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Clinical and microbiological characterization of carbapenem-resistant *Acinetobacter baumannii* bloodstream infections

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The incidence of carbapenem-resistant *Acinetobacter baumannii* infection is increasing, which might be associated with high morbidity and mortality among critically ill patients with limited therapeutic options. This study was conducted to evaluate the clinical and microbiological features of carbapenem-resistant *A. baumannii* bacteraemia. The medical records of 28 adult patients with this bacteraemia admitted to Korea University Guro Hospital, from January 2005 through December 2010, were reviewed. Using the 28 bloodstream isolates, we intended to detect genes encoding carbapenemases, and investigate the inoculum effect on each of the antimicrobial agents rifampicin, imipenem, colistin and tigecycline. With one blood isolate from a patient with pneumonia, rifampicin-inducible resistance was examined using the experimental mouse pneumonia model. Out of 28 carbapenem-resistant *A. baumannii* bloodstream infections (BIs), the most common primary focus was the central venous catheter (35.7 %) and then the lung (32.1 %). The 30 day overall mortality was 53.6 %; in most cases (80 %) the patients died within 10 days after the onset of the bacteraemia. By univariate analysis, inappropriate antimicrobial therapy (73.3 vs 30.8 %, $P=0.02$), mechanical ventilation (53.3 vs 15.4 %, $P=0.04$) and a high Pitt bacteraemia score (4.9 ± 1.9 vs 2.2 ± 1.2, $P<0.01$) were statistically significant risk factors for mortality, while only a high Pitt bacteraemia score (odds ratio 2.6; 95 % confidence interval 1.1–6.5) was independently associated with 30 day mortality by multivariate analysis. All 28 isolates had the bla_{OXA-51}-like gene with upstream IS*Abal*, 2 of which additionally had the bla_{OXA-58}-like gene and the bla_{OXA-23}-like gene. Inoculum effect and rifampicin inducible resistance were not detected. Considering the rapid progression to death in carbapenem-resistant *A. baumannii* BIs, early empirical antibiotic therapy would be warranted based on the local microbiological data in each hospital.

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INTRODUCTION

Acinetobacter baumannii can cause suppurative infections in virtually every organ system of the human body including pneumonia, surgical site infections, skin and soft tissue infections, urinary tract infections, post-operative meningitis and catheter-related infections (Munoz-Price & Weinstein, 2008; Peleg *et al.*, 2008). Bacteraemia is often associated with severe *A. baumannii* infections, and the overall mortality is approximately 25 %, and up to 54 % in intensive care units (ICUs) (Bergogne-Bérézin & Towner, 1996; Poutanen *et al.*, 1997). Carbapenems are the preferred therapeutic option for *A. baumannii* infections. In the past decade, carbapenem-resistant *A. baumannii* has emerged as a significant nosocomial pathogen worldwide; the carbapenem-resistance rate among *A. baumannii* has markedly increased to up to 60 % in Korea (Lee *et al.*, 2008). As for carbapenem-resistant *A. baumannii* infections, colistin and tigecycline have been suggested as possible effective therapeutic choices (Maragakis & Perl, 2008). Though rifampicin-based regimens also have shown favourable outcomes, rifampicin-induced resistance has become a concern (Saballs *et al.*, 2006; Song *et al.*, 2008). With limited therapeutic options, infections caused by carbapenem-resistant organisms might result in greater mortality, longer hospitalization and higher costs than those caused by susceptible organisms. The clinical and microbiological data for carbapenem-resistant *A. baumannii* bacteraemia are not sufficient, and the impact of early appropriate antimicrobial therapy on survival continues to be debated (Wareham *et al.*, 2008; Erbay *et al.*, 2009).

Abbreviations: BI, bloodstream infection; CI, confidence interval; ICU, intensive care unit.

The goal of this study was to evaluate the clinical and microbiological features of bloodstream infections (BIs) caused by carbapenem-resistant *A. baumannii*. To better characterize the microbiological aspects of carbapenem-resistant *A. baumannii* blood isolates, the prevalence of each type of carbapenemase, the MIC/inoculum effects of each antibiotic agent and inducible rifampicin resistance were assessed using clinical *A. baumannii* isolates from blood.

