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Outbreaks of Imipenem Resistant *Acinetobacter Baumannii* Producing OXA-23 β-Lactamase in a Tertiary Care Hospital in Korea

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Purpose: Since November 2006, imipenem-resistant *Acinetobacter baumannii* isolates have increased in Kyung Hee University Hospital in Seoul, Korea. The purpose of this study was to determine the genetic basis and molecular epidemiology of outbreak isolates. **Materials and Methods:** Forty-nine non-repetitive isolates of the 734 IRAB strains were investigated in order to determine their characteristics. The modified Hodge and the ethylenediaminetetraacetic acid (EDTA)-disk synergy test were performed for the screening of carbapenemase and metallo-β-lactamase production. Multiplex polymerase chain reaction (PCR) assays were performed for the detection of genes encoding for OXA-23-like, OXA-24-like, OXA-58-like and OXA-51-like carbapenemase. Pulsed-field gel electrophoresis (PFGE) was performed for strain identification. **Results:** All isolates showed 100% resistance to ciprofloxacin and gentamicin, 97.9% resistance to cefepime, piperacillin/tazobactam, aztreonam, ceftazidime and piperacillin, 93.9% resistance to tobramycin and 57.1% resistance to amikacin. All of the 49 isolates (100%) showed positive results in the modified Hodge test and negative results in the EDTA-disk synergy test. They all (100%) possessed the encoding gene for an intrinsic OXA-51-like carbapenemase and an acquired OXA-23-like carbapenemase in the multiplex PCR assay. PFGE patterns revealed that all isolates were clonally related from A1 to A14. **Conclusion:** It is concluded that all of the 49 IRAB isolates acquired resistance to imipenem by producing OXA-23 carbapenemase and they might have originated from a common source.

Key Words: Imipenem resistant *Acinetobacter baumannii*, outbreak, OXA-23

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INTRODUCTION

Acinetobacter baumannii is a non-fermenting, aerobic Gram-negative bacillus that is distributed evenly in the hospital environment,[1] and is an important opportunistic pathogen which causes nosocomial infections, especially in intensive care units. The known risk factors for *A. baumannii* colonization or infection include prolonged hospitalization, intensive care unit (ICU) admission, emergency surgical operation, total parenteral nutrition, invasive procedures, or previous broad-spectrum antibiotic use. *A. baumannii* causes a variety of nosocomial infections including septicemia, pneumonia, endocarditis, meningitis, wound infection and urinary tract infection.[1] Carbapenems are the antibiotics of choice against multidrug resistant *A. baumannii* infections. However, the incidence of carbapenem-resistant *A. baumannii* is now being increasingly reported worldwide, thus causing serious therapeutic problems.[2] Imipenem is one of the most effective carbapenems for the treatment for the infection caused by multidrug resistant *A. baumannii*. It causes good porin permeability of the outer

membrane, and has affinity for penicillin-binding proteins, and stable β-lactamase.[3] However, imipenem-resistant *A. baumannii* are being reported increasingly, ranging from 6.3% in 1999 to 13% in 2003 in Korea.[4,5]

Since November 2006, cases of imipenem-resistant *A. baumannii* have increased in Kyung Hee University Hospital in Seoul, Korea. The purpose of this study is to determine the genetic basis and molecular epidemiology of these outbreak isolates.

MATERIALS AND METHODS

Microbiologic evaluation

A total of 734 imipenem-resistant *A. baumannii* isolates were isolated from November 2006 to July 2007 at Kyung Hee University hospital in Seoul, Korea. The isolates were identified by conventional identification techniques and a MicroScan Walkaway 96 (Dade Behring, West Sacramento, CA, USA). Forty-nine (49) non-repetitive isolates of the 734 imipenem-resistant *A. baumannii* strains were investigated in order to determine their characteristics.

Antimicrobial susceptibility testing

The testing was performed by two methods; One was minimum inhibitory concentrations (MIC) using a commercially prepared panel (MicroScan Walkaway 96) for blood specimens, and the other was the disk diffusion method for other specimens. The results were interpreted according to the guidelines of the Clinical Laboratory Standards Institute (CLSI).[6]

