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ORIGINAL ARTICLE

Risk factors and clinical outcome of sulbactam nonsusceptibility in monomicrobial *Acinetobacter nosocomialis* bacteremia

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Background: Sulbactam is an effective antimicrobial agent against multidrug-resistant *Acinetobacter* spp. This retrospective study evaluated the risk factors of sulbactam nonsusceptibility (SNS) in monomicrobial *Acinetobacter nosocomialis* bacteremia and its related outcome.
Methods: This 9-year retrospective study included 267 patients who were admitted to a large teaching hospital in Taiwan with monomicrobial *A. nosocomialis* bacteremia. *A. nosocomialis* was identified to the species level using molecular methods. Antimicrobial susceptibilities were determined by the agar dilution method. To identify the risk factors of acquiring resistant strains, significant clinical variables derived from univariate analysis were entered into multivariate analysis. Polymerase chain reaction was used to identify bla_{TEM}. Clonality was determined by pulsed-field gel electrophoresis.
Results: A total of 41 of the 267 patients (15.4%) had SNS *A. nosocomialis* bacteremia. Compared to those with susceptible strains, these patients had higher 14-day mortality (17.1% vs. 7.5%, $p = 0.049$), were more likely to have higher Acute Physiology and Chronic

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Health Evaluation (APACHE) II score, were more frequently admitted to the intensive care unit, and had previously received broad-spectrum antibiotics and underwent invasive procedures. In multivariate analysis, the independent risk factors were high APACHE II score and prior use of arterial line [odds ratio (OR), 1.048; 95% confidence interval (CI), 1.007—1.091; $p = 0.022$ and OR, 2.936; 95% CI, 1.339—6.441; $p = 0.007$, respectively]. No outbreak was identified and SNS isolates did not harbor bla_{TEM}.

Conclusion: For monomicrobial *A. nosocomialis* bacteremia, the mortality of patients with SNS strains was higher. The SNS strains are more commonly recovered from patients with higher APACHE score and receiving more invasive procedures, especially arterial line.

Introduction

Acinetobacter species are Gram-negative, strictly aerobic, oxidase-negative, and nonmotile coccobacilli.[1] More than 30 different species have been identified.[1] They survive in adverse environments, including hospitals.[2,3] Nosocomial infections caused by *Acinetobacter* species have increased throughout the past 30 years, especially in cases with hospital-acquired pneumonia and bloodstream infections.[4–6] Most human infections are caused by *Acinetobacter baumannii*, *Acinetobacter nosocomialis*, and *Acinetobacter pittii*, which are collectively known as the *Acinetobacter calcoaceticus—baumannii* complex (Acb complex). These organisms are also notorious for their easy outbreak and high rate of antibiotic resistance.[4,7,8] The multidrug-resistant Acb complex has emerged worldwide. In the Taiwan Surveillance of Antimicrobial Resistance (TSAR) program,[9] the prevalence of highly drug-resistant Acb complex increased from 1.3% in 2002 to 41% in 2010, whereas resistance to carbapenem had increased to 58.7% by 2010.

Sulbactam is an effective treatment option for infections caused by the multidrug-resistant Acb complex.[1] However, despite the success of sulbactam-containing regimens,[10–13] the Acb complex is becoming increasingly resistant to sulbactam. According to the 2001—2004 SENTRY Surveillance Program, the resistance rate of Acb complex to ampicillin—sulbactam was around 40% in the Asia-Pacific region.[14] In Taiwan, Shi et al[15] reported a 33.5% *in vitro* resistance rate of the Acb complex to ampicillin—sulbactam and the TSAR program showed that the ampicillin—sulbactam nonsusceptibility (ampicillin—SNS) rate of the Acb complex from 2002 to 2010 was from 57.4% to 59.6% (range 57.4—64.1%).[9] The nonsusceptibility of *A. nosocomialis* bloodstream infections to sulbactam has accelerated in recent years.[16]

Because members of the Acb complex differ in their pathogenicity and virulence, the risk factors for each species should be separately investigated.[1] *A. nosocomialis* is an important pathogen in Taiwan, and is responsible for a similar number of bloodstream infections as caused by *A. baumannii*.[16,17] However, the outcome and factors for SNS in *A. nosocomialis* bloodstream infections remain unknown. Therefore, we performed a retrospective study to evaluate the outcome and risk factors of monomicrobial bacteremia caused by SNS *A. nosocomialis*.