METHODS

Study subjects and data collection. The medical records of 28 adult patients ($\geqslant$18 years old) with clinically significant carbapenem-resistant *A. baumannii* bacteraemia who were admitted to Korea University Guro Hospital (a 1000 bed tertiary care university hospital), from January 2005 through December 2010, were reviewed. The data collected included: age, gender, underlying illness, primary site of infection, severity of illness (as calculated by the Pitt bacteraemia score and Charlson's weighted index of morbidity), laboratory findings, antibiotic regimen, duration of hospitalization/ICU stay and 30 day mortality. The patients were divided into two groups according to the 30 day survival after the diagnosis of bacteraemia. The following medical conditions were also documented: treatment with immunosuppressive medications within 30 days before the bacteraemia, nasogastric tube, mechanical ventilation, haemodialysis and the presence of a central venous catheter. Immunosuppressant use was defined as treatment with prednisolone ($\geqslant$10 mg daily) or any other immunosuppressant during the 30 days prior to the diagnosis of bacteraemia.

Clinically significant *A. baumannii* bacteraemia was defined as one or more positive blood cultures, together with clinical features compatible with systemic inflammatory response syndrome. When a patient had more than one bacteraemic episode, only the first episode was included. Appropriate antibiotic therapy was defined as one of the following regimens given within 48 h after the blood culture was obtained: carbapenem–rifampicin-, carbapenem–sulbactam-, tigecycline- and colistin-based regimens.

Characterization of β-lactamases. In order to analyse the production of class B and D carbapenemase, carbapenem-resistant isolates were first screened by a modified Hodge test and an imipenem-EDTA double disc synergy test (Lee *et al.*, 2001). PCR was performed to detect bla_{OXA}, bla_{IMP} and bla_{VIM} genes using specific primers as previously described (Song *et al.*, 2007). The presence of the insertion element IS*Aba1* upstream of $bla_{OXA\text{-}51}$-like was also investigated by PCR (Turton *et al.*, 2006).

Antimicrobial susceptibility testing and inoculum effect. Antimicrobial susceptibilities were determined for imipenem, colistin sulfate, tigecycline and rifampicin according to Clinical and Laboratory Standard Institute guidelines using a broth microdilution method (CLSI, 2006). The bacteria were tested by two inocula sizes (10^5 and 10^7 c.f.u. ml^{-1}), and were incubated in ambient air at 37 °C for 24 h. The lowest drug concentration showing no growth was accepted as the MIC. Each isolate was considered resistant to carbapenem if the MIC against imipenem was $\geqslant$16 mg l^{-1}. The following concentrations were considered as the susceptibility breakpoints of the other tested antimicrobials: colistin, 4 mg l^{-1}; tigecycline, 2 mg l^{-1}; rifampicin, 2 mg l^{-1} (Giamarellos-Bourboulis *et al.*, 2001; Pankey, 2005). The changes of the MICs according to the inoculum size for imipenem, rifampicin and colistin were compared. An inoculum effect was defined as a fourfold or greater increase in the MIC on testing with the higher inoculum compared to the lower inoculum.

Inducible rifampicin resistance. Immunocompetent specific-pathogen-free CD-1 (ICR) young female mice, weighing on average 25 g (6–7 weeks old), were supplied by Orient Bio. All animal procedures were performed in accordance with the guidelines of Korea University Guro Hospital for the humane handling, care and treatment of research animals. An experimental mouse pneumonia model was used to evaluate the selection of rifampicin-resistant mutants of *A. baumannii* (Song *et al.*, 2009). Twenty mice were inoculated with an *A. baumannii* isolate from a patient with pneumonia and bacteraemia. Five mice were allocated to each time point (24, 48, 72 and 96 h after inoculation): two mice out of the five were controls (without treatment), and the other three were treated with 100 mg rifampicin kg^{-1} per day. The lungs of the mice were removed at each time point and homogenized for 2 min in 2 ml sterile saline. After 10-fold dilution, 0.1 ml was plated on sheep blood agar for 24 h at 37 °C and the counts were expressed as $\log_{10}$ c.f.u. (g tissue)$^{-1}$. The MIC of rifampicin was determined at each time point.