β-lactamase assays

A modified Hodge test was performed to screen carbapenemase production. A suspension of *Escherichia coli* ATCC 25922, which was adjusted to the turbidity of the McFarland No. 0.5 tube was inoculated evenly on a Mueller-Hinton agar plate. Then, an imipenem disk (30 μg, BBL) was placed at the center of the plate. Test strains were streaked heavily from the edge of the disk to the periphery of the plate. The presence of a distorted inhibition zone after 16 to 18 hours of incubation at 35˚C was interpreted as a positive modified Hodge test. An ethylenediaminetetraacetic acid (EDTA)-disk synergy test was used for the screening of metallo-β-lactamase production. The test strains were suspended to the turbidity of the McFarland No. 0.5 tube and used to swab and inoculate a Mueller-Hinton agar plate. A 30 μg imipenem disk and a blank filter paper disk were placed 10 mm apart from edge to edge on the agar plate. Ten μL of 0.5 M EDTA solution was applied to the blank disk, which resulted in approximately a 1.5 mg/disk. After 16 to 18 hours of incubation at 35˚C, the presence of an enlarged zone of inhibition was interpreted as EDTA-synergy test positive.[7]

Detection of carbapenem-resistant genes

A multiplex polymerase chain reaction (PCR) assay was performed for the detection of the carbapenem-resistant genes in the *A. baumannii* isolates according to the method described by Woodford, et al.[8] These primers were combined with eight primers which were designed to amplify fragments of genes encoding for OXA-23-like, OXA-24-like, OXA-58-like and OXA-51-like carbapenemase. The amplification conditions were: initial denaturation at 94˚C for 5 minutes, 30 cycles of 94˚C for 25 seconds, 52˚C for 40 seconds, 72˚C for 50 seconds, and a final elongation at 72˚C for 6 minutes (Table 1).

Pulsed-field gel electrophoresis

The sample plugs were digested with 150 μL of *ApaI* reaction buffer containing 10 U of the *ApaI* restriction enzyme (New England Biolabs, Ipswich, MA, USA). DNA fragments were separated by electrophoresis in a 1% SeaKem gold agarose gel, using a 0.5× TBE buffer (45 mM Tris, 45 mM boric acid, 1 mM EDTA, pH 8.0) with CHEF Mapper® XA (Bio-Rad Laboratories, Hercules, CA, USA) at 14˚C and 6 V/cm. The electrophoresis was carried out by using alternating pulses at a 120° angle, with a 5-20

Table 1. Multiplex PCR Primers for the Detection of Genes Encoding OXA Carbapenemase

Primers	Primer sequence (5'-3')	Product size (bp)
OXA-51-like	TAATGCTTTGATCGGCCTTG TGGATTGCACTTCATCTTGG	353
OXA-23-like	GATCGGATTGGAGAACCAGA ATTTCTGACCGCATTTCCAT	501
OXA-24-like	GGTTAGTTGGCCCCCTTAAA AGTTGAGCGAAAAGGGGATT	246
OXA-58-like	AAGTATTGGGGCTTGTGCTG CCCCTCTGCGCTCTACATAC	599

PCR, polymerase chain reaction.

Table 2. Clinical Characteristics of Patients in Imipenem Resistant *Acinetobacter Baumannii* Outbreak

