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Original Article

Clinical characteristics of patients with *Acinetobacter junii* infection

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Background and purpose: *Acinetobacter junii* is a human pathogen but *A. junii* infection is rarely reported. This study aimed to delineate the characteristics of *A. junii* infection.

Methods: The medical records of 34 patients who were treated at Taipei Veterans General Hospital, Taipei, Taiwan, from May 1999 to May 2007 and had *A. junii* isolated from sterile sites were reviewed. Isolates of *A. junii* were identified by using API ID 32 GN and were confirmed by analysis of the 16S-23S rRNA intergenic spacer region.

Results: Thirty five infections with *A. junii* were identified. The most common underlying conditions included prior antibiotic use (56%), central venous catheterization (50%), and malignancy (38%). Systemic inflammatory response syndrome and shock developing within 1 week were observed in 27 (77%) and 8 (23%) episodes, respectively. Eighty percent of the infectious episodes were hospital acquired. The infections were primary bacteremia (n = 32), empyema (n = 1), peritonitis (n = 1), and keratitis (n = 1). Polymicrobial infection was present in 9 episodes (26%). *A. junii* isolates remained susceptible to most of the tested antimicrobial agents, but the hospital-acquired isolates had higher resistance rates than the community-acquired isolates. Four patients (11.4%) died of *A. junii* infection despite appropriate antimicrobial therapy for 3 patients. Shock that developed within 1 week of bacteremia was associated with a poor outcome ($p = 0.01$).

Conclusions: *A. junii* is an opportunistic pathogen that mainly affects patients who have had prior antimicrobial therapy, invasive procedures, or malignancy. Newly emerging infections caused by *A. junii* and the increasing antimicrobial resistance among hospital-acquired *A. junii* isolates should be monitored.

Key words: *Acinetobacter*; *Acinetobacter* infections; Disease attributes; Epidemiology

Introduction

Acinetobacter spp. are encapsulated, non-fermentative, aerobic, Gram-negative coccobacilli that are ubiquitous in nature, and can survive either in animate or inanimate objects. They are the most common Gram-negative organisms carried on human skin, especially among hospital personnel [1-3]. *Acinetobacter* spp. has emerged as an important pathogen of nosocomial infections [4]. *Acinetobacter* spp. account for 1% and 5% of all nosocomial bloodstream infections in sentinel US and Latin American hospitals, respectively [5,6]. Among the genus, *Acinetobacter baumannii* is the most common encountered species in nosocomial infection. Other *Acinetobacter* species including *Acinetobacter junii* have also been associated with human infections. *A. junii* can be isolated from community and hospital settings, including food and clinical specimens [7], and is a potential human pathogen. However, infections caused by *A. junii* are rarely reported, and this species is mainly associated with bacteremia during nosocomial infection outbreaks among preterm infants and pediatric patients with malignancy [8-11]. In adults, *A. junii* results in septicemia [12], community-acquired bacterial meningitis

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[13], peritoneal dialysis–related peritonitis [14], and infections associated with corneal perforation [15].

Infection caused by *A. junii* has been increasing in recent years, from 0.0019 episodes/1000 patient days in 1999 to 2001 to 0.0057 episodes/1000 patient days in 2002 to 2004 and 0.0074 episodes/1000 patient days in 2005 to 2007, respectively. Therefore, this retrospective study was conducted to better understand the clinical, laboratory, and microbiologic features of *A. junii* infections.

Methods

Patient inclusion and data collection

Patients with *A. junii* isolates from sterile sites were identified from the microbiological records of patients treated at Taipei Veterans General Hospital, Taipei, Taiwan, from May 1999 to May 2007. The data were collected by retrospective chart review, and included demographic data, comorbidities, clinical symptoms and signs, presence of catheters, invasive procedures, microbiological data, antimicrobial therapies, and patients' outcomes.

