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□ ORIGINAL ARTICLE □

Clinical Characteristics of Tertiary Hospital Patients from Whom *Acinetobacter calcoaceticus-Acinetobacter baumannii* Complex Strains were Isolated

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Abstract

Objective *Acinetobacter baumannii* is a worldwide nosocomial pathogen that has become increasingly common over the past few decades, and strains of multidrug-resistant *A. baumannii* have been increasing. The aim of this study was to assess the clinical characteristics of *A. calcoaceticus-A. baumannii* complex (*Acb* complex) strains and to determine the risk factors of this infection.

Methods The medical records of 121 patients at Nagasaki University Hospital from whom *Acb* complex had been isolated between January 2007 and December 2009 were retrospectively reviewed. Patient backgrounds, sensitivity to antibiotics, risk factors for infection, and prognosis were evaluated.

Results Lower respiratory isolates accounted for 73% (147 strains) of all 201 isolates. Most of the isolates were sensitive to carbapenems. Of the 121 patients (74 males and 47 females; mean age: 62.1 years), 48 (39.7%) had malignancy and 75 (62.0%) were treated with antibiotics prior to isolation. Thirty-seven of the patients in this study (30.6%) were infected by Acb complex and the most frequent clinical manifestation was pneumonia (18 cases; 48.6%). Approximately 60% of infected patients were treated with β-lactam agent in combination with β-lactamase inhibitors or carbapenems. The mortality rate of infected patients was significantly higher than that of colonized patients (infected: 24.3%, colonized: 6.0%, $p<0.05$). Risk factors for *Acb* complex infection include being over 60 years of age, chronic liver disease, and the use of first-generation cephalosporins prior to isolation.

Conclusion *Acb* complex was relatively sensitive to antibiotics. The appropriate usage of antibiotics should be continued for the prevention of drug resistance in *Acb* complex.

Key words: *Acinetobacter baumannii*, pneumonia, risk factor, antibiotics

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Introduction

Acinetobacter baumannii is a nosocominal pathogen found throughout the world that has become increasingly common over the past decades and is associated with high rates of morbidity and mortality (1-3). *A. baumannii* causes pulmonary, urinary tract, bloodstream, and surgical wound infections (3, 4). Ventilator-associated pneumonia (VAP) is caused by *A. baumannii* more often than other pathogens (5). Risk factors for colonization and infection are invasive procedures such as mechanical ventilation, intensive care unit (ICU) stay, recent surgery, broad-spectrum antibiotics (6-8). Recently strains of drug-resistant *A. baumannii*

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have been increasing. The rate of carbapenem resistance in 3601 isolates of *A. baumannii* increased from 9% in 1995 to 40% in 2004 according to the Centers for Disease Control and Prevention (2, 9). The multidrug-resistance rate of *Acinetobacter* is the highest among gram-negative pathogens (10). Furthermore, infections with multidrug-resistant *A. baumannii* (MDRAB) are associated with worse prognoses than infections caused by non-MDRAB (11, 12). Therefore, it is very important to distinguish between colonization and infection and to use the appropriate antibiotics in order to prevent drug resistance. However, there are few reports which discuss the risk factors of *A. baumannii* infection (13, 14). Furthermore, the current condition of *A. baumannii* infection in Japan must be evaluated in particularly in reference to the recent troubling major outbreak of MDRAB at Teikyo University Hospital in Japan (15).

The purpose of the present study was to assess the sensitivity to antibiotics and background of *A. calcoaceticus-A. baumannii* complex (*Acb* complex) strains and to evaluate the risk factors and prognosis of this infection.

Materials and Methods

The medical records of 121 patients at Nagasaki University Hospital from whom *Acb* complex had been isolated between January 2007 and December 2009 were retrospectively reviewed.

