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Controlling an Outbreak of Multidrug-resistant *Acinetobacter baumannii* in a Pediatric Intensive Care Unit: a Retrospective Analysis

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The authors have no potential conflicts of interest to disclose.

ABSTRACT

Background: Multidrug-resistant *Acinetobacter baumannii* (MDRAB) is widespread among intensive care units worldwide, posing a threat to patients and the health system. We describe the successful management of a MDRAB outbreak by implementing an infection-control strategy in a pediatric intensive care unit (PICU).

Methods: This retrospective study investigated the patients admitted to the PICU in periods 1 (8 months) and 2 (7 months), from the index MDRAB case to intervention implementation, and from intervention implementation to cessation of MDRAB spread. An infection-control strategy was designed following six concepts: 1) cohort isolation of colonized patients, 2) enforcement of hand hygiene, 3) universal contact precautions, 4) environmental management, 5) periodic surveillance culture study, and 6) monitoring and feedback.

Results: Of the 427 patients, 29 were confirmed to have MDRAB colonization, of which 18 had MDRAB infections. Overall incidence per 1,000 patient days decreased from 7.8 (period 1) to 5.8 (period 2). The MDRAB outbreak was declared terminated after the 6-month follow-up following period 2. MDRAB was detected on the computer keyboard and in condensed water inside the ventilator circuits. The rate of hand hygiene performance was the lowest in the three months before and after index case admission and increased from 84% (period 1) to 95% (period 2). Patients with higher severity, indicated by a higher Pediatric Risk of Mortality III score, were more likely to develop colonization ($P = 0.030$), because they had invasive devices and required more contact with healthcare workers. MDRAB colonization contributed to an increase in the duration of mechanical ventilation and PICU stay ($P < 0.001$), but did not affect mortality ($P = 0.273$).

Conclusion: The MDRAB outbreak was successfully terminated by the implementation of a comprehensive infection-control strategy focused on the promotion of hand hygiene, universal contact precautions, and environmental management through multidisciplinary teamwork.

Keywords: *Acinetobacter baumannii*; Outbreak; Intensive Care Unit; Pediatric; Infection-control

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INTRODUCTION

Acinetobacter baumannii (*A. baumannii*), which is well known for its tenacious survival in the environment and its ability to confer antibiotic resistance to other coexisting bacteria,[1-3] and the antimicrobial resistance are crucial problems that have caused high morbidity and mortality in critically ill patients.[4-6] The Korean Nosocomial Infections Surveillance System showed that, since 2010, *A. baumannii* was the most relevant causative organism of ventilator-associated pneumonia (VAP), and its resistance to carbapenem increased from 53% in 2006 to 90% in 2013.[7] In a study conducted in 2012 at 162 intensive care units in 24 countries, *A. baumannii* was the most significant pathogen and had the highest antibiotic resistance among Gram-negative bacteria in bloodstream infections.[8] These results are in line with a study conducted at 173 hospitals in 2018.[9] The multidrug-resistant *A. baumannii* (MDRAB) pathogen is posing a serious threat to patient survival,[5,10] and desperate efforts to manage the spread of MDRAB in intensive care units have been widely documented.[11-13] However, controlling MDRAB outbreaks remains a clinical challenge.

In our hospital, we experienced an MDRAB outbreak that lasted 15 months after the index case was first admitted to the pediatric intensive care unit (PICU). When an MDRAB outbreak occurs in the intensive care unit (ICU), the most effective and simplest methods to address the outbreak is to close the unit and disinfect the internal environment.[14,15] However, since this was the only PICU in our region, it was virtually impossible to close the unit even temporarily. Instead of closing the unit, we tried to implement a comprehensive infection-control strategy and finally succeeded in eliminating the pathogen in the PICU.

In this study, we describe the successful strategy implemented to terminate the MDRAB in the PICU of our institution. In addition, we analyze the clinical impact of the MDRAB outbreak and share the process that led us to implement the infection-control strategy.

METHODS

This study was conducted in a tertiary-care teaching hospital by retrospectively reviewing the medical records of patients admitted to the PICU from June 2017 to August 2018. Subsequently, the results of microbiological tests conducted at the PICU were investigated through February 2019.