Bacterial isolates and antimicrobial susceptibility tests

For isolates identified from a patient in the same infection episode, only the first isolate was included in the study. The identification was initially obtained by using the API ID 32 GN kit (bioMérieux, Marcy-l'Etoile, France) and confirmed by analysis of the 16S-23S rRNA intergenic spacer (ITS) region, by the method described previously [16]. A stretch of DNA fragment comprising the 16S rRNA gene region, the ITS, and a small fragment of the 23S rRNA gene region were amplified with universal primers P-1512F (5'-GTCG TAACAAGGTAGCCGTA-3') and P-6R (5'-GGGTT C/TCCCCAGTTCRGAAAT-3'). The sequences were then analyzed using the Basic Local Alignment Search Tool (BLAST; available from: http://blast.ncbi.nlm.nih.gov/Blast.cgi). An identity with ≥98% to the reference strains was used to define a species. Antimicrobial susceptibility tests were performed by using the disk diffusion test according to the recommendation of the Clinical Laboratory Standards Institute [17].

Clonality study with pulsed-field gel electrophoresis analysis

Approximately half the isolates were randomly selected for pulsed-field gel electrophoresis (PFGE) study. Total DNA was prepared as described previously [18] and was digested by the restriction enzyme *Apa*I (New England Biolabs, Beverly, MA, USA). Restriction fragments were separated in 1% SeaKem Gold agarose gels (Cambrex Bio Science, Rockland, ME, USA)/0.5X tris-borate-ethylenediaminetetraacetic acid buffer (45 mM Tris, 45 mM boric acid, 1.0 mM ethylenediaminetetraacetic acid, pH 8.0) using the GenePath™ system (Bio-Rad Laboratories, Hercules, CA, USA) at 6 V for 24 h. After the run was completed, the gels were stained with ethidium bromide and photographed under ultraviolet light. Dendrograms showing percentage similarity were prepared by the Molecular Analyst Fingerprinting Software (Bio-Rad Laboratories) and compared using the unweighted pair-group method with arithmetic averaging method. A similarity coefficient above 80% was selected to define a major cluster.

Definitions

Prior antibiotic use within 1 month, steroid use of more than 2 doses within 2 weeks, and cytotoxic drug use within 6 weeks of infection were recorded. Invasive procedures were recorded if they were performed within 1 month of the start of the infection.

Systemic inflammatory response syndrome (SIRS) was defined as described in the American College of Chest Physicians/Society of Critical Care Medicine Consensus [19]. Fever was defined as a body temperature above 38°C. Shock was defined as systolic blood pressure <90 mm Hg.

An infection episode was considered to be community acquired when it developed before the first 48 h of hospital admission. A period of at least 2 weeks was stipulated to define the infection episode as community acquired in patients with previous hospital admissions [20,21]. Hospital-acquired infection episodes were defined as those occurring more than 48 h after admission. The definition of polymicrobial infection was isolation of 1 or more microorganisms other than *A. junii* from a specimen during the same episode. The antimicrobial therapies were classified as empirical or definitive, with the former being defined as the initial therapy before the results of culture were available and the latter being defined as therapy after the results of antibiotic susceptibility tests had been obtained. The antimicrobial therapy was considered appropriate if the treatment regimen included antibiotics active in vitro and the dose and route of administration conformed with current medical standards. Death was attributed to the infection episode if the patient died

within 14 days of the last positive culture and no other immediate causes of death were found.

Statistical analysis

Univariate analysis using chi-squared tests with Yates' correction or Fisher's exact test was performed to demonstrate the relation of possible risk factors with death attributable to *A. junii* infection. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows (Version 15.0; SPSS, Chicago, IL, USA). A p value of <0.05 was considered statistically significant.

Results

Bacterial isolates

During the study period, 41 isolates of *A. junii* were identified by using the phenotypic method. After sequencing and analysis of the ITS region, only 35 isolates were confirmed as *A. junii*; the other 6 isolates were identified as *Acinetobacter* genomic species 10.