Patient age, sex, isolates, underlying disease, clinical features, sensitivity to antibiotics, and frequency of infection and prognosis were evaluated. In addition to these parameters, the subgroup of *Acb* complex infection was compared with that of colonization. Furthermore, the subgroup of non-survivors infected with *Acb* complex was compared to that of survivors. If *Acb* complex had been isolated on multiple occasions within a 3-year period in the same patient, only the first episode of *Acb* complex colonization or infection was reviewed. All of the isolated strains were analyzed to assess their sensitivity to antibiotics.

Definition of infection

Infection was defined as the isolation of *Acb* complex from a normally sterile site. Bacteremia was defined as one or more positive blood cultures from patients with clinical signs of infection, such as fever, chills, and sweats, with or without local signs and symptoms. Pneumonia was diagnosed when new persistent pulmonary infiltrates not otherwise explained appeared on chest radiographs with the presence of local purulent respiratory secretions and systemic signs of inflammatory response (16). An infection was considered to be catheter-related when inflammatory signs were observed at the catheter insertion point or when the catheter culture was positive for *Acb* complex. Colonization was defined as the isolation of *Acb* complex from at least one clinical specimen in the absence of clinical symptoms consistent with infection (13).

Assessment of laboratory data

Systemic inflammatory response syndrome (SIRS) was recorded on the day a culture gave a positive result. SIRS was defined the presence of two or more of the following conditions: [1] body temperature >38℃ or <36℃; [2] Leukocyte count >1,2000/μL, <4,000/μL or >10% bands; [3] heart rate >90 beats/min; or [4] respiratory rate >20 beats/min or $PaCO_2$<32 Torr (17).

Identification of bacteria

All *Acb* complex isolates were identified by colony morphologic analysis and gram staining. Isolate identification was confirmed using the Phoenix System (Nippon Becton Dickinson Co., Ltd., Fukushima, Japan). The minimum inhibitory concentrations (MICs) of antibiotics were determined using a dilution antimicrobial susceptibility test according to the manufacturer's instructions (Eiken Chemical, Japan). All plates were incubated at 35℃ for 24 hours.

Antimicrobial treatment

The specific design of the initial antimicrobial treatment regimen was the responsibility of the physician. The first antibiotic used was changed only in the case of clinical non-response to treatment or side effects.

Statistical analysis

Patient characteristics and outcomes were compared using Microsoft Excel 2007 for Windows. The Fisher's test was used for univariate comparison of categorical data. Variables with a p-value <0.20 in the univariate analyses were considered for inclusion in forward stepwise multivariate logistic regression to determine risk factors of *Acb* complex infection and predictors associated with mortality for patients infected with *Acb* complex. A p-value <0.05 denoted the presence of a statistically significant difference.

Results

Characteristics of patients from whom Acb complex strains were isolated

Clinical characteristics of patients from whom *Acb* complex strains were isolated are summarized in Table 1. Lower respiratory isolates accounted for 73% (147 strains) of all 201 isolates. These patients from whom *Acb* complex were isolated consisted of 74 males and 47 females with the mean age of 62.1 years. Of the 121 patients in the study, 48 (39.7%) had malignancy and 30 (24.8%) had cardiovascular disease. Many patients had at least two comorbid conditions. Seventy-five cases (62.0%) were treated with antibiotics 30 days prior to isolation and 65 cases (53.7%) had urinary catheter-related problems.

Most of the 201 isolates were sensitive to antibiotics. The MIC_{50} and MIC_{90} values of imipenem were 0.5 μg/mL and 0.5 μg/mL, respectively (Table 2). Only one strain was resis-

Table 1. Clinical Characteristics of Patients at Nagasaki University Hospital from Whom *Acb* Complex Strains were Isolated

