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Short Communication

Molecular Epidemiology of an Outbreak of Imipenem-Resistant *Acinetobacter baumannii* Carrying the IS*Aba1*-$bla_{\text{OXA-51-like}}$ Genes in a Korean Hospital

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SUMMARY: Between January 2004 and December 2004, an outbreak of imipenem-resistant *Acinetobacter baumannii* (IRAB) in 2 intensive care units (ICU) of Chosun University Hospital, Korea affected 77 patients. A case-control study revealed that the time spent in the hospital and mechanical ventilation practices were risk factors. IRAB was isolated from the hands of 4% (5/124) of healthcare workers, and 27.3% (21/77) of the samples obtained from the ICU environment. A pulsed-field gel electrophoresis analysis showed that 82.1% (23/28) of clinical IRAB isolates and 85.7% (6/7) of environmental IRAB isolates were type A. The IS*Aba1*F/OXA-51-likeR PCR showed that 93.7% (30/32) of IRAB strains had the IS*Aba1* gene upstream of the $bla_{\text{OXA-51-like}}$ gene. Two IS*Aba1*F/OXA-51-likeR PCR-negative IRAB strains were $bla_{\text{IMP-1}}$ positive. All of the IRAB strains tested by PCR were negative for bla_{VIM}, bla_{SIM}, $bla_{\text{GIM-1}}$, $bla_{\text{SPM-1}}$, bla_{GES}, $bla_{\text{OXA-23-like}}$, $bla_{\text{OXA-24-like}}$, and $bla_{\text{OXA-58-like}}$ carbapenemase genes. After implementing an infection control strategy, a steady reduction in the attack rate of IRAB infection was observed.

Multidrug-resistant (MDR) *Acinetobacter* spp. have emerged as a threat to public health (1). *Acinetobacter baumannii* has shown an evident increase in resistance to carbapenems, because of various reasons, with the most predominant being related to carbapenemases. These carbapenemases are carbapenem-hydrolyzing class D (OXA-type) β-lactamases (2).

Similar to most of the other OXA-type carbapenemases, the OXA-51-like enzymes show weak carbapenemase activity; however, the insertion of IS*Aba1* upstream of the $bla_{\text{OXA-51-like}}$ gene provides a promoter that allows the overproduction of carbapenemase, which may result in carbapenem resistance (2,3).

We present here a molecular epidemiological analysis of an outbreak of imipenem-resistant *A. baumannii* (IRAB) in a university hospital of Korea; the carbapenemase activity of IRAB is associated with the presence of an IS*Aba1* insertion upstream of the $bla_{\text{OXA-51-like}}$ gene.

An apparent nosocomial outbreak of IRAB occurred in the medical intensive care unit (MICU) and the surgical intensive care unit (SICU) of Chosun University Hospital (CUH), a 707-bed tertiary care center in Gwangju, South Korea, between January 2004 and December 2004.

To identify the risk factors for infection with IRAB, a retrospective case control study was conducted by reviewing the medical records of 77 case patients who were colonized or infected with IRAB. A case patient was defined as a patient admitted to the MICU and SICU between January 1 and December 31, 2004, and from whom IRAB was isolated. Risk factors of the cases identified were recorded for the period preceding the first culture with IRAB. Control patients were selected randomly among the patients in the MICU and SICU during the same period but tested negative for IRAB. This study was designed as a 1:1 case-control study, and the case patients and control patients were matched by gender and age ($\pm$5 years). To analyze risk factors, demographic, administrative, and laboratory information was collected from the medical charts of the 77 case patients and 77 control patients.

Statistical analysis was performed using SPSS version 12.0 (SPSS, Chicago, Ill., USA). Univariate analyses of qualitative variables were conducted by the chi-square test or Fisher's exact test. Quantitative variables were compared using Student's *t* test. Variables with a *P*-

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value of <0.1 in the univariate analyses were included in a multiple logistic regression analysis, and odds ratios (ORs) and 95% confidence intervals (CIs) were also calculated. All tests were two-tailed, and a *P*-value of <0.05 was considered statistically significant.

The factors associated with IRAB, as determined by univariate analyses, were comorbidity, such as cardiac disease or pulmonary disease, the presence of a medical device, such as a bladder catheter, mechanical ventilator, or intubation, time at risk, prior exposure to an antimicrobial drug, such as first-generation cephalosporins or third-generations cephalosporins, and duration of drug use prior to infection with IRAB. The risk factors, which were identified by multiple logistic regression analysis, were time at risk (OR, 1.29; 95% CI, 1.14–1.46) and mechanical ventilation (OR, 6.41; 95% CI, 1.71–24.06).

