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The Changes in Epidemiology of Imipenem-Resistant *Acinetobacter baumannii* Bacteremia in a Pediatric Intensive Care Unit for 17 Years

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ABSTRACT

Background: *Acinetobacter baumannii* infections cause high morbidity and mortality in intensive care unit (ICU) patients. However, there are limited data on the changes of long-term epidemiology of imipenem resistance in *A. baumannii* bacteremia among pediatric ICU (PICU) patients.

Methods: A retrospective review was performed on patients with *A. baumannii* bacteremia in PICU of a tertiary teaching hospital from 2000 to 2016. Antimicrobial susceptibility tests, multilocus sequence typing (MLST), and polymerase chain reaction for antimicrobial resistance genes were performed for available isolates.

Results: *A. baumannii* bacteremia occurred in 27 patients; imipenem-sensitive *A. baumannii* (ISAB, n = 10, 37%) and imipenem-resistant *A. baumannii* (IRAB, n = 17, 63%). There was a clear shift in the antibiogram of *A. baumannii* during the study period. From 2000 to 2003, all isolates were ISAB (n = 6). From 2005 to 2008, both IRAB (n = 5) and ISAB (n = 4) were isolated. However, from 2009, all isolates were IRAB (n = 12). Ten isolates were available for additional test and confirmed as IRAB. MLST analysis showed that among 10 isolates, sequence type

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Disclosure

The authors have no potential conflicts of interest to disclose.

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138 was predominant (n = 7). All 10 isolates were positive for OXA-23-like and OXA-51-like carbapenemase. Of 27 bacteremia patients, 11 were male (41%), the median age at bacteremia onset was 5.2 years (range, 0–18.6 years). In 33% (9/27) of patients, *A. baumannii* was isolated from tracheal aspirate prior to development of bacteremia (median, 8 days; range, 5–124 days). The overall case-fatality rate was 63% (17/27) within 28 days. There was no statistical difference in the case fatality rate between ISAB and IRAB groups (50% vs. 71%; $P = 0.422$).

Conclusion: IRAB bacteremia causes serious threat in patients in PICU. Proactive infection control measures and antimicrobial stewardship are crucial for managing IRAB infection in PICU.

Keywords: Pediatric Intensive Care Units; *Acinetobacter baumannii*; Bacteremia

INTRODUCTION

Improved medical care and invasive procedures for high-risk pediatric intensive care unit (PICU) patients have led to a longer duration of survival and prolonged hospitalization. However, prolonged hospitalization results in a higher probability of healthcare-associated infection. Common bacterial pathogens in pediatric healthcare-associated infection are *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, coagulase negative staphylococci, *Escherichia coli*, and *Acinetobacter* spp.¹⁻³

Acinetobacter baumannii is an aerobic, Gram-negative bacterium associated with high morbidity and mortality in clinical settings. *A. baumannii* infection may lead to high health-care costs and prolonged hospitalization. The most common clinical manifestations are ventilator-associated pneumonia and bacteremia.⁴ Furthermore, the imipenem resistance rate of *A. baumannii* species is increasing worldwide.^{5,6}

However, there are limited data on long-term epidemiology of *A. baumannii* bacteremia among PICU patients.⁷⁻⁹ In this study, we analyzed the epidemiology of bacteremia caused by *A. baumannii* infection in PICU patients and molecular analysis of isolated bacteria.

METHODS

Collection of patient's information

A retrospective chart review was performed on pediatric patients < 19 years old who developed bacteremia caused by *A. baumannii* from January 2000 to December 2016 in the PICU at Samsung Medical Center, Seoul, South Korea. Matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) biotyper was not used during the study period. Clinical information and microbiological data were collected from all patients.

Bacterial isolates and species identification

A. baumannii were detected among patients with bloodstream infections in the PICU from January 2000 to December 2016. Only the first isolate from each patient was included in this study. Initially, isolates that were identified as *Acinetobacter* species by the VITEK 2 system (bioMérieux, Marcy l'Etoile, France) from clinical care were included. All of *A. baumannii* were differentiated to imipenem-sensitive *A. baumannii* (ISAB) and imipenem-resistant *A. baumannii* (IRAB).

From January 2010 to December 2016, *A. baumannii* were collected and species-level identification using partial *rpoB* gene sequences were performed,^{10,11} and were tested for antimicrobial susceptibility.