Methods

Study population

This retrospective study was conducted at Taipei Veterans General Hospital (T-VGH). The T-VGH is a 2900-bed tertiary care medical center in Taipei, Taiwan. All patients with monomicrobial *A. nosocomialis* infection from 2001 to 2009 were included in the study. Part of our patients had been included in the previous studies.[16,18,19] The medical records of the patients were collected on a standard form. Patients aged < 18 years or whose medical records were incomplete were excluded. Demographic characteristics, severity of disease, comorbid conditions, history of invasive procedures, exposure to antibiotics, infection foci, appropriateness of antibiotics use, and outcome were recorded for further analysis.

Definitions

The onset of bloodstream infection was defined as the day of blood culture collection. The origin of the bacteremia was defined as suggested by the Centers for Disease Control and Prevention.[20] Severity of disease was assessed within 72 hours prior to or after the bacteremia onset, and was based on the Acute Physiology and Chronic Health Evaluation (APACHE) II score.[21] Chronic lung diseases included chronic obstructive pulmonary disease, tuberculosis, and asthma. Renal impairment was defined as an estimated glomerular filtration rate $<$ 60 mL/minute/1.73 m^2. Immunosuppressive therapy was defined as the receipt of cytotoxic agents, corticosteroids (equivalent to $\geq$ 15 mg of prednisolone daily for 5 days), or other immunosuppressive agents within 4 weeks of the bacteremia onset. Neutropenia was defined as an absolute neutrophil count $<$ 500 cells/mm^3. Recent surgery was defined as operations performed within 4 weeks prior to the bacteremia onset. Shock was defined as hypotension [systolic blood pressure (SBP) $<$ 90 mmHg, mean arterial pressure $<$ 70 mmHg, or SBP decrease $>$ 40 mmHg], with evidence of end organ dysfunction.[22] Previous antibiotics exposure was defined as use of antimicrobial therapy within 4 weeks prior to the bacteremia onset. Broad-spectrum β-lactam antibiotics included antipseudomonal penicillins, antipseudomonal

cephalosporins, and antipseudomonal carbapenems. β-Lactam-β-lactamase inhibitor contained ampicillin/sulbactam, sulbactam alone, amoxicillin/clavulanate, and ticarcillin/clavulanate. The 14-day mortality was recorded. Whether the mortality was attributable to infections was judged by physicians. Appropriate antimicrobial therapy was defined as administration of ≥ 1 antimicrobial agent to which *A. nosocomialis* was susceptible to within 48 hours of bacteremia onset. This study was approved by the Institutional Review Board of T-VGH.

Genomic species identification and antimicrobial susceptibility testing

The phenotype of Acb complex was identified by the API ID 32 GN system (bioMérieux, Marcy-l'Étoile, France) or VITEK 2 system (bioMérieux). The bacteria were stored at −70°C in Trypticase soy broth (Difco Laboratories, Detroit, MI, USA) supplemented with 15% glycerol. *A. nosocomialis* was identified to the species level by 16S−23S ribosomal RNA intergenic spacer region sequencing.[23] Microorganisms confirmed as *A. nosocomialis* were selected for further testing of antimicrobial susceptibility. Antimicrobial susceptibilities were determined by the agar dilution method, as specified in the Clinical Laboratory Standards Institute criteria.[24] The SNS was defined as a minimal inhibitory concentration (MIC) $\geq$ 8 mg/L.

Determination of the presence of bla_{TEM}

A previous study showed that bla_{TEM} is responsible for the sulbactam resistance in *A. baumannii*.[25] Therefore, the nonsusceptible *A. nosocomialis* in our study were subjected to polymerase chain reaction (PCR) using primers specific for bla_{TEM} (5′-TAAAATTCTTGAAGACG-3′ and 5′-TTAC CAATGCTTAATCA-3′). The PCR program consisted of an initial denaturation at 95°C for 2 minutes, followed by 30 cycles of denaturation (95°C for 1 minute), annealing (54°C for 1 minute), and extension (72°C for 1 minute), with a final extension step at 72°C for 5 minutes. Amplified DNA product was resolved by electrophoresis in agarose 2% w/v gels, and stained with ethidium bromide.

Pulsed-field gel electrophoresis

The clonality of nonsusceptible strains was determined by pulsed-field gel electrophoresis (PFGE) as described previously.[26] In brief, the extracted DNA of randomly selected isolates was digested with *Apa*I. The DNA fragments were then subjected to PFGE in 1% SeaKem Gold agarose gels (Cambrex Bio Science, Rockland, ME, USA) in 0.5× TBE buffer (45mM Tris, 45mM boric acid, and 1.0mM EDTA at pH 8.0). The stained gel was photographed and analyzed by BioNumerics software (Applied Maths, Austin, TX, USA) to generate a dendrogram of relatedness among these isolates.