Statistical analysis. Data were analysed with SPSS 10.0 (SPSS). A P value of <0.05 was considered statistically significant. Student's t-test was used to compare continuous variables, and the Fisher exact test was used to compare categorical variables. Multivariate analysis was carried out using a stepwise logistic regression model.

RESULTS

Clinical characteristics and risk factors for mortality among patients with *Acinetobacter* bacteraemia

All 28 cases of *Acinetobacter* BI were nosocomial, and 89.3 % (25 among 28) of cases developed during an ICU stay. The median age of patients was 64 (range 23–88 years) and half of the patients were men (Table 1). The most common primary site of infection was a central venous catheter (10 patients; 35.7 %), followed by the lung (9 patients; 32.1 %), surgical site wound (3 patients; 10.7 %), urinary tract (3 patients; 10.7 %), intra-abdominal focus (2 patients; 7.1 %) and unknown sites (1 patient; 3.6 %). The finding of preceding colonization was identified in only five patients (17.9 %). A total of 3 out of 28 patients (10.7 %) presented with polymicrobial bacteraemia.

The 30 day overall mortality was 53.6 %. In 12 of the 15 fatal cases (80 %) the patients passed away within 10 days after the onset of the bacteraemia; the median interval from bacteraemia onset to death was 7 days (range 3–30 days). When the characteristics of those who survived were compared to the patients who did not survive, the demographic and clinical characteristics were indistinguishable for age, gender, underlying medical conditions, primary site of infection, Charlson's weighted index of co-morbidity, immunosuppressant use and hospital/ICU stay before onset of bacteraemia (Table 1). Inappropriate antimicrobial therapy (73.3 vs 30.8 %, P=0.02), mechanical ventilation (53.3 vs 15.4 %, P=0.04) and a high Pitt bacteraemia score (4.9 ± 1.9 vs 2.2 ± 1.2, $P<0.01$) were statistically significant risk factors of mortality. For multivariate analysis, only a

Table 1. Demographic and clinical characteristics of patients with carbapenem-resistant *A. baumannii* BI: comparison based on the clinical outcome

Patient characteristic	Survived (n=13)	Died (n=15)	Total (n=28)	P value
Age (years)	57.7±18.9	62.5±15.1	60.3±16.8	0.46
Sex: no. of males (%)	6 (46.2)	9 (60.0)	15 (53.6)	0.46
Underlying illness				
Diabetes mellitus	5 (38.5)	3 (20.0)	8 (28.6)	0.28
Chronic liver diseases	3 (23.1)	3 (20.0)	6 (21.4)	0.84
Chronic renal insufficiency	2 (15.4)	4 (26.7)	6 (21.4)	0.47
Cerebrovascular diseases	3 (23.1)	4 (26.7)	7 (25.0)	0.83
Haematological malignancy	0 (0)	3 (20.0)	3 (10.7)	0.09
Solid tumour	2 (15.4)	1 (6.7)	3 (10.7)	0.46
Chronic obstructive lung diseases	1 (7.7)	1 (6.7)	2 (7.1)	0.27
Congestive heart failure	1 (7.7)	1 (6.7)	2 (7.1)	0.92
Charlson's weighted index of co-morbidity	4.0±1.7	4.9±2.7	4.5±2.3	0.29
Pitt bacteraemia score	2.2±1.2	4.9±1.9	3.6±2.1	<0.01
Primary infection site (of bacteraemia)				0.28
Central venous catheter	5 (38.5)	5 (33.3)	10 (35.7)	–
Lung	4 (30.8)	5 (33.3)	9 (32.1)	–
Urinary tract	2 (15.4)	1 (6.7)	3 (10.7)	–
Intra-abdominal focus	2 (15.4)	0 (0)	2 (7.1)	–
Surgical site wound	0 (0)	3 (20.0)	3 (10.7)	–
Unknown origin	0 (0)	1 (6.7)	1 (3.6)	–
Polymicrobial bacteraemia	2 (15.4)	1 (6.7)	3 (10.7)	0.46
Risk factors				
Immunosuppressant use	2 (15.4)	7 (46.7)	9 (32.1)	0.08
Nasogastric tube	8 (61.5)	11 (73.3)	19 (67.9)	0.51
Total parenteral nutrition	5 (38.5)	9 (60.0)	14 (50.0)	0.26
Mechanical ventilation	2 (15.4)	8 (53.3)	10 (35.7)	0.04
Haemodialysis	2 (15.4)	1 (6.7)	3 (10.7)	0.46
Hospital stay before bacteraemia (days)	23.9±25.5	31.7±34.5	28.1±30.4	0.50
ICU stay before bacteraemia (days)	13.3±13.7	20.2±25.2	17.0±20.6	0.39
Inappropriate antibiotic therapy	4 (30.8)	11 (73.3)	15 (53.6)	0.02
Microbiological eradication	13 (100)	3 (20.0)	16 (57.1)	<0.01