Antimicrobial susceptibility testing

Antimicrobial susceptibility was confirmed for available isolates using the broth microdilution method following the Clinical and Laboratory Standards Institute (CLSI) guidelines.¹² The minimum inhibitory concentrations (MICs) of 12 antimicrobial agents, including imipenem, meropenem, cefotaxime, cefepime, ceftazidime, amikacin, ciprofloxacin, tetracycline, piperacillin-tazobactam, colistin, polymyxin B, and tigecycline were determined. Susceptibility was defined according to CLSI breakpoints,¹² using *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 as controls. All tests were performed in duplicate, and each test included three biological replicates per strain.

Multilocus sequence typing (MLST) and antimicrobial resistance genes

MLST was performed for *A. baumannii* isolates as previously described.¹³ All MLST data were submitted to the *A. baumannii* MLST database and Oxford scheme was applied.^{14,15} Clonal complexes were determined using the eBURST program.¹⁶ For all of the IRAB isolates, resistance genes, including *bla*_{IMP}, *bla*_{VIM}, *bla*_{GIM}, *bla*_{SIM}, *bla*_{KPC}, *bla*_{NDM-1}, *bla*_{OXA-48}, *bla*_{OXA-23-like}, *bla*_{OXA-24-like}, *bla*_{OXA-51-like}, and *bla*_{OXA-58-like} were detected by polymerase chain reaction, as described previously.¹⁷

Statistical analysis

Fisher's exact test was used to analyze categorical variables. A *P* value of < 0.05 was considered statistically significant. Overall survival rates were estimated using the Kaplan-Meier method, and differences in survival curves were compared using the log-rank test by GraphPad Prism version 9.3.1 (GraphPad Software, San Diego, CA, USA).

Ethics statement

The Institutional Review Board (IRB) at Samsung Medical Center, Seoul, South Korea, reviewed and approved this study (approval number: 2020-05-020-002). Informed consent was exempted by IRB.

RESULTS

Patient characteristics and epidemiology

Bacteremia episodes occurred in 27 patients; ISAB (n = 10) and IRAB (n = 17). Male patients were 41% (11/27), and the median age at the onset of bacteremia was 5.2 years (range, 0–18.6 years). Among the underlying conditions in patients with *A. baumannii* bacteremia, hematology-oncology disease was the most common underlying condition (14/27, 52%) followed by neurological diseases (4/27, 15%) (Table 1).

In 33% (9/27, ISAB = 3/10, IRAB = 6/17) of patients, *A. baumannii* was isolated from tracheal aspirate prior to the development of bacteremia with a median duration of 8 days (range, 5–124).

Epidemiological changes in imipenem susceptibility and antimicrobial resistance pattern

There was a clear shift in the antibiogram of *A. baumannii* during the study period. From 2000 to

Table 1. Characteristics of patients with underlying diseases

Parameters	All (N = 27)	ISAB (n = 10)	IRAB (n = 17)
Median age, yr	5.2	1.9 (range, 0.6–16)	5.4 (0–18.6)
Male	11	5	6
Median ICU stay prior to bacteremia, day	5	5 (range, 0–51)	4 (0–48)
Underlying disease			
Hematology and oncology	14	2	12
HCT	8	0	8
Cardiology ^a	3	2	1
Pulmonology	2	1	1
Neurology	4	3	1
Others ^b	3	2	1
No underlying disease	1	1	0

ISAB = imipenem-sensitive *A. baumannii*, IRAB = imipenem-resistant *A. baumannii*, ICU = intensive care unit, HCT = hematopoietic cell transplantation.

^aThere was one neonate under 28 days with congenital heart disease was included.

^bPrimary immunodeficiency, renal disease, vascular malformation.

2003, all *A. baumannii* isolates were ISAB (n = 6). From 2005 to 2008, both IRAB (n = 5) and ISAB (n = 4) were isolated. However, from 2009, all *A. baumannii* isolates were IRAB (n = 12) (Fig. 1).

In 2011, an outbreak of IRAB occurred causing six patients with IRAB bacteremia (patient number 20–25).

Among 27 *A. baumannii* bacteremia episodes, 10 isolates were available. All 10 isolates were resistant to imipenem and meropenem. They were also all resistant to amikacin and ciprofloxacin. Five isolates were sensitive to tetracycline, and three were sensitive to tigecycline. All of the isolates were sensitive to colistin with MIC ≤ 2 mg/L and polymyxin B with MIC ≤ 1 mg/L by microdilution methods (Table 2).