Statistical analysis

The Chi-square test with Yate's correction or Fisher's exact test and Student's *t* test or Mann−Whitney *U* test were used for categorical variables and continuous variables, respectively. Categorical variables were expressed as percentages, whereas continuous variables were represented by their medians and interquartile ranges. Separate univariate analyses were performed for all risk variables to ascertain their odds ratio (OR) and 95% confidence interval (CI). All variables scoring $p \leq 0.10$ in the univariate analyses and identified in at least 10% of the patients were included in the logistic regression model of the multivariate analysis. A backward selection process was used. All analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA).

Results

During the study period, 319 patients with *A. nosocomialis* bacteremia and complete medical data were identified. Fifty two of these patients who presented with polymicrobial bacteremia were excluded. Data from the remaining 267 patients were retained for further analysis. Among these, 41 (15.4%) patients were not susceptible to sulbactam (Table 1).

Demographic characteristics, previous antimicrobial exposure, sources of underlying infectious diseases, and outcome of patients with SNS and sulbactam-susceptible (SS) *A. nosocomialis* bacteremia are listed in Table 1. No significant differences between these two groups were found in age, sex, hospital duration, and length of hospitalization before the onset of bacteremia. Patients with SNS *A. nosocomialis* bacteremia had higher APACHE II score (23 vs. 18, $p = 0.003$) and were admitted to the intensive care unit more often (70.7% vs. 48.2%, $p = 0.008$). Nonsusceptible strains were also more common in patients who had previously used broad-spectrum β-lactams and fluoroquinolones (26.8% vs. 13.3%, $p = 0.027$, and 9.8% vs. 3.1%, $p = 0.048$). Patients with chronic lung disease were more likely to acquire SNS strains (24.4% vs. 12.8%, $p = 0.054$). Among the 41 patients whose bloodstream infections were nonsusceptible to sulbactam, a single patient had been previously exposed to sulbactam-containing regimens. The 14-day mortality was higher in patients with SNS *A. nosocomialis* bacteremia (17.1% vs. 7.5%, $p = 0.049$). The survivors of the SNS group tended to have lower APACHE II score (22 vs. 34, $p = 0.002$, Table S1 in the supplementary material online) and received more appropriate antimicrobial therapy (50% vs. 14.3%, $p = 0.083$).

Previous exposures to invasive procedures in these two groups are shown in Table 2. The total number of invasive procedures received were significantly higher in patients with SNS strains than in patients with SS (4 vs. 1, $p = 0.002$). These procedures included arterial line (36.6% vs. 12.8%, $p < 0.001$), central venous catheters (58.5% vs. 33.2%, $p = 0.002$), hemodialysis (14.6% vs. 3.5%, $p = 0.003$), nasogastric tubes (61% vs. 41.6%, $p = 0.022$), and mechanical ventilators (56.1% vs. 31.4%, $p = 0.002$).

Multivariate analyses (Table 3) revealed two independent risk factors for SNS *A. nosocomialis* acquisition—APACHE II score and prior administration of arterial line (OR, 1.048; 95% CI, 1.007−1.091; $p = 0.022$ and OR, 2.936; 95% CI, 1.339−6.441; $p = 0.007$, respectively). A total of 23 of 41 SNS isolates were randomly selected for further PCR and PFGE. PCR did not detect the presence of bla_{TEM} in SNS

Table 1 Demographic characteristics and underlying diseases of patients with monomicrobial SNS and SS *Acinetobacter nosocomialis* bacteremia