Sex (male/female)	74/47
Mean age (years)	62.1±22.2
Isolates	201
Sputum	147(73.1)
Blood	17(8.5)
Urine	7(3.5)
Stool	5(2.5)
Others	25(12.4)
Underlying disease	
Malignant tumor	48(39.7)
Cardiovascular disease	30(24.8)
Respiratory disease	20(16.5)
Diabetes mellitus	19(15.7)
Central nervous system disease	17(14.0)
Chronic renal failure	12(9.9)
Chronic liver disease	11(9.1)
Autoimmune/allergic disease	5(4.1)
Burn	5(4.1)
Trauma	5(4.1)
Others	13(10.7)
Cormorbid conditions	
Urinary catheter	65(53.7)
Surgery	59(48.8)
Intravenous hyperalimination catheter	51(42.1)
Mechanical ventilation	50(41.3)
ICU stay	47(38.9)
Immunosuppressive drug or corticosteroid use	18(14.8)
Antineoplastic therapy	13(10.7)
Transplantation	6(5.0)
Use of antibiotics prior to isolation	75(62.0)
Penicillins	20(16.5)
Third-generation cephalosporins	13(10.7)
First-generation cephalosporins	13(10.7)
Glycopeptides	10(8.3)
Antifungal agent	9(7.4)
Quinolones	8(6.6)
Oxazolidinones	6(5.0)
Carbapenems	6(5.0)
Second-generation cephalosporins	6(5.0)
Others	11(9.1)
Mortality	14(11.6)

[a]Data are the mean ± SD.

Table 2. The MICs of *Acb* Complex Strains

	MIC range (μg/mL)	MIC_{50}	MIC_{90}
PIPC	1 - ≥32	16	≥32
SBT/ABPC	2 - 8	4	8
CTM	16 - ≥32	≥32	≥32
CZX	2 - ≥32	8	16
CAZ	≤0.5 - ≥32	4	16
CTRX	2 - ≥32	8	16
CFPM	≤0.5 - ≥32	2	8
SBT/CPZ	≤0.5 - ≥32	1	2
IPM	≤0.5 - ≥32	≤0.5	≤0.5
MEPM	≤0.5 - 16	≤0.5	≤0.5
AZT	4 - ≥32	16	≥32
GM	≤0.5 - ≥32	1	2
AMK	2 - ≥32	4	4
MINO	≤0.5 - 4	≤0.5	≤0.5
CPFX	≤0.5 - ≥32	≤0.5	≤0.5
LVFX	≤0.5 - 16	≤0.5	≤0.5

PIPC: piperacillin, SBT/ABPC: sulbactam/ampicillin, CTM: cefotiam, CZX: ceftizoxime, CAZ: ceftazidime, CTRX: ceftriaxone, CFPM: cefepime, SBT/CPZ: sulbactam/cefoperazone, IPM: imipenem, MEPM: meropenem, AZT: aztreonam, GM: gentamicin, AMK: amikacin, MINO: minocycline, CPFX: ciprofloxacin, LVFX: levofloxacin

Table 3. Characteristics of Patients Infected with *Acb* Complex

No. of patients	37
Infection site	
Pneumonia	18(48.6)
Bacteremia	9(24.3)
Urinary tract infection	4(10.8)
Skin and soft-tissue infection	4(10.8)
Intravascular catheter- related infection	3(8.1)
Treatment	
β-lactam agent in combination with the β-lactamase inhibitor	13(35.1)
Carbapenems	10(27.0)
Fourth-generation cephalosporins	3(8.1)
Third-generation cephalosporins	3(8.1)
Quinolones	2(5.4)
Others	2(5.4)
SIRS	27(73.0)
Mortality	9(24.3)

SIRS: systemic inflammatory response syndrome

tant to carbapenems (imipenem: MIC≥32 μg/mL, meropenem: MIC=16 μg/mL).The patient infected with this carbapenem-resistant strain died as a result of pneumonia.

Characteristics of patients infected with Acb complex

Of the 121 patients in this study, 37 (30.6%) were infected with *Acb* complex. The most frequent clinical manifestation was pneumonia (18 cases; 48.6%). Eight (44%) of the pneumonia cases were VAP. Approximately 60% of infected patients were treated with β-lactam + β-lactamase inhibitors or carbapenems. Twenty-seven cases (73.0%) were diagnosed with SIRS. The mortality of infected patients was 24.3% (Table 3).