No.	Isolate	Age / gender	Hospital ward	Specimen	PFGE pattern	Days since admission	Underlying- disease	Diagnosis
1	06.11.21	76 / F	MICU	Sputum	A7	4	Intracranial hemorrhage	Pneumonia, UTI
2	06.11.27	55 / M	NICU	Sputum	A1	43	Intracranial hemorrhage	Pneumonia
3	06.12.15	75 / F	MICU	Wound	A2	61	Pancreatitis	Pneumonia, UTI
4	07.01.15	68 / M	MICU	Blood	A1	71	Acute myeloid leukemia	Pneumonia
5	07.01.19	77 / F	SICU	Blood	A4	11	Duodenal ulcer perforation	Pneumonia
6	07.02.05	63 / M	General ward	Sputum	A4	165	Acute renal failure	Septicemia
7	07.02.05	77 / M	MICU	Sputum	A1	19	Chronic renal failure	Pneumonia
8	07.02.05	71 / M	MICU	Sputum	A4	43	Congestive heart failure	Pneumonia
9	07.02.06	68 / M	MICU	Sputum	A1	56	Pulmonary tuberculosis	Pneumonia, UTI, Septicemia
10	07.02.06	66 / F	MICU	Sputum	A1	43	End stage renal disorder	Pneumonia, Sepsis
11	07.02.07	84 / M	MICU	Sputum	A4	169	Acute cholecystitis	Pneumonia, UTI
12	07.02.08	60 / F	SICU	Sputum	A1	11	Liver abscess	Pneumonia
13	07.02.08	48 / M	MICU	Sputum	A4	20	Liver cirrosis, Hepatic encephalitis	Pneumonia
14	07.02.09	83 / M	MICU	Sputum	A5	28	Duodenal ulcer bleeding	Pneumonia
15	07.02.19	68 / M	General ward	Sputum	A7	17	Bladder tumor	
16	07.02.19	58 / M	General ward	Sputum	A4	25	Paralytic ileus	Asymptomatic bacteremia
17	07.02.19	71 / M	MICU	Sputum	A1	30	Lung cancer	Pneumonia
18	07.02.19	47 / M	MICU	Sputum	A4	20	Pulmonary tuberculosis	
19	07.02.19	78 / M	MICU	Sputum	A4	10	Acute renal failure	Pneumonia, UTI
20	07.02.24	78 / M	MICU	Blood	A6	15	Acute renal failure	Pneumonia, UTI
21	07.03.22	77 / M	MICU	Blood	A5	26	Idiopathic pulmonary fibrosis	Pneumonia
22	07.04.02	72 / F	MICU	Blood	A13	13	Idiopathic pulmonary fibrosis	Pneumonia
23	07.04.06	42 / F	NICU	Nose	A2	12	Intracranial hemorrhage	Pneumonia
24	07.04.09	17 / F	SICU	Sputum	A12	86	End stage renal disorder	Pneumonia
25	07.04.09	66 / M	MICU	Others	A7	13	Lymphoma	Pneumonia
26	07.04.09	56 / M	NICU	Sputum	A7	11	Cerebral hemorrhage	Pneumonia
27	07.04.16	62 / M	NICU	Blood	A14	75	Acute renal failure	Pneumonia, Sepsis
28	07.04.20	86 / F	NICU	Nose	A7	10	Subcortical hemorrhage	Pneumonia
29	07.04.21	80 / F	General ward	Sputum	A7	17	Cerebral infarction	Pneumonia
30	07.04.24	78 / F	MICU	Sputum	A7	29	Congestive heart failure	Pneumonia
31	07.04.24	76 / F	General ward	Wound	A1	52	Paraplegia	UTI
32	07.04.24	65 / F	MICU	Sputum	A7	25	Cerebral infarction	UTI
33	07.04.26	65 / M	SICU	Nose	A7	65	Esophageal cancer	Pneumonia
34	07.05.04	71 / M	MICU	Sputum	A1	3	Lung cancer	Pneumonia
35	07.05.04	65 / M	SICU	Sputum	A9	74	Esophageal cancer	Pneumonia
36	07.05.07	84 / F	MICU	Urine	A7	16	Cerebral infarction	Pneumonia
37	07.05.08	84 / F	MICU	Nose	A10	17	Cerebral infarction	Pneumonia
38	07.05.08	66 / F	MICU	Sputum	A10	13	Cerebral infarction	Sepsis
39	07.05.09	72 / M	NICU	Nose	A10	58	Hypoxic brain damage	Pneumonia
40	07.05.09	77 / M	MICU	Nose	A8	9	Acute cholangitis	Septic shock
41	07.05.09	91 / F	NICU	Nose	A7	361	Cerebral infarction	Pneumonia, UTI
42	07.05.10	84 / F	MICU	Sputum	A7	20	Congestive heart failure	Pneumonia
43	07.05.10	84 / F	MICU	Wound	A11	20	Congestive heart failure	Pneumonia
44	07.05.11	52 / M	NICU	Throat	A7	15	Cerebral hemorrhage	Pneumonia
45	07.06.20	77 / M	MICU	Sputum	A3	51	Cerebral infarction	Pneumonia, septic shock, DIC
46	07.06.20	58 / M	MICU	Sputum	A1	13	Lung cancer	Pneumonia
47	07.06.20	64 / M	MICU	Sputum	A7	19	Idiopathic pulmonary fibrosis	Pneumonia, septic shock, DIC
48	07.06.22	72 / M	NICU	Wound	A7	102	Hypoxic brain damage	Pneumonia
49	07.07.06	63 / M	MICU	Blood	A7	13	Hemophilia A, acute renal failure	Sepsis

MICU, medical intensive care unit; NICU, neurosurgical intensive care unit; SICU, surgical intensive care unit; PFGE, pulsed field gel electrophoresis; UTI, urinary tract infection; DIC, Disseminated intravascular coagulation.