Hospital setting

The PICU at our institution has ten open beds and three isolation rooms (**Fig. 1**), and approximately 400 medical-surgical critically ill children (age < 19 years) are admitted to the unit every year. During the outbreak, four physicians worked exclusively at the PICU, and four sporadically provided care at the unit. There were 26 nurses assigned to the PICU, and the nurse-to-patient ratio was 1:2, with one nurse caring for two to three patients. In our hospital, the regular infection-control policy for MDRAB is based on the infection-control guidelines of the Korea Disease Control and Prevention Agency for multidrug-resistant microorganisms in healthcare facilities (**Table 1**).[16]

Definitions

Throughout this study, specific parameters were defined as follows: colonization refers to the presence of the pathogen on the skin or body fluids, including sputum and urine, without causing

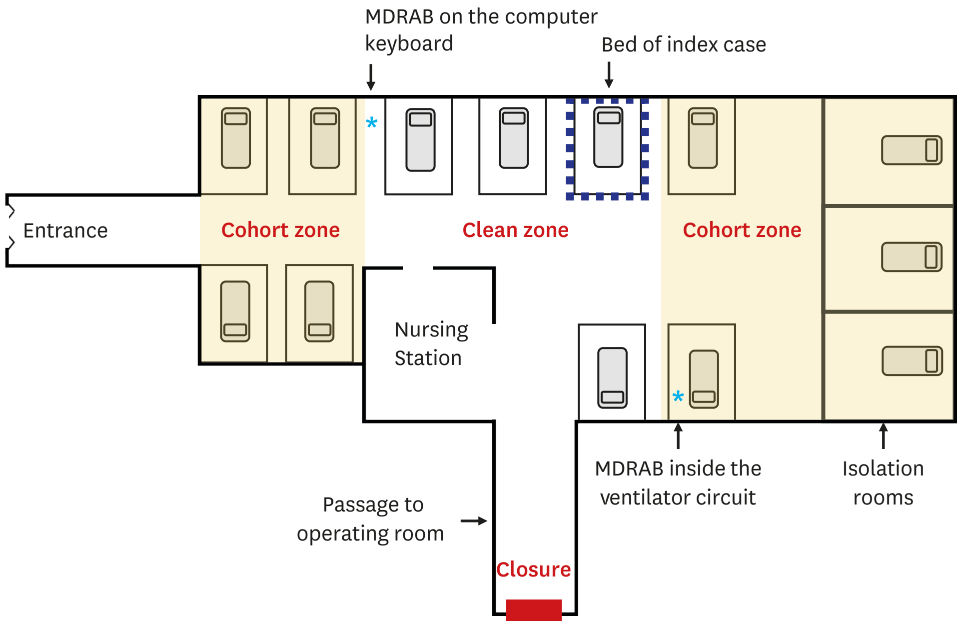

Fig. 1. Schematic map of the pediatric intensive care unit and the implementation of a comprehensive infection-control strategy. MDRAB-colonized patients were isolated in isolation rooms, or in the cohort zone if isolation rooms were unavailable. One entrance was closed. The asterisks represent the sites where MDRAB was detected.
MDRAB = multidrug-resistance *A. baumannii*.

Table 1. Summary of the infection-control strategy for MDRAB outbreaks and comparisons with infection-control policies for MDRAB in our hospital

Concepts	Implemented interventions	Details	Policies of our hospital
Cohort isolation	Cohort isolation of colonized patients	Mandatory	Recommended
Enforcement of hand hygiene	Regular education programs on hand hygiene	Including circulating staff	Not regular
	Monitoring of hand hygiene performance	Daily for the first month; then three times per week	Twice a month
Universal contact precautions	Wearing gloves and plastic gowns during contact in the patient zone	For all patients	For affected patients only
Environmental cleaning and disinfection	Extensive management using checklists	Under the supervision of the unit manager	None
	Patient zone	Three times a day	Once a day
	Environment except the patient zone	Twice a day	Once a day
Surveillance cultures	Initial and periodic cultures for all patients	Once a week	None
	Environmental surveillance cultures	Once a week	None
	Assessment of bacterial colonization for staff	Including circulating staff	None
Monitoring and feedback	Discussions on the performance of the infection-control strategy	Monthly	None

MDRAB = multidrug-resistant *A. baumannii*.

disease. Infection indicates any of the following three MDRAB-caused diseases: bloodstream infection, pneumonia, and urinary tract infection. When MDRAB was detected in blood culture, it was diagnosed as a bloodstream infection. Pneumonia, particularly VAP, which develops after more than 48 hours of mechanical ventilation, was defined as new or progressive pulmonary infiltration that was detected on chest radiography with supportive clinical findings. A urinary tract infection was diagnosed when MDRAB was detected in the urine of patients with a fever, leukocytosis, and pyuria. The term "MDRAB group" refers to patients with either MDRAB colonization or infection, whereas the other participants are referred to as the control group.