Risk factors of infection

The univariate analyses of risk factors associated with *Acb* complex infection are shown in Table 4. In univariate analyses, the male-to-female ratio and mean age did not differ between the colonized group and the infected group. Chronic liver disease was a risk factor for *Acb* complex infection. There was no relationship between infection and the use of antibiotics 30 days prior to isolation. However, the use of first-generation cephalosporins was more frequent in the infected group than in the colonized group (p=0.02). In contrast, the use of penicillins was more frequent in the colonized group (p=0.03). The mortality of the infected group was significantly higher than that of the colonized

Table 4. Univariate Analysis of Risk Factors Associated with *Acb* Complex Infection

Variables	Colonized (n=84)	Infected (n=37)	p value[a]
Male gender	53(63.1)	21(56.8)	0.54
Age ≥ 60	50(59.5)	29(78.4)	0.06
Underlying disease			
Malignant tumor	30(35.7)	18(48.6)	0.23
Cardiovascular disease	22(26.2)	8(21.6)	0.65
Respiratory disease	17(20.2)	3(8.1)	0.12
Diabetes mellitus	13(15.5)	6(16.2)	1.00
Central nervous system disease	12(14.8)	5(13.5)	1.00
Chronic renal failure	7(8.3)	5(13.5)	0.51
Chronic liver disease	4(4.8)	7(18.9)	0.03
Autoimmune/allergic disease	5(6.0)	0(0.0)	0.32
Burn	4(4.8)	1(2.7)	1.00
Trauma	3(3.6)	2(5.4)	0.64
Cormorbid conditions			
Urinary catheter	41(48.9)	24(64.9)	0.11
Surgery	41(48.9)	18(48.6)	1.00
Intravenous hyperalimination catheter	36(42.9)	15(40.5)	0.84
Mechanical ventilation	37(44.0)	13(35.1)	0.43
ICU stay	34(40.5)	13(35.1)	0.69
Immunosuppressive drug or corticosteroid use	15(17.9)	3(8.1)	0.27
Antineoplastic therapy	7(8.3)	6(16.2)	0.21
Transplantation	4(4.8)	2(5.4)	1.00
Use of antibiotics prior to isolation	50(59.5)	25(67.6)	0.42
Penicillins	18(21.4)	2(5.4)	0.03
Third-generation cephalosporins	10(11.9)	3(8.1)	0.75
First-generation cephalosporins	5(6.0)	8(21.6)	0.02
Glycopeptides	8(9.5)	2(5.4)	0.72
Antifungal agent	6(7.1)	3(8.1)	1.00
Quinolones	8(9.5)	0(0.0)	0.10
Oxazolidinones	3(3.6)	3(8.1)	0.37
Carbapenems	4(4.8)	2(5.4)	1.00
Second-generation cephalosporins	3(3.6)	3(8.1)	0.37
Mortality	5(6.0)	9(24.3)	0.02

[a]Fisher analysis

Table 5. Multivariate Analysis of Risk Factors Associated with *Acb* Complex Infection

Risk factor	OR (95%CI)	p value
Age ≥ 60	3.46 (1.27-9.47)	0.016
Respiratory disease	ND	ND
Chronic liver disease	5.51 (1.34-22.60)	0.018
Urinary catheter	ND	ND
Penicillins	ND	ND
First-generation cephalosporins	5.80 (1.54-21.89)	0.009
Quinolones	ND	1.000

ND: not detected

group (24.3% vs. 6.0%; p=0.02). Independent predictors associated with infection in the multivariate analyses were: being over 60 years of age (p=0.016), chronic liver disease (p=0.018), and the use of first-generation cephalosporins prior to isolation (p=0.009) (Table 5).