Characteristics	SNS isolates (n = 41)	SS isolates (n = 226)	p
Demographic characteristics			
Age, y	72 (55–81)	73 (58–79)	0.896
Hospitalization duration, d	56 (28–73)	37 (23–68)	0.229
Admission to the intensive care unit	29 (70.7)	109 (48.2)	0.008
Male sex	28 (68.3)	157 (69.5)	0.881
APACHE II score	23 (17–32)	18 (14–25)	0.003
Length of hospitalization before onset of bacteremia, d	18 (9–32)	15 (8–25)	0.192
Recent surgery	18 (43.9)	89 (39.4)	0.587
Shock	10 (24.4)	45(19.9)	0.514
Previous antibiotics exposure			
Broad-spectrum β-lactam[a]	11 (26.8)	30 (13.3)	0.027
Aminoglycosides	5 (12.2)	36 (15.9)	0.542
Fluoroquinolones	4 (9.8)	7 (3.1)	0.048
Glycopeptides	3 (7.3)	27 (11.9)	0.388
β-Lactam-β-lactamase inhibitor[b,c]	3 (7.3)	22 (9.7)	0.625
Underlying diseases			
Solid tumor	17 (41.5)	84 (37.2)	0.602
Hypertension	13 (31.7)	72 (31.9)	0.985
Type 2 diabetes mellitus	11 (26.8)	56 (24.8)	0.781
Chronic lung diseases	10 (24.4)	29 (12.8)	0.054
Renal impairment	9 (22.0)	45 (19.9)	0.765
Coronary artery diseases	8 (19.5)	37 (16.4)	0.621
Cerebrovascular diseases	7 (17.1)	44 (19.5)	0.72
Congestive heart failure	5 (12.2)	22 (9.7)	0.631
Smoking	4 (9.8)	40 (17.7)	0.207
Chemotherapy	3 (7.3)	28 (12.4)	0.351
Collagen vascular diseases	1 (2.4)	7 (3.1)	0.82
Hematologic malignancies	1 (2.4)	12 (5.3)	0.432
Use of immunosuppressive therapy	1 (2.4)	9 (4)	0.632
Liver cirrhosis	1 (2.4)	16 (7.1)	0.263
Neutropenia	1 (2.4)	6 (2.7)	0.937
Peripheral arterial occlusive disease	1 (2.4)	4 (1.8)	0.771
Trauma	1 (2.4)	12 (5.3)	0.432
Infection sources			
Respiratory tract	20 (48.8)	88 (38.9)	0.237
Primary bacteremia	8 (19.5)	78 (34.5)	0.059
Catheter related	7 (17.1)	24 (10.6)	0.235
Intra-abdominal	3 (7.3)	16 (7.1)	0.957
Soft tissue or wound	2 (4.9)	10 (4.4)	0.897
Urinary tract	1 (2.4)	10 (4.4)	0.556
14-d mortality	7 (17.1)	17 (7.5)	0.049
Appropriate antimicrobial therapy	18 (43.9)	90 (39.8)	0.624

[a] Antipseudomonal penicillins, cephalosporins, and carbapenems.
[b] Ampicillin/sulbactam, sulbactam alone, amoxicillin/clavulanate, and ticarcillin/clavulanate.
[c] 1 and 4 sulbactam-containing regimens were implemented in SNS and SS isolates, respectively.
Data are presented as median values (interquartile ranges) for continuous variables and number of cases (%) for categorical variables. APACHE II = Acute Physiology and Chronic Health Evaluation II; IQR = interquartile range; SNS = sulbactam nonsusceptible; SS = sulbactam susceptible.

strains and PFGE did not detect identical SNS isolates (Figure S1 in the supplementary material online).

Discussion

This retrospective study revealed higher mortality in patients with SNS *A. nosocomialis* bacteremia. The independent risk factors for SNS *A. nosocomialis* were high APACHE II score and prior use of arterial line. To our knowledge, this is the first report on the outcome and risk factors associated with sulbactam resistance in the Acb complex.

Sulbactam effectively treats infections caused by the Acb complex in both animal model and clinical patients,[10,12,27] and is also recommended as an adjuvant

Table 2 Prior use of invasive procedures in patients with monomicrobial SNS and SS *Acinetobacter nosocomialis* bacteremia

Invasive procedures	SNS isolates (n = 41)	SS isolates (n = 226)	p
Nasogastric tube	25 (61)	94 (41.6)	0.022
Central venous catheter	24 (58.5)	75 (33.2)	0.002
Mechanical ventilator	23 (56.1)	71 (31.4)	0.002
Urinary catheterization	22 (53.7)	93 (41.2)	0.137
Arterial line	15 (36.6)	29 (12.8)	<0.001
Hemodialysis	6 (14.6)	8 (3.5)	0.003
Pulmonary arterial catheter	6 (14.6)	18 (8.0)	0.17
Tracheostomy	5 (12.2)	15 (6.6)	0.214
Abdominal drain	4 (9.8)	16 (7.1)	0.549
Total parenteral nutrition	3 (7.3)	11 (4.9)	0.517
Thoracic drain	2 (4.9)	12 (5.3)	0.909
Total numbers, median (IQR)	4 (1–5)	1 (0–4)	0.002