The incidence density rate was used to report the results of this study and refers to the number of cases of newly detected MDRAB in 1,000 patient days. Cases were determined after the detection of MDRAB in any type of specimen. The patient days and new incidence number per month were investigated.

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Table 2. In vitro activities of antimicrobial agents against *A. baumannii* isolated from the index case

Antimicrobial agents	MIC	Activities
Ampicillin/sulbactam	16 or ≥ 32	I or R
Cefotaxime	≥ 64	R
Cefepime	≥ 64	R
Ceftazidime	≥ 64	R
Ciprofloxacin	≥ 4	R
Gentamicin	≥ 16	R
Imipenem	≥ 16	R
Meropenem	≥ 16	R
Minocycline	≤ 1	S
Piperacillin/tazobactam	≥ 128	R
Tigecycline	4	I
Trimethoprim/sulfamethoxazole	≥ 160 or ≥ 320	R
Colistin	≤ 0.5	S

Four types of profiles were found depending on the minimal inhibitory concentration difference of ampicillin/sulbactam and trimethoprim/sulfamethoxazole.
MIC = minimal inhibitory concentration, I = intermediate, R = resistance, S = susceptible.

Index case and bacterial spread

A female patient was born at another hospital and underwent congenital diaphragmatic hernia repair surgery at our hospital's neonatal ICU on her first day of life.[17] On day 7, the patient was transferred to the PICU for extracorporeal membrane oxygenation due to septic shock that was diagnosed on June 6, 2017, and eventually died from multiorgan failure on day 20. Throughout her stay at the PICU, MDRAB was consistently detected in blood cultures (**Table 2**).

The seriousness of bacterial spread was not perceived until sporadic MDRAB colonization and infection were detected about 2 months after the index case admission. As the number of cases continued to increase, measures were implemented to strengthen hand hygiene, undertake active surveillance culture tests, and to clean the PICU environment; however, these efforts could not contain the bacterial spread. In mid-January 2018, a comprehensive infection-control strategy focusing on preventing new MDRAB colonization was implemented by a multidisciplinary team consisting of the PICU staff, a pediatric infectious disease specialist, the Infection Prevention and Control Department, and the Department of Laboratory Medicine.

Study period and patients

The study duration was divided into two periods. Period 1 comprised the first eight months from the MDRAB introduction to the implementation of the infection-control strategy. Period 2 consisted of the seven months from intervention implementation to the month of discharge of the last MDRAB-colonized patient. The follow-up period for monitoring the incidence of MDRAB colonization or infection in the PICU lasted six months. All patients admitted to the PICU during periods 1 and 2 were included in this study. Patient demographics, results of the microbiologic study, PICU stay, mechanical ventilation days, the Pediatric Risk of Mortality III (PRISM III) score, and mortality were investigated.

Interventions

The infection-control intervention comprised six concepts and is shown in **Table 1**. The strategy of these interventions is described in greater detail in the following list.

1) MDRAB-colonized patients were isolated in isolation rooms. A clean zone was designated, and in the absence of isolation rooms, patients were quarantined in areas other than the

clean zone. Patient isolation ended only when three consecutive surveillance bacterial culture tests conducted on alternate days yielded MDRAB-negative results. Medical equipment was used exclusively for one patient if feasible, and shared equipment, such as echocardiogram and electrocardiogram machines, were thoroughly disinfected before and after use. To prevent cross-contact, nurses were separately designated to provide care for either the MDRAB-colonized or non-colonized patients.