Prognostic factors

The univariate analyses of predictors associated with mortality of *Acb* complex infection are shown in Table 6. Infection site, treatment, and SIRS did not differ between survivors and nonsurvivors. Immunosuppressive drug or corticosteroid use was a predictor of mortality (p=0.01). However, the multivariate analyses showed no predictors of mortality for patients with *Acb* complex infection (Table 7).

Discussion

A. baumannii is an increasingly common nosocominal pathogen found throughout the world; it is associated with high rates of morbidity and mortality (1-3). Furthermore, drug-resistant strains of *A. baumannii* have been increasing. However, little was known about the status of patients in Japan from whom *A. baumannii* were isolated. Thus, it is very important to assess the clinical characteristics of *A. baumannii* and to evaluate the risk factors of infection for appropriate antibiotic treatments. In the present study, the underlying disease, infection site, sensitivity to antibiotics, antibiotic choice and risk factors of infection with *Acb* complex were investigated.

Many of the patients from whom *Acb* complex was isolated received measures such as antibiotics, surgery, mechanical ventilation and ICU stay, as previously reported (3, 4). Thus, attention should be paid to *Acb* complex colonization or infection in these cases. Strains of drug-

Table 6. Univariate Analysis of Predictors Associated with Mortality for Patients with *Acb* Complex Infection

Variables	Survivors (n=28)	Nonsurvivors (n=9)	p value[a]
Male gender	17(60.7)	4(44.4)	0.46
Age ≥ 60	22(78.6)	7(77.8)	1.00
Underlying disease			
Malignant tumor	14(50.0)	4(44.4)	1.00
Cardiovascular disease	6(21.4)	2(22.2)	1.00
Respiratory disease	3(10.7)	0(0.0)	0.56
Diabetes mellitus	3(10.7)	3(33.3)	0.14
Central nervous system disease	5(17.9)	0(0.0)	0.31
Chronic renal failure	5(17.9)	0(0.0)	0.31
Chronic liver disease	4(14.3)	3(33.3)	0.32
Autoimmune/allergic disease	0(0.0)	0(0.0)	1.00
Burn	0(0.0)	1(11.1)	0.24
Trauma	2(7.1)	0(0.0)	1.00
Use of antibiotics prior to isolation	18(64.3)	7(77.8)	0.69
Cormorbid conditions			
Urinary catheter	19(67.9)	5(55.6)	0.69
Surgery	14(50.0)	4(44.4)	1.00
Intravenous hyperalimination catheter	10(35.7)	5(55.6)	0.44
Mechanical ventilation	10(35.7)	3(33.3)	1.00
ICU stay	8(28.6)	5(55.6)	0.23
Immunosuppressive drug or corticosteroid use	0(0.0)	3(33.3)	0.01
Antineoplastic therapy	4(14.3)	2(22.2)	0.62
Transplantation	0(0.0)	2(22.2)	0.05
Infection site			
Pneumonia	12(42.9)	6(66.7)	0.27
Bacteremia	6(21.4)	3(33.3)	0.67
Urinary tract infection	4(14.3)	0(0.0)	0.55
Skin and soft-tissue infection	4(14.3)	0(0.0)	0.55
Intravascular catheter- related infection	2(7.1)	1(11.1)	1.00
Treatment			
β-lactam agent in combination with the β-lactamase inhibitor	9(32.1)	4(44.4)	0.69
Carbapenems	10(35.7)	2(22.2)	0.69
Fourth-generation cephalosporins	3(10.7)	0(0.0)	0.56
Third-generation cephalosporins	3(10.7)	0(0.0)	0.56
Quinolones	1(3.6)	1(11.1)	0.43
SIRS	18(64.3)	9(100.0%)	0.08

[a] Fisher analysis

Table 7. Multivariate Analysis of Predictors Associated with Mortality for Patients with *Acb* Complex Infection