Significant risk factors shown to be associated with the acquisition of IRAB infection include previous admission to the ICU (4–6), previous antibiotic use (4–6), and prolonged stay in the hospital (5,7). Risk factors that have been described to be associated with antibiotic use include previous use of multiple classes of antibiotics (4), prior exposure to imipenem (4,6) or third-generation cephalosporins (6), and aminoglycoside use (7). Other risk factors have also been described, such as previous admission to a respiratory care unit (4), mechanical ventilation (8), hemodialysis (8), and malignancy (8).

The risk factors in the present study, time at risk (corresponding to prolonged stay in the unit of hospital) and mechanical ventilation, were similar to those found in previous studies. This study found that previous antibiotic use was not statistically significant in multivariate analyses, although it was significant factor in univariate analyses.

The cause of the differences in risk factors among reports is not clear. The differences may be attributable to difference in age and coexisting disease of patients, as well as usual pattern of therapy, including specific antibiotic usage of each department and hospital, involved in the other studies.

To assess environmental contamination, environmental samples were obtained in March and April 2004 using sterile swabs. The swab collected from environmental samples were inoculated onto blood agar plates and cultured at 36°C in a CO_2 incubator. After overnight incubation, suspected *A. baumannii* colonies were further identified and their susceptibility patterns were determined.

The following items were surveyed: surfaces of the ventilator and ventilator monitor, patient's drainage fluid from the drainage vessel in the respiratory circuit of the ventilator, fluid in the bottle containing a suction tip, surface of the bed sheet, bed rail, electrocardiograph cord and monitor, intravenous fluid line, dresser shelves, recording sheet, chart, keyboard and monitor of computer, O_2 supplier, washing stands, humidifier, top surface of dressing car, canister lid, and table of station. IRAB spread by contact was also determined by swabbing the fingers of both hands of the nursing staff and doctors working in the MICU and SICU.

We found that 27.3% (21/77) of environment samples were contaminated with IRAB. The sites of IRAB contamination were as follows: 53.8% (7/13) of samples from ventilator (surface of ventilator and drained fluid from patient contained in drainage vessel located in the respiratory circuit of ventilator), 70.0% (7/10) of samples from bed (surface of bed sheet and bed rail), 22.2% (2/9) of samples from the top surface of the dressing car (top surface of dressing car), 33.3% (2/6) of samples of fluid in bottle containing suction tip, 16.7% (1/6) of samples from the electrical cord of the electrocardiograph and all samples (100%) of the surface of the intravenous fluid line and dresser shelf. IRAB was also isolated from 4.0% (5/124) of the samples from cultures of the hands of healthcare workers (HCWs).

Because almost all clinical IRAB (c-IRAB) strains showed very similar antimicrobial susceptibility test results, we suspected that they originated from the same or a similar clone. The c-IRAB strains randomly collected each month from both the SICU and MICU were used for the present study.

For the molecular typing of carbapenemase genes by pulsed-field gel electrophoresis (PFGE) and PCR, 35 IRAB strains, consisting 28 c-IRAB and 7 environmental IRAB (e-IRAB) strains, and 9 imipenem-susceptible *A. baumannii* (ISAB) control strains were studied.

PFGE was performed and interpreted as previously described (9). After restriction endonuclease digestion of chromosomal DNA with *Apa*I (Roche Biochemicals, Mannheim, Germany), the restriction fragments were separated by a contour-clamped homogeneous electric field (CHEF-DRII system; BioRad, Munich, Germany) in 0.5 × Tris-borate-EDTA buffer at 12°C and 200 V with pulse times of 5–13 s.

Strain identification and antimicrobial susceptibility test were performed using the Vitek 2 GN Card with Vitek AST-N017 kit (bioMérieux, Durham, N.C., USA) according to the manufacturer's instructions. Further, the minimum inhibitory concentrations (MICs) of the imipenem and meropenem were determined using the agar dilution method according to the Clinical and Laboratory Standards Institute (CLSI) guidelines (10).