Demographic data, underlying characteristics, and clinical features

Thirty five infection episodes were identified in 34 patients. A patient with lung cancer had 2 episodes of bacteremia, which occurred approximately 50 days apart and were both related to a port A catheter. Among the 34 patients, 25 were men. The mean age (± standard deviation) was 55.4 ± 21.8 years. Two patients were younger than 18 years. A 12-year-old boy experienced peritoneal dialysis–related peritonitis. A 10-year-old girl had undergone allogenic bone marrow transplantation for acute myelogenous leukemia before infection. After excluding 1 patient who acquired *A. junii* keratitis 341 days after admission, infection with *A. junii* occurred after 15.5 ± 26.6 days of hospital admission.

The underlying diseases and predisposing factors of the 34 patients are shown in Table 1. All of the patients had at least 1 underlying disease or had undergone an invasive procedure. Among the thirteen patients with malignancies (38%), 10 (77%) had at least 1 central venous catheter in situ and 6 (46%) had recently received chemotherapy. Of the 2 patients who did not have significant underlying disease before the infection, 1 underwent abdominal surgery twice because of a choledochal cyst and experienced subsequent bile leakage just 1 day before the start of the infection and 1 with candidal endocarditis had *A. junii* isolated from the pleural effusion.

Table 1. Underlying diseases and predisposing factors of 34 patients with *Acinetobacter junii* infection

Underlying condition	No. of patients (%)
Prior antibiotic use	19 (56)
Central venous catheters use[a]	17 (50)
Jugular venous catheter	6 (18)
Femoral venous catheter	1 (3)
Port A catheter	9 (26)
Hickman catheter	3 (9)
Malignancy	13 (38)
Solid tumor	11 (32)
Hematologic malignancy	2 (6)
Transplantation	3 (9)
Intensive care unit stay within 2 weeks	10 (29)
Ventilator use within 2 weeks	9 (26)
Diabetes mellitus	8 (24)
Steroid use	8 (24)
Cytotoxic drug use	8 (24)
Surgery within 1 month	6 (17)
Cerebrovascular accident	5 (15)
Immunologic diseases[b]	4 (12)
Confined to bed	3 (9)
Liver cirrhosis	2 (6)
End-stage renal disease	2 (6)
Total parenteral nutrition	1 (3)

[a]Some patients had more than 1 catheter.

[b]Includes Raynaud's disease, systemic lupus erythematosus, progressive systemic sclerosis, and multicentric reticulohistiocytosis.

More than half of the patients had received antibiotics prior to the infection. Cephalosporin was the most commonly used agent (84%), followed by penicillin derivatives, including penicillin, oxacillin, ampicillin/sulbactam, amoxicillin/clavulanic acid, ticarcillin/clavulanic acid, piperacillin/tazobactam (37%), and aminoglycosides (32%). Among the 10 patients (29%) who stayed in the intensive care unit, the mean Acute Physiology and Chronic Health Evaluation II score was 19.7 ± 9.0, and all except 1 patient received mechanical ventilation.

The clinical manifestations and laboratory data at the time of the culture collection is shown in Table 2. Most of the patients presented with fever (83%) and were considered to have SIRS (77%).

Microbiological data

Most of the episodes were hospital-acquired infection (80%). The PFGE study demonstrated that almost all of the isolates did not have a clonal relationship (Fig. 1). Thirty two isolates were recovered from blood (91%), and 1 isolate each was recovered from pleural effusion, peritoneal fluid, and corneal fluid. Polymicrobial infection was found in 9 patients (26%).

Table 2. Clinical manifestations and laboratory data for *Acinetobacter junii* infection (n = 35).