Predictor	OR (95%CI)	p value
Immunosuppressive drug or corticosteroid use	ND	1.00
Transplantation	ND	1.00
SIRS	ND	1.00
Diabetes mellitus	8.50 (0.61-118.64)	0.11

ND: not detected

resistant *A. baumannii* have been increasing around the world. Lockhart et al reported that the rate of MDRA isolates increased from 6.7% in 1993 to 29.9% in 2004 (10). Other investigators showed that bacterial sensitivity to carbapenems has dramatically decreased in recent years (11, 18). In contrast, the present study revealed that most of the 201 isolates were sensitive to antibiotics, particularly carbapenems. An antimicrobial resistance surveillance study in Japan suggested that the resistant rate of *Acinetobacter* spp to imipenem was 0.6% and it was equally low for other antibiotics (19). Thus, the results of the present study support the findings of the previous study.

In the present study, the risk factors for *Acb* complex infection (using multivariate analyses) were: being over 60 years of age (p=0.016), chronic liver disease (p=0.018), and the use of first-generation cephalosporins prior to isolation (p=0.009). A previous study showed that approximately 30% of patients with bacteremia caused by *A. baumannii* had hepatobiliary disease (20). Another study reported that one of the conditions associated with community-acquired pneumonia was liver cirrhosis (21). There may be some relationship between *Acb* complex infection and liver disease. In the present study, the use of first-generation cephalosporins prior to isolation was a risk factor for *Acb* complex infection. This may be because first-generation cephalosporins were frequently used as prophylactic antibiotics in surgery and the use of first-generation cephalosporins, which are mainly effective with gram-positive bacteria, selected *Acb* complex. The present study is the first report to describe a relationship between first-generation cephalosporins and *Acb* complex infection. Shelburne et al suggested that the use of

expanded-spectrum cephalosporin or quinolone was a risk factor for *Acb complex* infection (13). These differences might be due to the sensitivity of *Acb* complex. In their study, approximately 80% of isolates acquired multidrug-resistance. Furthermore, another study showed that MDRAB accounted for 46.3% of *A. baumannii* infections (14).

The mortality of patients from whom *Acb* complex strains were isolated was 11.6%, which was lower than those of previous reports (13, 14). This could be due to the fact that *Acb* complex in this study had greater sensitivity to antibiotics. Generally, infection with MDRAB is associated with worse patient outcomes than infections due to non-MDRAB (11, 12). It is reported that colonization with MDRAB is associated with increased mortality (22). In the present study, the patient infected with the carbabenem-resistant strain died as a result of pneumonia. Therefore, it is very important to provide timely and proper antibiotic therapy and to conduct regular surveillance studies in order to prevent drug resistance.

The prognostic factor of *Acb* complex infection was examined because the mortality rate was higher in the infected group. However, no significant predictors associated with mortality were found. More cases need to be examined and the definition of infection reevaluated in future studies.

In this study, *Acinetobacter* genospecies were not analyzed. *Acinetobacter* genospecies 1 (*A. calcoaceticus*), genospecies 2 (*A. baumannii*), genospecies 3, and genospecies 13TU are phenotypically similar and are referred to as the *Acb* complex (23).The identification method used in the present study could not distinguish these species. A recent study suggested that genospecies 2 bacteremia could be the predictor associated with mortality of *Acb* complex bacteremia (24, 25). Therefore, the influence of genospecies of *Acb* complex on clinical outcomes needs to be evaluated.

In conclusion, this study showed that *Acb* complex isolates were sensitive to antibiotics, which differed from studies in other countries. Thus, the mortality rate was lower, but the mortality rate of the infection group was higher than that of the colonization group. Risk factors for infection were: being over 60 years of age, chronic liver disease, and the use of first-generation cephalosporins prior to isolation. The appropriate usage of antibiotics should be continued and surveillance studies should be conducted regularly to prevent drug resistance in *Acb* complex.

The authors state that they have no Conflict of Interest (COI).

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