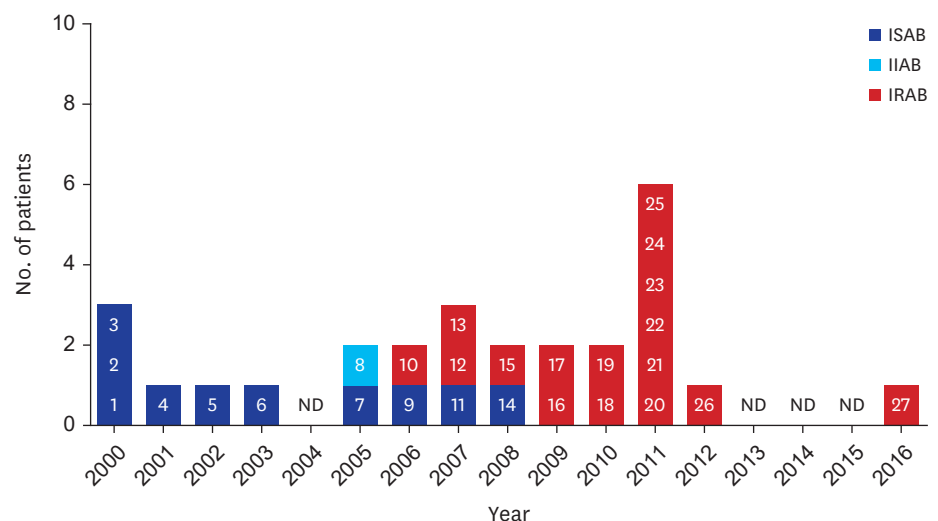


Fig. 1. Epidemiology of *A. baumannii* bacteremia in pediatric intensive care unit from 2000 to 2016.

Numbers shown in each bar refer to the isolate number.

ISAB = imipenem-sensitive *A. baumannii*, IIAB = imipenem-intermediate-resistant *A. baumannii*, IRAB = imipenem-resistant *A. baumannii*, ND = not detected.

Table 2. Antimicrobial susceptibility profiles of *A. baumannii* isolates

Isolate	MIC, mg/L (antimicrobial susceptibility category)											
	IMI	MRP	CTX	CFP	CAZ	AMK	CIP	TET	P/T	CL	PB	TIG
Ab10-18	> 64 (R)	> 64 (R)	> 128 (R)	> 64 (R)	> 64 (R)	> 128 (R)	> 64 (R)	16 (R)	> 256/4 (R)	1 (S)	1 (S)	4 (I)
Ab10-19	> 64 (R)	> 64 (R)	> 128 (R)	> 64 (R)	> 64 (R)	64 (R)	> 64 (R)	> 64 (R)	> 256/4 (R)	2 (S)	1 (S)	8 (R)
Ab11-20	> 64 (R)	> 64 (R)	> 128 (R)	> 64 (R)	> 64 (R)	> 128 (R)	> 64 (R)	4 (S)	> 256/4 (R)	1 (S)	1 (S)	4 (I)
Ab11-21	> 64 (R)	> 64 (R)	> 128 (R)	64 (R)	> 64 (R)	> 128 (R)	> 64 (R)	8 (I)	> 256/4 (R)	1 (S)	1 (S)	4 (I)
Ab11-22	> 64 (R)	> 64 (R)	> 128 (R)	> 64 (R)	> 64 (R)	> 128 (R)	64 (R)	4 (S)	> 256/4 (R)	1 (S)	1 (S)	4 (I)
Ab11-23	> 64 (R)	> 64 (R)	> 128 (R)	> 64 (R)	> 64 (R)	> 128 (R)	64 (R)	4 (S)	> 256/4 (R)	1 (S)	1 (S)	2 (S)
Ab11-24	> 64 (R)	> 64 (R)	> 128 (R)	> 64 (R)	> 64 (R)	> 128 (R)	> 64 (R)	16 (R)	> 256/4 (R)	1 (S)	1 (S)	4 (I)
Ab11-25	> 64 (R)	> 64 (R)	> 128 (R)	> 64 (R)	> 64 (R)	> 128 (R)	64 (R)	4 (S)	> 256/4 (R)	1 (S)	1 (S)	2 (S)
Ab12-26	> 64 (R)	> 64 (R)	> 128 (R)	> 64 (R)	64 (R)	> 128 (R)	64 (R)	8 (I)	> 256/4 (R)	2 (S)	1 (S)	2 (S)
Ab16-27	> 64 (R)	> 64 (R)	> 128 (R)	> 64 (R)	> 64 (R)	> 128 (R)	> 64 (R)	4 (S)	> 256/4 (R)	1 (S)	1 (S)	4 (I)

MIC = minimum inhibitory concentration, IMI = imipenem, MRP = meropenem, CTX = cefotaxime, CFP = ceftazidime, CAZ = ceftazidime, AMK = amikacin, CIP = ciprofloxacin, TET = tetracycline, P/T = piperacillin-tazobactam, CL = colistin, PB = polymyxin B, TIG = tigecycline, R = resistant, I = intermediate-resistant, S = susceptible, Ab#-# = *A. baumannii* isolated year-patient number.

