)	11 (4.2)	0.517
Infection sources			
Pneumonia	48 (71.6)	107 (40.8)	<0.001
Primary bacteremia	7 (10.4)	78 (29.8)	0.001
Catheter-related infections	7 (10.4)	31 (11.8)	0.752
Intra-abdominal infections	3 (4.5)	16 (6.1)	0.774
Skin and soft tissue infections	1 (1.5)	14 (5.3)	0.322
Urinary tract infections	1 (1.5)	13 (5.0)	0.316

Data presented as number of cases (%).

isolates, which included ICU admission, chronic lung disease, previous arterial line catheterization, total parenteral nutrition, and, most importantly, previous use of carbapenems. In addition, our study revealed that ciprofloxacin, ceftazidime, cefepime, and sulfamethoxazole/trimethoprim had the highest susceptibility rate against INS isolates.

Numerous clinical studies have delineated the risk factors for INS *A. baumannii* infections.[10,13,14,19,20] Hospital settings (ICU stay, length of hospital stay prior to infection),[19,21] underlying diseases (chronic lung diseases),[22] prior colonization with *A. baumannii*,[11] multiple invasive procedures (catheterizations, mechanical ventilation),[23–25] and prior antibiotic use (especially use of carbapenems)[10,25,26] have been linked to the presence of INS isolates. However, evidence regarding the risk factors for infection with INS *A. nosocomialis*, which is the second most clinically relevant species, is lacking. The increasing rate of nonsusceptibility of *A. nosocomialis* to imipenem[27] may pose a threat to infection control against *A. baumannii* as INS *A. nosocomialis* could serve as a reservoir of resistant genes for *A. baumannii*.[28] Understanding risk factors associated with INS *A. nosocomialis* bacteremia helps to guide infection control measures and to reduce the transmission of drug-resistant pathogens.[12] This study showed that the independent risk factors for INS *A. nosocomialis* were similar to those for INS *A. baumannii*. Among them, carbapenem exposure is the most important risk factor for infection with INS *A. baumannii*. The risk of infection with INS isolates was six times higher in those previously treated with carbapenems, as reported by studies on INS ABC.[10,13,19,26] Moreover, other risk factors identified in our study, such as ICU stay, multiple invasive procedures, and chronic lung diseases, were consistent with those in previous studies on INS ABC,[19,21–24] which implied the roles of susceptible hosts, available access, and antecedent antimicrobial exposure.

The optimal therapy for INS *A. nosocomialis* is unknown because most of the clinical study focused on *A. baumannii*.[3] In addition, the rarity of recovery of *A. nosocomialis* prohibits a prospective study. Based on the *in vitro* susceptibility results in our study, ciprofloxacin, ceftazidime, cefepime, or sulfamethoxazole/trimethoprim may be the reasonable treatment of choice, which has been also successfully used for *A. baumannii*.[3,18]

As the presence of carbapenemase did not necessarily lead to resistance to antimicrobial agents other than carbapenems,[29] the different antimicrograms (Table 3) for INS

Table 5 Multivariate analyses of risk factors for bacteremia with imipenem-nonsusceptible (INS) *Acinetobacter nosocomialis*

Variables	Univariate analysis		Multivariate analysis	
	Odds ratio (95% confidence interval)	p	Odds ratio (95% confidence interval)	p
Intensive care unit admission	7.51 (3.57–15.79)	<0.001	3.85 (1.65–8.96)	0.002
Chronic lung diseases	2.67 (1.42–5.02)	0.002	2.72 (1.27–5.83)	0.010
Previous use of arterial line catheterization	6.30 (3.47–11.43)	<0.001	2.31 (1.11–4.81)	0.026
Previous use of total parenteral nutrition	4.42 (1.76–11.13)	0.002	5.49 (1.65–18.39)	0.006
Previous use of carbapenems	10.27 (3.74–28.23)	<0.001	6.36 (2.00–20.21)	0.002

A. baumannii and INS *A. nosocomialis* may indicate the different ways of acquiring resistance mechanisms. Accumulation of resistance gene cassettes or islands by integrons or transposons has been reported repeatedly for INS *A. baumannii* but rarely for *A. nosocomialis*.[30] To delineate the resistance mechanisms toward these antimicrobial agents, such as alterations in porins, the presence of an efflux pump[31] or other beta-lactamases,[29] or point mutations in *gyrA* or *parC*,[32] is beyond the scope of this study. Therefore, further studies targeting the resistance mechanisms of *A. nosocomialis* toward antimicrobial agents other than carbapenems are needed.

This study had some limitations. Its retrospective nature precluded investigation of the role of previous infections with INS *A. nosocomialis*, which needs further study. One positive feature is that a large number of patients with *A. nosocomialis* bacteremia were included in this study. In addition, the isolation of *A. nosocomialis* from the blood of patients with concurrent symptoms and signs of sepsis reduced the chances of contamination.

In conclusion, compared to patients with IS *A. nosocomialis* bacteremia, risk factors for INS *A. nosocomialis* infections included ICU admission, chronic lung diseases, previous arterial line catheterization, total parenteral nutrition, and carbapenems. A regulated antibiotic control policy against carbapenems and infection control measures targeting patients with these risk factors may be beneficial.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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