high Pitt bacteraemia score [odds ratio 2.6; 95 % confidence interval (CI) 1.1–6.5] was independently associated with 30 day mortality; the odds ratios for mortality were 2.1 (95 % CI 0.2–23.3) with inappropriate antimicrobial therapy, and 5.2 (95 % CI 0.4–61.9) with mechanical ventilation. In the cases with catheter-related infections, catheter removal was the most important factor for patient survival; none of the infected patients survived without catheter removal (83.3 % with removal vs 0 % without removal, P=0.02) (Table 2). Meropenem–rifampicin was effective against pneumonia with low level carbapenem-resistant *A. baumannii* regardless of the rifampicin MIC; 72.7 % (8 among 11 cases) survived with meropenem–rifampicin treatment. Three out of four fatal cases with rifampicin-based regimens were related to high-level rifampicin resistance (MIC >128 mg l^{-1}) (Table 2).

Antimicrobial susceptibility testing and inoculum effect

In the total of 28 tested *A. baumannii* isolates, rifampicin, imipenem, colistin and tigecycline were not associated with an inoculum effect. The MIC_{50s} of rifampicin, imipenem, colistin, and tigecycline were 4, 32, 4 and 2 mg l^{-1}, respectively, with the standard inoculum tests, which was not increased more than twofold with the higher inoculum tests (Table 2). Four *A. baumannii* isolates had a rifampicin MIC >128 mg l^{-1} regardless of the inoculum size.

Characterization of β-lactamases

All carbapenem-resistant *A. baumannii* isolates were positive by the modified Hodge test, but negative by the imipenem-EDTA double disc synergy test. All 28 isolates carried the bla_{OXA-51}-like gene, 2 of which also had the bla_{OXA-58}-like gene and bla_{OXA-23}-like genes (Table 2). IS*AbaI* was upstream of bla_{OXA-51}-like in all 28 isolates. A metallo-β-lactamase producing organism was not detected.

Induced rifampicin resistance

The MICs of rifampicin did not increase with rifampicin treatment (600 mg per day). They were maintained around 8 mg l^{-1} for up to 96 h in both the treatment and control groups (Table 3).

Table 2. Characterization of carbapenemase and standard/high inoculum MICs of 20 carbapenem-resistant *A. baumannii* isolates