Variable	No. (%)
Clinical manifestation	
Fever	29 (83)
Systemic inflammatory response syndrome	27 (77)
Shock within 1 week	8 (23)
Laboratory data (mean ± SD [range])	
White blood cell ($\times 10^9$/L)	10.28 ± 6.89 (0.45-29.7)
Hemoglobin (g/L)	109 ± 20 (79-160)
Platelets ($\times 10^9$/L)	228.7 ± 151.4 (9.0-761.0)
C-reactive protein (nmol/L)	67.6 ± 70.4 (5.0-290.4)
Creatinine (μmol/L)	167.9 ± 221.0 (44.2-1105.0)
Alanine aminotransferase (U/L)	57.1 ± 83.1 (7-370)

Abbreviation: SD = standard deviation.

The concomitant isolated organisms included *Enterobacter aerogenes, Flavobacterium odoratum*, *A. baumannii*, *Stenotrophomonas maltophilia*, *Pseudomonas aeruginosa*, *Comamonas acidovorans*, *Streptococcus viridans*, *Staphylococcus aureus*, and coagulase-negative *Staphylococcus*.

The results of the antimicrobial susceptibility tests are shown in Table 3. There was good susceptibility to cephalosporins — above 80% for third-generation cephalosporins and 100% for fourth-generation cephalosporins. Among the aminoglycosides, the susceptibility rate to gentamycin was the lowest (67.5%). For the β-lactam/β-lactamase inhibitor combination, the susceptibility rate was 100%. Isolates from nosocomial infections had a higher resistance rate than those from community-acquired infections.

Antimicrobial therapy and outcomes

Among the 35 infection episodes, empirical antimicrobial therapy was considered appropriate for 20 episodes (57%), and definitive antimicrobial therapy was appropriate for 25 episodes (71%). The attributed mortality rate was 11.4% (4 patients). The underlying diseases of these 4 patients were severe aplastic