2) A pediatric infectious disease specialist and nurses of the Infection Prevention and Control Department imparted regular education programs on hand hygiene for healthcare workers at the PICU and operation rooms; healthcare workers included monthly rotation staff, radiographers, and rehabilitation therapists. The Infection Prevention and Control Department monitored the hand hygiene performance of healthcare workers during work and provided immediate feedback daily for the first month, then three times a week. In addition, aseptic techniques were reinforced for all invasive procedures performed at the PICU and operating room.
3) Regardless of the MDRAB colonization status, universal contact precautions were applied by wearing gloves and plastic gowns during contact with all PICU patients. Contact precautions should be ensured when entering the patient zone, which includes both a patient and his or her surroundings. Healthcare workers received monitoring and feedback from the Infection Prevention and Control Department on appropriate contact precautions, including the donning and removal of personal protective equipment. For patients receiving mechanical ventilation, only a closed suction system was used, and the disconnection of the ventilator circuit was minimized.
4) Environmental management checklists were created to ensure the cleaning and disinfection of the environment. In accordance with the checklist, nursing and cleaning staff thoroughly recorded the site and time of cleaning and disinfection under the supervision of the unit manager. Nursing staff cleaned the environment of the patient zone and the medical equipment during their duty hours three times a day, and the cleaning staff cleaned the walls surrounding patients, computer supplies, tables, washbasins, and doors, twice a day. Computer keyboards were covered with fresh plastic wrap every day after cleaning and wiped with alcohol every hour. Alcohol and various dilutions and concentrations of hypochlorous acid-based disinfectants were used for their intended use in medical equipment and the environment.
5) The initial surveillance culture test was mandated for all patients admitted to the PICU, and periodic cultures were conducted once a week. Culture specimens were collected from tracheal aspirates from intubated or tracheostomized patients and nasopharyngeal swabs from non-intubated patients. Surveillance culture tests for the PICU environment and operating room, including mechanical ventilators, ventilator circuits, suctioning equipment, bedrails, infusion pumps, medication carts, washbasins, and cardiovascular bypass equipment, were performed initially and then followed-up weekly. Nasopharyngeal swab cultures of all related medical staff of the PICU and operating room were performed to assess MDRAB colonization. A specific laboratory code for culture detection of MDRAB was developed to accelerate the detection process and reduce the workload of laboratory technicians.
6) Monthly meetings were held to discuss the performance of the control strategy, results of hand hygiene monitoring, and incidence rate of MDRAB colonization and infection.

In addition, access to the PICU was restricted to permit only visits related to patient care, and one of the two entrances was closed. All patients older than two months of age received a 2% chlorohexidine bath every day.

Microbiology

Antimicrobial susceptibility tests were conducted to identify antimicrobial agents using VITEK-2 (BioMerieux, Marcy L'Etoile, France) following the recommendations of the Clinical and Laboratory Standards Institute (CLSI) 2015. Susceptibility testing for colistin is not routinely performed in our hospital; however, the broth microdilution method was used to analyze some patient specimens. For the broth microdilution method, the cation-adjusted Mueller–Hinton Broth (BBL; Becton Dickinson, Franklin Lakes, NJ, USA) was used according to CLSI recommendations.[18] The breakpoint for colistin resistance was ≥ 4 μg/mL.

Statistical analysis

Statistical analysis was performed using the SPSS version 21 (IBM, Armonk, NY, USA). The normality test was performed on continuous variables with the Shapiro-Wilk test. The difference in clinical variables between the MDRAB and the control groups was analyzed to infer the mechanism of bacterial spread. MDRAB colonization and infection groups were compared to determine the clinical impact of MDRAB infection. The χ^2 and Fisher's exact tests were used for comparisons of categorical variables. Between-group differences for continuous variables were compared using an independent *t*-test and the Mann-Whitney *U* test as appropriate. Logistic regression analysis was conducted to identify factors significantly related to colonization. A *P* value of less than 0.05 was considered statistically significant.

Ethics statement

This study was approved by the Institutional Review Board of Pusan National University Yangsan Hospital, Korea, with waived informed consent owing to the retrospective nature of the analyses (No. 05-2020-098).

RESULTS

Incidence and surveillance

Of the 427 patients treated during the outbreak, a total of 29 were confirmed to have MDRAB colonization (18 and 11 patients during periods 1 and 2, respectively). The antibiotic susceptibility test profile of *A. baumannii* detected in colonized patients was identical to that of the four types of MDRAB found in the index case. MDRAB was detected in the aspirated sputum of all patients in the MDRAB group. The mean interval from the day of PICU admission to the first identification of MDRAB was 7.3 ± 5.4 days (median, 5; range, 2–20).