A PCR assay was used to detect various OXA-type carbapenemases genes, including $bla_{\text{OXA-23-like}}$, $bla_{\text{OXA-24-like}}$, $bla_{\text{OXA-58-like}}$, and $bla_{\text{OXA-51-like}}$ genes (11). Genes coding for Ambler class B and A carbapenemases were detected by PCR with primers specific for $bla_{\text{IMP-1}}$, $bla_{\text{IMP-2}}$, $bla_{\text{IMP-4}}$, $bla_{\text{IMP-11}}$, $bla_{\text{IMP-18}}$, $bla_{\text{IMP-19}}$, $bla_{\text{VIM-1}}$, $bla_{\text{VIM-2}}$, $bla_{\text{SIM-1}}$, $bla_{\text{GIM-1}}$, $bla_{\text{SPM-1}}$, and bla_{GES} (12,13). To determine whether IS*Aba1* was present upstream of the $bla_{\text{OXA-51-like}}$ gene, PCR mapping experiments using IS*Aba1* forward/OXA-51-like reverse primers (IS*Aba1*F/OXA-51-likeR PCR) were performed (3).

PFGE showed that the major type of c-IRAB outbreak strains were A (18/28, 64.3%) and A subtype (5/28, 17.9%). Almost all (6/7, 85.3%) e-IRAB strains showed the same major PFGE type (type A). In contrast, 7 out of the 9 ISAB showed patterns different from each other and from outbreak strains (Table 1).

The clone with PFGE type A, the major clone of this outbreak (9), contained an unusual class 1 integron—integron-IS*26*—on its chromosome (14). However, this did not explain the carbapenemase activity.

The resistance rates of 35 IRAB to almost all the antibiotics tested (e.g., gentamicin, netilmicin, tobramy-

Table 1. Results of PFGE analysis, MIC determination for imipenem (IPM) and meropenem (MEM), and PCR assay for carbapenemase in 44 strains tested including 28 clinical imipenem-resistant *A. baumannii* (c-IRAB), 9 imipenem-susceptible *A. baumannii* (ISAB), and 7 environmental IRAB isolates (e-IRAB) strains

Isolate	PFGE	IPM	MEM	IS*Aba1*-OXA-51	OXA-51	IMP-1	VIM-2	Isolate	PFGE	IPM	MEM	IS*Aba1*-OXA-51	OXA-51	IMP-1	VIM-2
c-IRAB								c-IRAB							
108	A	16	64	P	P	N	N	113	B	16	1	N	P	P	N
110	A	>256	128	P	P	N	N	115	B	16	—	N	P	P	N
203	A	32	64	P	P	N	N	101	P	32	64	P	P	N	N
119	A	—	—	—	P	N	N	106	P	—	—	P	P	N	N
121	A	32	64	P	P	N	N	136	D	—	—	—	P	N	N
124	A	—	—	—	P	N	N	e-IRAB							
125	A	—	—	P	P	N	N	302	A	—	—	P	P	N	N
128	A	16	64	P	P	N	N	304	A	32	64	P	P	N	N
129	A	64	64	P	P	N	N	306	A	32	64	P	P	N	N
130	A	32	64	P	P	N	N	309	A	32	64	P	P	N	N
133	A	16	—	P	P	N	N	312	A	32	64	P	P	N	N
134	A	16	64	P	P	N	N	314	A	32	64	P	P	N	N
135	A	32	64	P	P	N	N	316	G	32	64	P	P	N	N
137	A	16	16	P	P	N	N	ISAB							
140	A	32	64	P	P	N	N	213	N	1	32	N	P	N	N
141	A	16	—	P	P	N	N	214	E	1	2	N	P	N	N
143	A	32	64	P	P	N	N	220	J	2	2	N	P	N	N
145	A	32	—	P	P	N	N	224	H	2	2	N	P	N	N
111	A1	16	64	P	P	N	N	227	H1	4	2	N	P	N	N
112	A1	32	128	P	P	N	N	230	L	4	2	N	P	N	N
139	A1	32	64	P	P	N	N	114	C	≤0.5	1	N	P	N	P
144	A1	—	—	P	P	N	N	118	F	≤0.5	1	N	P	N	N
117	A2	—	—	P	P	N	N	226	I	—	—	—	P	N	N

P, positive; N, negative.

cin, isepamicin, ciprofloxacin, pefloxacin, trimethoprim/sulfamethoxazole, and all the β-lactams, including imipenem) were higher than 90%. All of the 35 IRAB strains were susceptible to colistin.