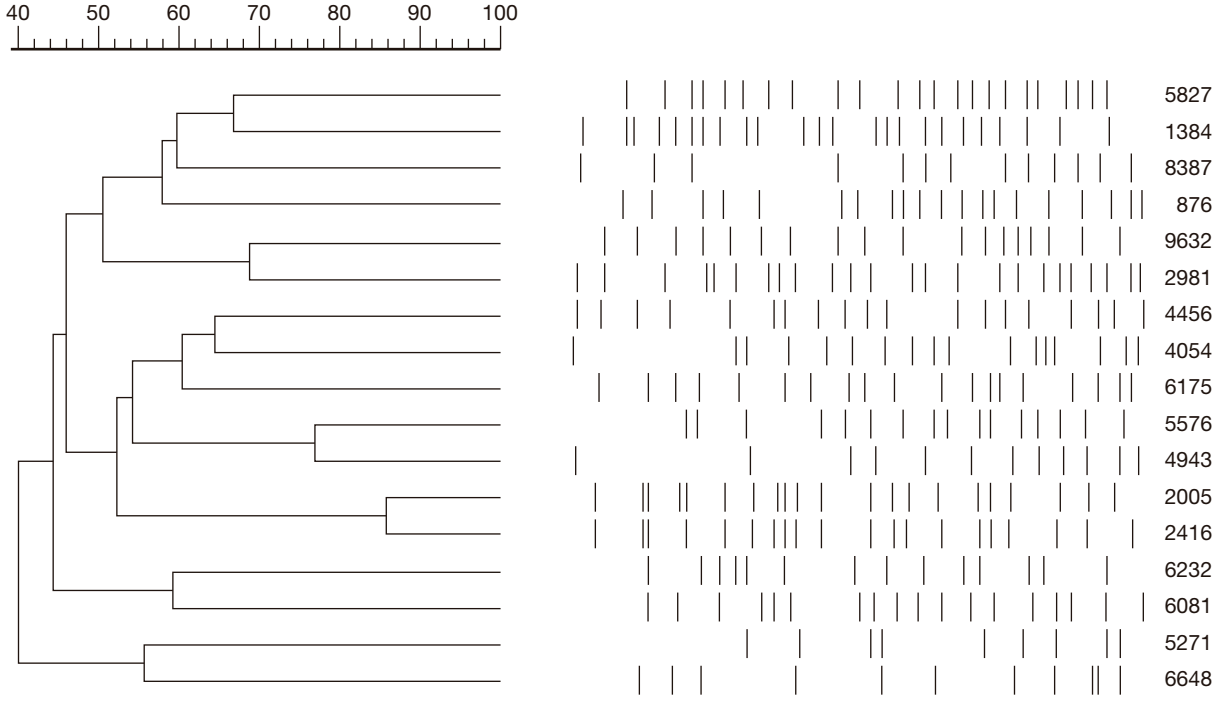

Fig. 1. Pulsed-field gel electrophoresis dendrogram of 17 randomly selected *Acinetobacter junii* isolates. There was no clonal relationship among the isolates, except for isolates 2005 and 2416, which were collected from 2 patients who were admitted to the same ward.

Table 3. Antimicrobial susceptibility rates of *Acinetobacter junii* isolates (n = 35).

Antimicrobial agent	All isolates (n = 35)			Community-acquired isolates (n = 7)			Hospital-acquired isolates (n = 28)		
	Sensitive	Intermediate	Resistant	Sensitive	Intermediate	Resistant	Sensitive	Intermediate	Resistant
Ceftriaxone	84.2	10.5	5.3	100.0	0	0	81.3	12.5	6.3
Ceftazidime	97.1	0	2.9	100.0	0	0	96.4	0	3.6
Cefepime	100.0	0	0	100.0	0	0	100.0	0	0
Gentamicin	74.3	0	25.7	71.4	0	28.6	55.3	0	44.7
Amikacin	88.6	0	11.4	100.0	0	0	85.7	0	14.3
Tobramycin	89.5	0	10.5	100.0	0	0	87.5	0	12.5
Ampicillin/sulbactam	100.0	0	0	100.0	0	0	100.0	0	0
Piperacillin/tazobactam	100.0	0	0	100.0	0	0	100.0	0	0
Ciprofloxacin	83.9	0	16.1	85.7	0	14.3	83.3	0	16.7
Imipenem	97.1	0	2.9	100.0	0	0	96.4	0	3.6

anemia with allogenic bone marrow transplantation, squamous cell carcinoma of the lung, external ventricular drainage for hemorrhage due to a ruptured arteriovenous malformation, and pneumonia. One of the 4 patients had polymicrobial infection and 1 did not receive definitive antimicrobial therapy because he died before the culture result was available. The statistical relevance between possible risk factors and mortality is shown in Table 4. Shock within 1 week of bacteremia was associated with mortality.

Table 4. Univariate analysis of risk factors associated with death attributable to *Acinetobacter junii* infection.

Risk factor	Deaths (No.)	Survival (No.)	*p*
Sex			
Male	3	22	0.94
Female	1	8	
Immunocompromised state[a]			
Yes	2	14	0.85
No	2	17	
Systemic inflammatory response syndrome			
Yes	3	24	0.91
No	1	7	
Shock within 1 week			
Yes	3	5	0.01
No	1	26	
Inappropriate antimicrobial therapy			
Yes	1	9	0.87
No	3	22	
Polymicrobial infection			
Yes	1	8	0.97
No	3	23	

[a]Neutropenia, liver cirrhosis, steroid use, solid organ or stem cell transplantation, or treatment with cytotoxic agents.

Discussion

Acinetobacter spp. are difficult to identify by using the phenotypic method [16], as also demonstrated in this study. The ITS sequencing analysis was used to identify the species; this method has been successfully used for the identification of many bacteria, including *Acinetobacter* spp. belonging to the *Acinetobacter calcoaceticus-A. baumannii* complex [16].

Although *A. junii* is still an uncommon pathogen, infections caused by this species have been increasing at the Taipei Veterans General Hospital. Previously, *A. junii* infection outbreaks mainly occurred in preterm infants or pediatric patients [9-11]. In this series, most of the patients were elderly, with more than half being older than 60 years, implicating a change in the patient population.