second pulse time gradient for 19 hours. Cluster analysis was performed using the unweighted pair group method with mathematical averaging (UPGMA). DNA relatedness was calculated using the band-based Dice coefficient with a tolerance setting of 1.0% band tolerance and 1.0% optimization setting for the entire profile. A similarity of less than 80% following dendogram analysis was considered to represent different PFGE types, while a similarity of greater than 80% was considered to represent PFGE subtypes.[9]

RESULTS

Strain identification

Data collected from the patient's medical records showed 30 isolates (61.2%) in the medical intensive care unit (MICU), 9 isolates (18.4%) in the Neurosurgical ICU (NICU), 5 isolates (10.2%) in the Surgical ICU (SICU), and 5 isolates (10.2%) in the general wards. Twenty-eight isolates (57.1%) were obtained from sputum samples. 7 isolates (14.3%) from noses, 7 isolates from blood samples and 4 isolates (8.2%) from wounds. In addition to those, 3 isolates were from urine, throat and other sites (Table 2).

Antimicrobial susceptibilities

All isolates showed 100% resistance to ciprofloxacin and gentamicin, 97.9% resistance to cefepime, piperacillin/tazobactam, aztreonam, ceftazidime and piperacillin, 93.9% resistance to tobramycin, and 57.1% resistance to amikacin (Table 3).

The modified Hodge and the EDTA-disk synergy test

Among the 49 imipenem-resistant *A. baumannii* isolates, all 49 isolates (100%) showed positive results in the modified Hodge test and negative results in the EDTA-disk synergy test.

Detection of carbapenem-resistant genes

All 49 isolates (100%) possessed the encoding gene for an intrinsic OXA-51-like carbapenemase and an acquired OXA-23-like carbapenemase (Fig. 1).

Pulsed-field gel electrophoresis analysis

All 49 imipenem-resistant *A. baumannii* isolates showed an identical band pattern and were classified as pulsotype A. Pulsotype A isolates were separated into fourteen subtypes, named subtypes A1 to A14. Sixteen isolates were subtype A7, three were A10, and two were A2 and A5. The other subtypes had one isolate each (Fig. 2).

DISCUSSION

A. baumannii is an organism which can colonize on the skin of healthy people. It has the ability to survive for a long time even in dry condition and the potential for air-

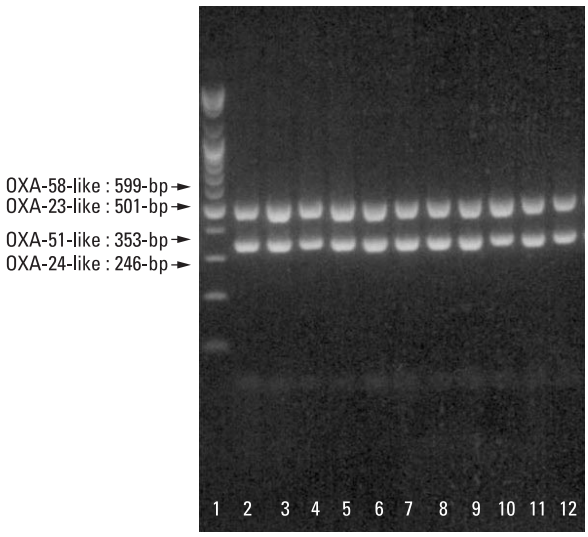

Fig. 1. Detection of genes encoding OXA carbapenemase by Multiplex PCR. Lane 1,100 bp Plus DNA Ladder (Bioneer, Daejeon, Korea); Lane 2-12, OXA-23-like and OXA-51-like. PCR, polymerase chain reaction.