Primary infection site for each patient	30 day mortality	Appropriateness of antibiotic regimen	Type of carbapenemase	MIC (mg l^{-1}) of each agent at inocula of 10^5 and 10^7 c.f.u. ml^{-1}							
				Rifampicin*		Imipenem†		Colistin‡		Tigecycline§	
				10^5	10^7	10^5	10^7	10^5	10^7	10^5	10^7
Pneumonia	Dead	Meropenem (I)	OXA-51	4	8	16	32	4	8	2	4
Catheter-related infection	Dead	Meropenem + rifampicin (I)	OXA-51	>128	>128	32	64	4	8	2	2
Catheter-related infection‖	Survived	Meropenem (I)	OXA-51	4	8	64	128	4	8	2	4
Surgical site infection	Dead	Ciprofloxacin (I)	OXA-51	4	4	32	128	4	4	2	4
Catheter-related infection‖	Dead	Colistin (I)	OXA-51	128	128	64	128	8	8	2	2
Catheter-related infection‖	Survived	Colistin (A)	OXA-51	>128	>128	>128	>128	4	8	1	2
Unknown	Dead	None (I)	OXA-51	4	8	32	64	2	4	2	2
Surgical site infection	Dead	Ceftizoxime (I)	OXA-51	8	8	64	64	2	4	2	4
Surgical site infection	Dead	Colistin + meropenem (A)	OXA-51	4	4	64	64	4	8	2	4
Pneumonia	Survived	Meropenem + rifampicin (I)	OXA-51	4	8	16	32	4	8	2	4
Pneumonia	Survived	Meropenem + rifampicin (I)	OXA-51	4	8	16	16	4	8	2	2
Catheter-related infection	Dead	Colistin + rifampicin (I)	OXA-51	>128	>128	16	32	4	8	2	2
Catheter-related infection	Dead	Meropenem + rifampicin (A)	OXA-51	4	8	64	128	4	8	1	2
Catheter-related infection‖	Survived	Colistin + meropenem (A)	OXA-51	8	8	16	16	4	8	1	2
Catheter-related infection	Dead	Meropenem (I)	OXA-51	8	8	16	32	4	8	1	2
Pneumonia	Dead	Meropenem + rifampicin (I)	OXA-51	>128	>128	64	128	4	8	1	2
Intra-abdominal infection	Survived	Colistin + meropenem (A)	OXA-51	8	8	16	32	4	8	1	2
Pneumonia	Survived	Meropenem + rifampicin (A)	OXA-51, OXA-58	4	8	32	32	4	16	0.25	1
Intra-abdominal infection	Survived	Meropenem + rifampicin (A)	OXA-51, OXA-23	64	128	32	32	2	4	0.5	2
Catheter-related infection‖	Survived	Meropenem + rifampicin (A)	OXA-51	4	4	64	128	8	8	2	2
Pneumonia	Survived	Meropenem + rifampicin (A)	OXA-51	4	8	32	32	2	4	2	2
Urinary tract infection	Survived	Colistin (A)	OXA-51	4	4	64	128	2	2	1	2
Pneumonia	Dead	Tigecycline (A)	OXA-51	4	8	64	128	2	2	1	2
Pneumonia	Dead	None (I)	OXA-51	4	8	64	64	2	4	2	4
Catheter-related infection‖	Survived	Meropenem + rifampicin (A)	OXA-51	4	4	32	32	2	2	2	4
Urinary tract infection	Dead	None (I)	OXA-51	4	8	32	64	2	4	1	2
Pneumonia	Survived	Meropenem + rifampicin (A)	OXA-51	4	4	16	32	2	2	1	2
Urinary tract infection	Survived	Meropenem (I)	OXA-51	4	4	32	32	1	2	0.5	1
MIC_{50}				4	8	32	64	4	8	2	2
MIC_{90}				>128	>128	64	128	4	8	2	4

A, Appropriate; I, inappropriate.

*Susceptible $\leqslant$2 mg ml^{-1}, resistant $\geqslant$4 mg ml^{-1}; working party report of the British Society for Antimicrobial Chemotherapy.

†Susceptible $\leqslant$4 mg ml^{-1}, resistant $\geqslant$16 mg ml^{-1}; Clinical and Laboratory Standards Institute.

‡Susceptible $\leqslant$4 mg ml^{-1}, resistant $\geqslant$8 mg ml^{-1}; British Society for Antimicrobial Chemotherapy.

§Susceptible $\leqslant$2 mg ml^{-1}, resistant $\geqslant$8 mg ml^{-1} by Wyeth Research.

‖Catheter was removed.