The imipenem MICs of 21 c-IRAB and 6 e-IRAB strains ranged from 16 to >256 mg/L. The meropenem MICs of 17 c-IRAB and 6 e-IRAB ranged from 1 to 128 mg/L. The $MIC_{50/90}$ of imipenem and meropenem for these isolates were 32/32 and 64/64 mg/L, respectively. The previously reported range of imipenem MICs for imipenem-intermediate *A. baumannii* (IIAB) or IRAB strains carrying the IS*Aba1*-$bla_{\text{OXA-51-like}}$ genes were somewhat variable: imipenem MICs of 73 IRAB strains, 1–64 mg/L (15); 32 IRAB strains, 2–>16 mg/L (16); 8 IIAB or IRAB strains, 1–8 mg/L (17); and 3 IRAB strains, 16–128 mg/L (18). The reported range of meropenem MICs of 8 imipenem-nonsusceptible *A. baumannii* were 8–>32 mg/L (17). The MIC range of imipenem or meropenem in the present study was relatively wider than those described previously. The reason of this difference is not clear, but it may suggest region or strain variance or differences in other combined resistance mechanisms.

The results of the assay for resistance determinants for carbapenemase are shown in Table 1. All 7 e-IRAB and 23 out of the 25 c-IRAB showed positive reactions for IS*Aba1*F/OXA-51-likeR PCR, although all 8 ISAB showed negative reactions. Therefore, we hypothesized that carbapenemase activity is attributable to the presence of IS*Aba1* upstream of the OXA-51 gene.

Two $bla_{\text{IMP-1}}$-positive c-IRAB strains (PFGE type B) showed a negative reaction for IS*Aba1*F/OXA-51-likeR PCR. All ISAB strains, except one, were found to be $bla_{\text{VIM-2}}$ negative on PCR. It is unclear why one *A. baumannii* strain with the $bla_{\text{VIM-2}}$ gene was imipenem susceptible, but we surmise that the expression of the gene is suppressed by some unknown mechanism.

None of the 44 *A. baumannii* strains had positive PCR results for $bla_{\text{GIM-1}}$, $bla_{\text{SPM-1}}$, bla_{GES}, $bla_{\text{OXA-23-like}}$, $bla_{\text{OXA-24-like}}$, and $bla_{\text{OXA-58-like}}$, and none of the 30 *A. baumannii* strains tested for $bla_{\text{SIM-1}}$ showed a positive PCR reaction.

Sequence analysis revealed that the product of the IS*Aba1*F/OXA-51-likeR PCR exhibited 99% identity with the IS*Aba1*-$bla_{\text{OXA-66/OXA-51-like}}$ carbapenemase gene of several *A. baumannii* strains (GenBank accession nos. GQ849191.1, EF433476.1, and DQ923479.1) (1,3,19). The IS*Aba1* was located 7-bp upstream of $bla_{\text{OXA-66}}$, a finding also observed in previous studies (1,3,17,19).

Infection control measures implemented included strict environmental cleaning of the ICU with dedicated cleaning equipment, effective sterilization of reusable medical equipment, attention to proper hand hygiene practices, use of contact precautions, and continued ICU personnel educational programs, appropriate administrative guidance, and support. Adequate compliance with the control program was supervised by an infection control nurse, who attended to the ICUs daily after the implementation of the infection control measure in April 2004.

The epidemic curve of the outbreak is shown in Fig.