Data are presented as the number of cases (%) for categorical variables.
IQR = interquartile range; SNS = sulbactam nonsusceptible; SS = sulbactam susceptible.

therapy for carbapenem-resistant strains.[28,29] The sulbactam-containing regimen is also effective against the multidrug-resistant Acb complex infections, especially in patients with lower APACHE II score.[28] Corbella et al[10] and Levin et al[28] showed that sulbactam-containing regimens improved nosocomial infections caused by the multidrug-resistant Acb complex in 39/42 (93%) and 27/40 (67.5%) patients, respectively. The increasing sulbactam resistance is a cause of worry because inappropriate therapy, including sulbactam, is associated with worse outcome.[30,31] In this study, the proportion of SNS *A. nosocomialis* is 15.1%. Similar results were recently reported in another Taiwanese tertiary care center (18.2%).[17] Our study revealed that the 14-day mortality was higher in the SNS group, which may be related to higher APACHE II score and inappropriate therapy. Infections by drug-resistant *Acinetobacter* spp. were associated with higher mortality rate.[32,33] Previous study has also revealed the attribution of disease severity and timely antimicrobial therapy to the poor outcome in patients contracted with resistant pathogens.[34] Unfortunately, the limited case number in our study did not allow for further analysis.

Multivariate analysis showed that high APACHE II score was one of the independent factors of acquisition of SNS strains. Previous studies[29,30] also showed that multidrug-resistant *Acinetobacter* infections occurred in more critically ill patients. Intriguingly, use of an arterial line was also a risk factor. Clustering of catheter-related infection should be considered. However, the proportion of catheter-related infections between the SNS and SS groups was similar. Although PFGE identified a clone using a cutoff value of 85% similarity, only two of the seven isolates were identical, which is not typical for an outbreak. In addition, only one isolate was associated with catheter-related infections (Figure S1 in the supplementary material online). Arterial line is used in critically ill patients, indicating that use of arterial line may represent the disease severity.

Few studies have investigated the mechanism of SNS in the Acb complex. Previous epidemiological studies have associated resistance rate with the presence of the $bla_{\text{TEM-1}}$ gene in clinical isolates.[35] One recent study[25] showed a positive correlation between the level of $bla_{\text{TEM-1}}$ expression in clinical strains of *A. baumannii* and the MICs of sulbactam. However, PCR did not detect the presence of $bla_{\text{TEM-1}}$ in all of our nonsusceptible isolates. Therefore, other mechanisms may be responsible for the sulbactam resistance in *A. nosocomialis*.

One limitation of this study is potential bias incurred by the retrospective nature of the study. However, the effects of this bias may be diminished by the large sample size. This study was performed in one tertiary hospital in Taiwan and

Table 3 Multivariate analysis of independent risk factors for bacteremia caused by SNS *Acinetobacter nosocomialis*

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Chronic lung diseases	2.191 (0.972–4.938)	0.058		
Intensive care unit admission	2.594 (1.261–5.338)	0.01		
APACHE II score	1.063 (1.024–1.103)	0.001	1.048 (1.007–1.091)	0.022
Hemodialysis	4.671 (1.529–14.275)	0.007		
Arterial line	3.919 (1.860–8.260)	<0.001	2.936 (1.339–6.441)	0.007
Central venous catheter	2.842 (1.44–5.612)	0.003		
Nasogastric tube	2.194 (1.111–4.335)	0.024		
Mechanical ventilator	2.790 (1.416–5.494)	0.003		
Primary bacteremia	0.478 (0.211–1.087)	0.078		
Broad-spectrum β-lactams[a]	2.396 (1.087–5.281)	0.03		
Fluoroquinolones	3.382 (0.943–12.127)	0.061		
Total numbers of invasive procedure	1.281 (1.107–1.482)	0.001		

[a] Antipseudomonal penicillins, cephalosporins, and carbapenems.
APACHE II = Acute Physiology and Chronic Health Evaluation II; CI = confidence interval; SNS = sulbactam nonsusceptible; OR = odds ratio.

the results may not be generalized to other institutions. Strengths of this study are the species-level identification of *A. nosocomialis* by molecular methods, selection of bloodstream infections to reduce the likelihood of contamination, and exclusion of polymicrobial infections.

In conclusion, the mortality of patients with SNS *A. nosocomialis* was higher than those with susceptible strains. For monomicrobial *A. nosocomialis* bacteremia, SNS strains are more commonly recovered from patients with higher APACHE score and receiving more invasive procedures, especially arterial line.

Conflicts of interest

All contributing authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jmii.2014.06.004.

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