Almost all of the patients had at least 1 underlying disease. Furthermore, approximately half of the patients were immunocompromised, with conditions such as neutropenia, liver cirrhosis, steroid use, solid organ or stem cell transplantation, or treatment with cytotoxic agents, suggesting that *A. junii* is an opportunistic pathogen. For patients with malignancy, the immunocompromised state and the presence of a central venous catheter were the 2 most important factors relating to *A. junii* infection. If the patients with peritoneal dialysis or recent surgery were added, the proportion of patients who underwent recent invasive procedures reached 63%. Seifert et al have reported that bacteremia due to *Acinetobacter* spp. other than *A. baumannii* is mostly sporadic and almost exclusively related to intravascular devices [22,23]. In addition, several studies have demonstrated that more than 40% of healthy volunteers carried *Acinetobacter*

spp. on their bodies [3,24,25], and that the frequency of *A. junii* colonization on human skin varied from 1.6% to 35.0% of *Acinetobacter* spp. [3,25,26]. It has been postulated that catheter-related infection may be associated with skin organisms colonized around the catheter insertion site [27,28]. The distribution of *A. junii* on human skin may explain the correlation between *A. junii* infection and central venous catheter insertion. Overall, the risk factors for *A. junii* infection were similar to those of the most clinically important *Acinetobacter* spp., *A. baumannii*. These risk factors included immunosuppression, unscheduled admission to hospital, respiratory failure at intensive care unit admission, prior antimicrobial therapy, previous sepsis in the intensive care unit, and the invasive procedures index [29-32].

The symptoms and signs of *A. junii* infection were not specific. The most common symptom was fever and approximately 80% of patients developed SIRS, and septic shock ensued in 25% of patients in this study, indicating the true pathogenicity of the species. The results also indicated a low possibility of pseudobacteremia in these patients.

A. baumannii is an important nosocomial pathogen, that causes many therapeutic problems due to its resistance to multiple antimicrobial agents [29]. Even though similarities in risk factors exist between *A. junii* and *A. baumannii* bacteremia, their antimicrobial resistances are different. Compared with *A. baumannii*, *A. junii* has a lower degree of resistance to most antimicrobials [26,33]. In this study, *A. junii* exhibited more susceptibility to antibiotic therapy than *A. baumannii*, which is similar to other reports [12,33]. The higher antibiotic resistance rate of hospital-acquired isolates suggests that *A. junii* may acquire resistance to antimicrobial agents in the hospital environment. Recently, plasmid-mediated carbapenem-hydrolyzing β-lactamases and metallo-β-lactamases were detected in *A. junii* isolates [34,35]. Therefore, *A. junii* may develop resistance as well as *A. baumannii*, which will create clinical problems and therapeutic difficulties.

The empirical and definitive antimicrobial therapies were considered appropriate for 57% and 71% of patients, respectively. It is interesting that 29% of the patients received inappropriate antimicrobial therapy even after the availability of the antibiotic susceptibility result. One of the reasons could be the continued improvement of these patients. This result was in contrast to that observed for *A. baumannii*, as inappropriate antimicrobial treatment for *A. baumannii* bacteremia contributes to mortality [31]. This result might also indicate a lower virulence of *A. junii* than of *A. baumannii*.

The predictive factors for mortality could not be well established in this study due to the small case number. However, inappropriate therapy seemed to have no association with poor prognosis. Three of the patients who died of the infection had received appropriate therapy, indicating the determination of some host factors of the 4 patients or virulence factors of the 4 isolates regarding the poor prognosis. Nevertheless, patients who present with shock should be aggressively treated.

In conclusion, *A. junii* is a newly emerging pathogen that mainly affects patients with comorbidities, including malignancies, invasive procedures, or prior antimicrobial therapies. The course of the infection is generally benign, but in some circumstances, infection with this species can be severe.

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