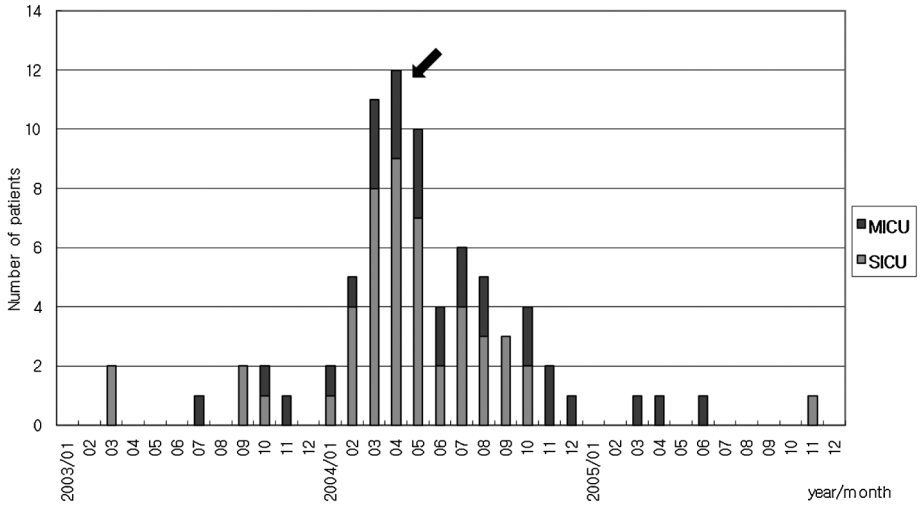

Fig. 1. Epidemic curve showing the number of patients colonized or infected with imipenem-resistant *A. baumannii* (IRAB) during the epidemic period (January 2004–December 2004). Occurrence of patients with IRAB in the year of 2003 and 2005 were depicted also to show basal rate of IRAB occurrence. The arrow indicates the month of implementation of the infection control measure. SICU, surgical intensive care unit; MICU, medical intensive care unit.

1. The implementation of the infection control program resulted in a steady reduction of the outbreak rate of IRAB to a basal rate of infection.

The risk factors for IRAB acquisition in this study were the time at risk and mechanical ventilation practices. Three of 4 SICU patients with IRAB infection or colonization at an early stage of the outbreak (February 2004) received mechanical ventilation therapy with a ventilator. The PFGE types of e-IRAB strains isolated from the ventilator culture (e-IRAB strains 309 and 312) were type A, which were of the same types as that of the major outbreak clone (Table 1). Four of 6 patients who received mechanical ventilation therapy had pulmonary diseases. All 4 c-IRAB strains isolated from those patients were PFGE type A. After collectively considering all of the above findings, we suspected the ventilator to be the source of the IRAB outbreak in the SICU.

Environmental persistence of MDR *A. baumannii* is thought to facilitate horizontal transmission from the hands of HCWs after they touch infected patients and contaminated medical equipment and/or are in a contaminated environment (20). In this study, the environmental contamination with the IRAB clone from the ventilator may have acted as the reservoir for the dissemination of the IRAB clone throughout the ICU. Therefore, the risk of contracting the IRAB outbreak clone would be increased in patients with a longer time at risk, which suggest a longer stay in the ICU. In addition, it may be possible that the contaminated hands of HCWs may have contributed to the transmission of IRAB among patients admitted to the ICU.

Most molecular epidemiological studies of IRAB strains carrying the IS*Aba1*-$bla_{\text{OXA-51-like}}$ genes have focused on frequencies of several types of carbapenemases and have characterized antimicrobial susceptibility patterns or genotypes of IRAB strains collected from multiple institutes to elucidate the distribution and characteristics of IRAB strains in particular countries (16–19,21). In contrast, the main aims of the present study were to determine the risk factors and to characterize epidemiological findings that would be helpful in controlling an outbreak in a university hospital.

There have been few reports of detailed epidemiological characteristics of IRAB outbreak strains carrying the IS*Aba1*-$bla_{\text{OXA-51-like}}$ carbapenemase genes, and studies containing risk factor analysis and environmental culture data to elucidate the source of the outbreak have been infrequent because the role of the IS*Aba1*-$bla_{\text{OXA-51-like}}$ gene as a carbapenemase has only recently been elucidated.

Lin et al. reported a hospital-wide outbreak of extensively drug-resistant *A. baumannii* (XDRAb) at a medical center in Taiwan. All 32 clinical XDRAb isolates, obtained from 13 patients, harbored IS*Aba1*-$bla_{\text{OXA-51-like}}$ and $bla_{\text{OXA-72}}$ genes. Although the source or vehicle of the outbreak was not identified, the hospital successfully managed the outbreak with strict infection control measures (22). Culebras et al. have described an outbreak of IRAB strains carrying the IS*Aba1*-$bla_{\text{OXA-51-like}}$ genes in 15 patients in Spain. A single clone was responsible for all of the infections, but risk factor analysis was not performed in that study (23).

In summary, we reported an outbreak of IRAB carrying the IS*Aba1*-$bla_{\text{OXA-51-like}}$ genes, with a description of risk factors and the possible source of IRAB contamination in a university hospital in Korea. Although we believe that carbapenemase activity may be explained by the presence of IS*Aba1* upstream of the $bla_{\text{OXA-51}}$ gene, other secondary mechanisms, including efflux pump, permeability change, or expression of other carbapenemase genes, may also affect the activity of carbapenems in our strains; therefore, confirmatory studies are needed.

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Conflict of interest None to declare.

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