As shown in **Fig. 2**, the cumulative incidence of MDRAB cases increased steadily during period 1, reaching the highest number of cases (n = 8) in December 2017. In this month, MDRAB patients occupied 7 of 13 beds per day. The rate of hand hygiene performance was the lowest (72%) in the three months before and after index case admission and increased from 84% (period 1) to 95% (period 2). The highest incidence density rate was 17.0, and was observed in September 2017. The overall incidence density rate decreased from 7.8 in period 1 to 5.8 in period 2. New colonization did not occur during the follow-up period of six months. The MDRAB outbreak was declared terminated and the infection-control intervention was discontinued. Thereafter, we reinstituted the regular infection-control policy of our hospital, but with continued hand hygiene education and monitoring.

In the initial environmental culture tests, MDRAB was detected on the computer keyboard and in condensed water inside ventilator circuits in the PICU in 2 of the 24 swab samples.

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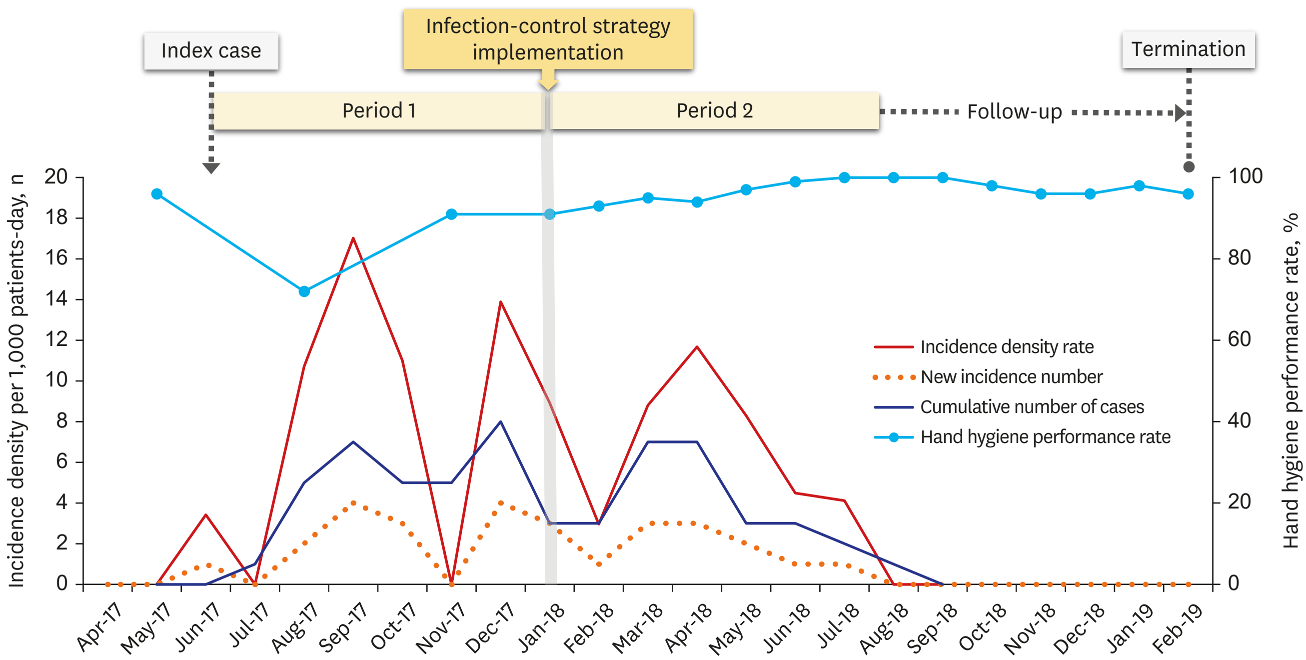

Fig. 2. Monthly incidence of the MDRAB colonization and hand hygiene performance rate during MDRAB outbreak. A comprehensive infection-control strategy was implemented in January 2018. The overall incidence per 1,000 patient days decreased to 5.8 in period 2 from 7.8 in period 1. The last new colonization occurred in July 2018, and the last MDRAB colonization patient was discharged in August 2018. The MDRAB outbreak was declared terminated after the 6-month follow-up following period 2.
MDRAB = multidrug-resistance *A. baumannii*.

However, MDRAB was not detected in follow-up weekly tests that were conducted until August 2018. The nasopharyngeal swab cultures of 48 healthcare workers were performed to assess MDRAB colonization, and the results were all negative.

Clinical characteristics of patients

Table 3 shows the clinical characteristics of the MDRAB group and the control group during the outbreak. All patients in the MDRAB group received mechanical ventilation support, and the duration of mechanical ventilation and PICU stay was significantly longer than in patients in the control group. All four mortality cases in the MDRAB group occurred because of the exacerbation of the underlying disease and were unrelated to MDRAB infection. There was no statistical difference in the characteristics of MDRAB-colonized patients in periods 1 and 2.