MLST and antimicrobial resistance genes

Among the 10 isolates tested for molecular analysis, nine were isolated from 2010 to 2012 (Table 3). During that period, seven of them were sequence type (ST) 138 and two isolates from patients who were transferred from outside hospitals, were ST75 and ST92.

Following the 2011 outbreak, there were no *A. baumannii* bacteremia cases from 2013 to 2015. An IRAB isolate with ST191 was identified in 2016 in a patient transferred from outside hospital and this was not progressed to additional outbreak in the PICU.

Among the resistance genes tested (*bla_{IMP}*, *bla_{VIM}*, *bla_{GIM}*, *bla_{SIM}*, *bla_{KPC}*, *bla_{NDM-1}*, *bla_{OXA-48}*, *bla_{OXA-23-like}*, *bla_{OXA-24-like}*, *bla_{OXA-51-like}*, and *bla_{OXA-58-like}*), carbapenemase Ambler class A and B genes were not detected. All ten isolates were positive to class D genes (OXA-23 like and OXA-51 like) and negative to OXA-24-like and OXA-54-like genes (Table 3).

Treatment outcome

Overall, among the 27 patients (ISAB: n = 10, IRAB: n = 17), the case-fatality rate within 28 days from bacteremia was 63% (17/27). There was no statistical difference in the fatality rate between the ISAB and IRAB groups (5/10, 50% vs. 12/17, 71%; *P* = 0.422). In Kaplan-Meier survival curve, no significant difference between the two groups was observed (Fig. 2). However, the case fatality rate of hematology-oncology patients was higher than that of rest of other patients (86% vs. 38%, *P* = 0.011).

Table 3. Genotypes of *A. baumannii* and identification of OXA-type carbapenemase genes

Isolate No.	Year	CC	ST	OXA-23-like	OXA-24-like	OXA-51-like	OXA-58-like
Ab10-18	2010	CC92	ST138	+	-	+	-
Ab10-19 ^a	2010	CC92	ST75	+	-	+	-
Ab11-20	2011	CC92	ST138	+	-	+	-
Ab11-21	2011	CC92	ST138	+	-	+	-
Ab11-22	2011	CC92	ST138	+	-	+	-
Ab11-23	2011	CC92	ST138	+	-	+	-
Ab11-24	2011	CC92	ST138	+	-	+	-
Ab11-25 ^c	2011	CC92	ST92	+	-	+	-
Ab12-26	2012	CC92	ST138	+	-	+	-
Ab16-27 ^c	2016	CC92	ST191	+	-	+	-

All of the *A. baumannii* isolates were negative to *bla_{IMP}*, *bla_{VIM}*, *bla_{NDM}*, *bla_{GIM}*, *bla_{SIM}*, and *bla_{SPM}*. CC = clonal complex, ST = sequence type, Ab#-# = *A. baumannii* isolated year-patient number. ^aThese patients were transferred from outside hospital.

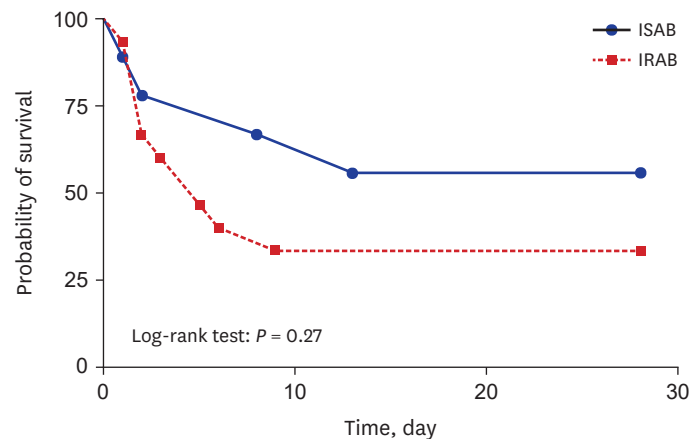


Fig. 2. Survival curve of ISAB and IRAB group.
ISAB = imipenem-sensitive *A. baumannii*, IRAB = imipenem-resistant *A. baumannii*.