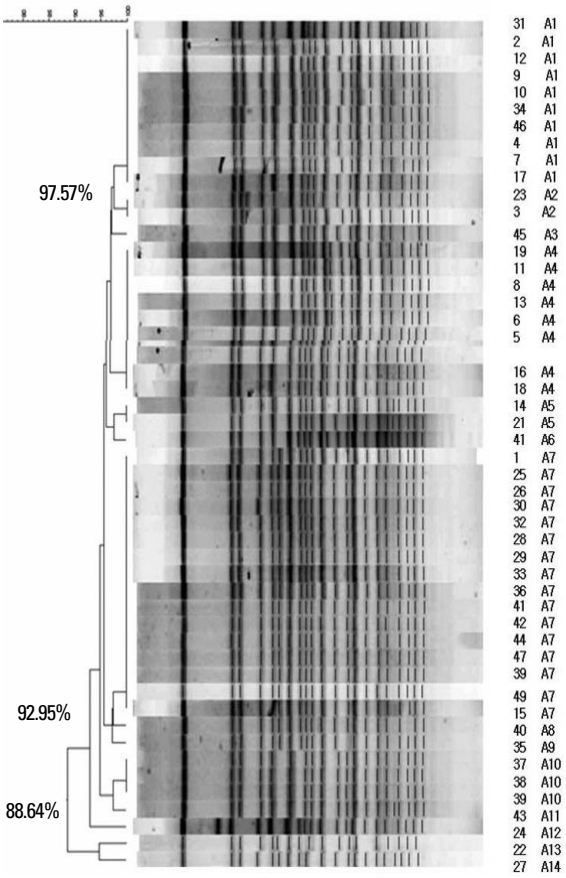

Fig. 2. PFGE profiles of *ApaI*-digested genomic DNA from isolates of *A. baumannii*., PFGE, pulsed-field gel electrophoresis; *A. baumannii, Acinetobacter baumannii*.

Table 3. Antimicrobial Susceptibility of *Acinetobacter Baumannii* Isolates

No	PFGE pattern	AK	CIP	GM	FEP	IPM	TZP	ATM	CAZ	PIP	TOB
1	A7	R	R	R	R	R	R	R	R	R	R
2	A1	R	R	R	R	R	R	R	R	R	R
3	A2	R	R	R	R	R	R	R	R	R	R
4	A1	R	R	R	R	R	R	R	R	R	R
5	A4	R	R	R	R	R	R	R	R	R	R
6	A4	R	R	R	R	R	R	R	R	R	R
7	A1	R	R	R	R	R	R	R	R	R	R
8	A4	R	R	R	R	R	R	R	R	R	R
9	A1	R	R	R	R	R	R	R	R	R	R
10	A1	R	R	R	R	R	R	R	R	R	R
11	A4	R	R	R	R	R	R	R	R	R	R
12	A1	R	R	R	R	R	R	R	R	R	R
13	A4	R	R	R	R	R	R	R	R	R	R
14	A5	R	R	R	R	R	R	R	R	R	R
15	A7	R	R	R	S	R	S	R	R	R	R
16	A4	R	R	R	R	R	R	R	R	R	R
17	A1	R	R	R	R	R	R	R	R	R	R
18	A4	R	R	R	R	R	R	R	R	R	R
19	A4	R	R	R	R	R	R	R	R	R	R
20	A6	R	R	R	R	R	R	R	R	R	R
21	A5	R	R	R	R	R	R	R	R	R	R
22	A13	IM	R	R	R	R	R	R	R	R	R
23	A2	S	R	R	R	R	R	R	R	R	R
24	A12	R	R	R	R	R	R	R	R	R	R
25	A7	S	R	R	R	R	R	R	R	R	R
26	A7	S	R	R	R	R	R	R	R	R	R
27	A14	R	R	R	R	R	R	R	R	R	R
28	A7	S	R	R	R	R	R	R	R	R	IM
29	A7	S	R	R	R	R	R	R	R	R	R
30	A7	S	R	R	R	R	R	R	R	R	R
31	A1	S	R	R	R	R	R	R	R	R	S
32	A7	S	R	R	R	R	R	R	R	R	R
33	A7	S	R	R	R	R	R	R	R	R	R
34	A1	R	R	R	R	R	R	R	R	R	R
35	A9	R	R	R	R	R	R	R	R	R	R
36	A7	R	R	R	R	R	R	R	R	R	R
37	A10	S	R	R	R	R	R	R	R	R	R
38	A10	S	R	R	R	R	R	R	R	R	R
39	A10	S	R	R	R	R	R	R	R	R	R
40	A8	S	R	R	R	R	R	R	R	R	R
41	A7	S	R	R	R	R	R	R	R	R	R
42	A7	S	R	R	R	R	R	R	R	R	R
43	A11	S	R	R	R	R	R	R	R	R	R
44	A7	S	R	R	R	R	R	R	R	R	R
45	A3	S	R	R	R	R	R	R	R	R	IM
46	A1	S	R	R	R	R	R	R	R	R	R
47	A7	S	R	R	R	R	R	R	R	R	R
48	A7	R	R	R	R	R	R	IM	R	R	R
49	A7	R	R	R	R	R	R	R	R	R	R

PFGE, pulsed-field gel electrophoresis; AK, amikacin; CIP, ciprofloxacin; GM, gentamicin; FEP, cefepime; IPM, imipenem; TZP, piperacillin / tazobactam; ATM, aztreonam; CAZ, ceftazidime; PIP, piperacillin; TOB, tobramycin; R, resistant; IM, intermediate; S, susceptible.