Table 3. Rifampicin MICs for carbapenem-resistant *A. baumannii* isolates 24, 48, 72 and 96 h after treatment with rifampicin

Time interval after rifampicin trial (h)	Mouse no.	Cell count [log c.f.u. (g tissue)$^{-1}$]	MIC (mg l^{-1})
24	1	4.96	8
	2	6.78	8
	3	4.38	8
	Control 1	9.58	8
	Control 2	9.28	8
48	1	1.76	8
	2	1.54	8
	3	2.39	8
	Control 1	9.70	8
	Control 2	9.23	8
72	1	1.64	4
	2	1.48	8
	3	2.32	8
	Control	No survivors	
96	1	1.51	8
	2	2.42	8
	3	1.34	8
	Control	No survivors	

DISCUSSION

In this study, the clinical and microbiological characteristics of bacteraemia due to carbapenem-resistant *A. baumannii* are described. Clinical manifestations of *A. baumannii* induced BIs ranged from self limiting, transient bacteraemia to fulminant disease with a high mortality (Seifert *et al.*, 1995). The overall mortality rate of *Acinetobacter* bacteraemia has been reported to be high, ranging from 22 to 61.6 % according to the study population (Bergogne-Bérézin & Towner, 1996; Kwon *et al.*, 2007; Wareham *et al.*, 2008; Erbay *et al.*, 2009; Metan *et al.*, 2009). In this study, the overall mortality was 53.6 %, with rates of 30.8 and 73.3 % for patients who received appropriate and inappropriate antibiotic therapy within 48 h, respectively. Compared to previous studies, the mortality rate was remarkably high, and in most cases the patients died within 10 days after the onset of the bacteraemia. The differences in this study might have been due to the severity of illness as shown by the high Pitt bacteraemia score; only carbapenem-resistant cases were included. Because routine surveillance cultures were not performed for *A. baumannii*, preceding colonization was documented in only five patients (17.9 %). In the endemic setting of carbapenem-resistant *A. baumannii*, empirically targeted antibiotic treatment and late de-escalation of treatment would be warranted. Consistent with previous reports, most cases had the risk factors for *A. baumannii* infection including a central venous catheter, total parenteral nutrition, a nasogastric tube and mechanical ventilation; catheter-related infections and pneumonias were the most common primary focus of bacteraemia (Glew *et al.*, 1977). In cases with catheter-related BI, catheter removal was invariably required.

Carbapenem-resistant *A. baumannii* infection has been increasing and this is a significant concern. A recent study in Korea reported that most isolates acquired low-level carbapenem resistance due to the upregulation of the OXA-51-like enzyme; enzyme expression is known to be variable according to the presence of IS*Aba* (Héritier *et al.*, 2006; Poirel & Nordmann, 2006; Corvec *et al.*, 2007). Likewise, IS*AbaI* was upstream of $bla_{\text{OXA-51}}$-like in all 28 isolates in this study. Meropenem–rifampicin- and colistin-based combinations have been regarded as effective regimens, and use of the appropriate antibiotic therapy was related to the clinical outcome in this study.

It is assumed that high bacterial loads in patients with severe infection would affect the antibiotic response. Among carbapenem-resistant *A. baumannii* isolates, however, an inoculum effect was not found with any of the antibiotic agents imipenem, colistin, rifampicin and tigecycline. Rifampicin, considered inactive against Gram-negative bacteria, has emerged as one of the therapeutic options for infections caused by carbapenem-resistant *A. baumannii*. It is hypothesized that substantial changes in the outer membrane of multi-drug resistant *A. baumannii* may enable greater access to the target site (Li *et al.*, 2007). When it comes to combination with other antibiotics, colistin is known to induce damage to the cell-wall structures of Gram-negative bacteria, thereby allowing the accelerated penetration of rifampicin (Song *et al.*, 2008; Aoki *et al.*, 2009). Moreover, Bernabeu-Wittel *et al.* (2004) reported that meropenem at sub-MIC levels induced spheroplastic changes (>3 μm in size) of *A. baumannii* isolates, which might also increase the intracellular penetration of rifampicin.

Although some previous studies reported inducible rifampicin resistance during treatment (Pachón-Ibáñez *et al.*, 2006; Saballs *et al.*, 2006), a change of the rifampicin MIC was not found up to 96 h after treatment in this study. However, high-level resistance (MIC >128 mg l^{-1}) would be predictive of a poor clinical and microbiological response as previously reported (Song *et al.*, 2008).

In conclusion, low-level carbapenem-resistant *A. baumannii* strains with OXA-51-like carbapenemase were prevalent in the study population. Considering the rapid progression to death in carbapenem-resistant *A. baumannii* BIs, early empirical antibiotic therapy would be warranted based on the local microbiological data in each hospital.

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