The median interval from *A. baumannii* bacteremia onset to death was two days (range, 0–13) in ISAB and it was also two days in IRAB (range, 0–9) group. When IRAB group was examined further in detail, 35% (6/17) of patients with IRAB bacteremia died within 2 days before the culture and susceptibility test results became available and 67% (4/6) of patients had previous positive culture for IRAB from the tracheal aspirate before bacteremia developed.

A total of 78% (21/27) of all the patients were treated with susceptible antibiotics within 2 days from bacteremia onset, 62% (13/21) of patients died. In ISAB group, six patients (6/10) were treated with carbapenem and 33% (2/6) died. Whereas four patients (4/10) were treated without carbapenem and 75% (3/4) died ($P = 0.519$). In IRAB group, seven patients (7/17, 41%) were treated with colistin and 71% (5/7) died. Ten patients (10/17, 59%) in IRAB group did not receive colistin and 70% (7/10) died ($P = 0.949$).

Infection control

With an alert on IRAB outbreak in 2011, environmental culture including the hands of medical workers, computers and telephones of the nursing station, sink, and all of 15 bed rails was performed in 2011–2012. Reeducation of contact precaution and hand hygiene were performed to PICU medical workers. IRAB isolation frequency was dramatically decreased after infection control intervention. Antibiotic stewardship was strengthened.

DISCUSSION

This was a study on the long-term epidemiology of *A. baumannii* bacteremia and antibiotic resistance in PICU for 17 consecutive years of pre-MALDI-TOF period. We observed a dramatic shift in antibiotic susceptibility from all ISAB before 2004 to all IRAB in 2009 that was followed by an outbreak with high mortality due to ST138 IRAB. This outbreak peaked in 2011 and was controlled after an extensive infection control intervention.

Resistance to the carbapenem is a global issue. In the United States, the rate of *A. baumannii* resistance to imipenem and meropenem in 2008 was reported as 48% and 57.4% respectively.¹⁸ In Korea, the rate of *A. baumannii* resistance to carbapenem among adult patients was 85% in 2015.¹⁹ Imipenem resistance among pediatric patients is also increasing.^{9,20} In other study of

Korean PICU and neonatal intensive care unit (ICU) of Taiwan, the rapid emergence of IRAB was also observed.^{9,21} Cases of colistin-resistant AB were reported among patients who were treated with colistin to treat carbapenem-resistant *A. baumannii* (CRAB) infection.²²

We observed that all isolates were positive for OXA-23 like and clonal complex 92. OXA-23 like β -lactamase is a main carbapenemase of *A. baumannii*.^{23,24} Clonal complex 92 is a widely distributed clone and major cause of *A. baumannii* outbreaks worldwide.²⁵ It is also a major clone in Korean CRAB.²⁶ The distribution of sequence type and resistant gene change according to year of isolation with ST191 predominance was observed among isolated *A. baumannii* in Korean tertiary hospitals.^{23,27}

In this study, 35% (6/17) of patients with IRAB bacteremia died within 2 days before the culture and susceptibility test results became available. Among the six patients, 67% (4/6) had previous positive culture for IRAB from the tracheal aspirate before bacteremia onset. Active surveillance for preceding tracheal colonization or pneumonia and proactive antibiotic treatment strategy may allow the early initiation of appropriate antibiotic treatment in high risk rapidly deteriorating patients.²⁸

In the ICU, the early identification and prevention of an outbreak are important. The infection control team consisting of healthcare personnel expertise is important.²⁹ In a study of Korean adults in ICU, active surveillance and cohorting of patients for the CRAB infected or colonized patients reduced CRAB infection.³⁰ In this study, infection control efforts in PICU were sustained to prevent additional outbreak. As a result, there was not a single case of *A. baumannii* bacteremia (both ISAB and IRAB) for three years (2013–2015). When we have there was one IRAB bacteremia patient transferred from an outside hospital in 2016, this was not progressed to outbreak due to strict infection control measures (**Fig. 1**). Multifaceted infection control approaches including timely feedback, regular education and revisiting of control measures among infection control team, pediatric infectious disease experts, critical care physicians, and nursing staffs are essential.

This study has some limitations. Although the study period was relatively long (17 years), this was a retrospective study, and not all bacterial isolates were tested. Therefore, MLST or bacterial resistance analysis could not be performed on isolates from the early period. In addition, the source of the outbreak was not clear.

In conclusion, this was a long-term epidemiology study that evaluated IRAB bacteremia in PICU patients. Antimicrobial stewardship programs and multifaceted infection control approaches are essential to reduce outbreak caused by a resistant pathogen such as IRAB in high-risk PICU patients.

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