borne transmission.[10,11] Because *A. baumannii* spreads easily through contamination of medical equipment used in patient monitoring or therapy, and from contamination by both patient and staff during handling of other environmental sources, these are difficult infections to control.[1,12,13] Generally, carbapenems (imipenem and meropenem) are the most active agents for treating nosocomial infections caused by *A. baumannii*. However, the emergence of imipenem-resistant *A. baumannii* has become a worldwide problem which is causing serious therapeutic complications.[2]

Mechanism of *A. baumannii* resistance to carbapenems include the production of carbapenemase, the decreased outer-membrane permeability caused by the loss or reduced expression of porins, and the modification of penicillin-binding proteins. The most common resistance mechanism involves the acquisition of carbapenem-hydrolysing β-lactamase which belong to Ambler class B (metalloenzymes) and predominantly, Ambler class D (oxacillinase).[14,15]

Ambler class B is a powerful carbapenemase. It is classified as a metallo β-lactamase (MBL) because it requires Zn^{2+} for the efficient hydrolysis of β-lactams. Acquired MBLs are divided in to five types; IMP, VIM, SIM, SPM and GIM. However, only the first three of these types have been identified in *A. baumannii*. MBLs are susceptible to *in vitro* inhibition by EDTA, a chelater of divalent cations.[14,15] IMP types have been reported worldwide, and VIM-2 and SIM-1 have been reported in *A. baumannii* isolates from South Korea.[14,16,17]

The Ambler class D carbapenemases of *A. baumannii* are divided into four phylogenetic subgroups; OXA-23-like (OXA-23, -27 and -49), OXA-24-like (OXA-24/40, -25, -26 and -72), OXA-58-like (OXA-59 and -96), and OXA-51-like carbapenemases. The OXA-23 subgroup was first reported in *A. baumannii* in Scotland in 1995 and was originally named ARI-1, but was renamed OXA-23.[19-21] OXA-24 has been reported in Spain. OXA-40 in France, Spain and Portugal, OXA-23 in Brazil, French Polynesia, Spain, South Korea and England, and OXA-58 worldwide.[22-29]

The OXA-51-like subgroup may be intrinsic to *A. baumannii*, evidenced by its chromosomal location and its ubiquitous distribution among *A. baumannii* strains. However, it is not found in other *Acinetobacter* species. This enzyme may be involved in the expression of carbapenem-resistance under certain circumstances.[30]

Treatment for imipenem-resistant *A. baumannii* infections is sophisticated. Polymyxins (colinstimethate and polymyxin B) may be the only remaining therapeutic option. Colistin was used in the 1960s and 1970s, however was stopped due to severe adverse effects which included nephrotoxicity and neurotoxicity, as well as the emergence of safer alternative antimicrobials.[3]

The isolates of imipenem-resistant *A. baumannii* have increased abruptly since November 2006. Therefore, our infection control team was alarmed and started the surveillance program and the outbreak control. During the outbreak period, environmental contamination with IRAB was found on patient's bed, accessories of the mechanical ventilator and the surrounding environment. And the use of carbapenem was the significant risk factor for the acquisition of IRAB during December 2006 in multivariate analysis (p = 0.014). To control the outbreak, the hand washing after each patient contact, use of gloves and gowns, reinforcement of the environmental disinfection and the adequate management of the mechanical ventilator were rigorously enforced. The imipenem-resistant *A. baumannii* outbreak sustained for 9-months at our hospital from November 2006 to July 2007.

In 2005, the OXA-23-producing clones were reported in a University hospital, Busan, Korea that was the first report in Asia. Now we are certain that theses clones spread all over the nation.

In our study, all imipenem-resistant *A. baumannii* isolates were positive for carbapenemase production and negative for metallo-β-lactamase. They all possessed the encoding gene for an intrinsic OXA-51-like carbapenemase and an acquired OXA-23-like carbapenemase. All isolates analyzed had an identical band pattern, therefore this outbreak was caused by the spread of a clonally related epidemic.

The incidence of nosocomial infections due to multidrug resistant *A. baumannii* strains is increasing worldwide. These *A. baumannii* strains are rapidly adapting to the hospital environment, so that it is difficult to control the outbreaks. Early recognition of imipenem resistant *A. baumannii* clones is very important to prevent spreading within the hospital environment. Molecular typing for multidrug-resistant *A. baumannii* could be helpful in identification of a common source or cross contamination. This is an important step in tracing epidemiology of these strains.

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