To determine the route of bacterial transmission, logistic regression analysis was performed, including the variables that showed significant between-group differences: open-heart surgery (odds ratio [OR], 3.02; 95% confidence interval [CI], 1.26–7.23; $P = 0.013$) and PRISM III score (OR, 1.06; 95% CI, 1.01–1.12; $P = 0.030$) were significantly correlated with the MDRAB colonization. We investigated possible transmission routes related to open-heart surgery, including cardiopulmonary bypass equipment, environment- and healthcare worker-related transmission in the operating room, and the patient's transport path. We also monitored the implementation of aseptic techniques, but the transmission route was not identified.

Among the 29 patients with MDRAB colonization, 18 were diagnosed with infection, from which 13 had VAP, four bloodstream infection accompanied by VAP, and one urinary tract infection. As few antibiotics were effective against this pathogen, ampicillin/sulbactam, colistin, tigecyclin, and minocycline were used alone or in combination. The treatment

Table 3. Clinical characteristics and outcomes of the patients in the MDRAB group and comparisons with the control group

Variables	All (n = 427)	MDRAB (n = 29)	Control (n = 398)	*P* value
Sex, male	240 (56.2)	21 (72.4)	219 (55.0)	0.082
Age, mon	50.6 ± 68.7	14.8 ± 40.5	53.2 ± 69.6	< 0.001
Underlying disease	414 (97.0)	29 (100)	385 (96.7)	0.395
Neurologic disease	51 (11.9)	4 (13.8)	47 (11.8)	0.208
Cardiovascular disease	255 (59.7)	22 (75.9)	233 (58.5)	0.029
Respiratory disease	30 (7.0)	-	30 (7.5)	0.112
Renal disease	22 (5.2)	-	22 (5.5)	0.204
Gastrointestinal disease	14 (3.3)	2 (6.9)	12 (3.0)	0.183
Hemato-oncologic disease	30 (7.0)	1 (3.4)	29 (7.3)	0.264
Metabolic disease	12 (2.8)	-	12 (3.0)	0.425
Specific consideration				
Open heart surgery	225 (52.7)	22 (75.9)	203 (51.0)	0.012
Immunocompromised	22 (5.2)	-	22 (5.5)	0.385
Mechanical ventilation	350 (82.0)	29 (100)	321 (80.7)	0.005
PRISM III score	5.6 ± 5.5	7.8 ± 3.9	5.5 ± 5.6	0.025
MV days, day	8.7 ± 19.4	38.0 ± 39.0	6.0 ± 13.8	< 0.001
PICU stay, day	9.1 ± 19.1	44.6 ± 41.9	6.5 ± 13.1	< 0.001
Mortality	34 (8.0)	4[a] (13.8)	30 (7.5)	0.273

Data are given as number (%) or mean ± standard deviation.
MDRAB = multidrug-resistance *A. baumannii*, PRISM III = Pediatric Risk of Mortality III, MV = mechanical ventilation, PICU = pediatric intensive care unit.
[a]Mortality reported is unrelated to the MDRAB infection.

succeeded in all MDRAB-infected patients. The median duration of mechanical ventilation (42 days [interquartile range {IQR}: 73.2] vs. 8 days [IQR: 8], *P* = 0.002) and PICU stay (50 days [IQR: 6]) vs. 8 days [IQR: 25], *P* = 0.001) was significantly longer in the MDRAB-infection group than in the MDRAB-colonization group.

DISCUSSION

In this study, we described the successful management of an MDRAB outbreak for 15 months through the implementation of an infection-control strategy in the PICU. The outbreak in question was caused by MDRAB from the index case, as evidenced by the identical antibiotic susceptibility profiles of MDRAB isolates from all affected patients. The mean interval from PICU admission to colonization in our patients was much shorter than the reported average of approximately more than a month.[19] The outbreak caused by the major MDRAB strain seemed to spread rapidly through environmental contamination. The presence of MDRAB on the surface of the computer keyboard and in condensed water in the ventilator circuit led us to infer that the outbreak presumably initiated through pathogens in the MDRAB colonized patient's respiratory droplets, contaminated environment, and decidedly poor hand hygiene of healthcare workers, who facilitated bacterial dissemination. As seen in several reports of *Acinetobacter* species outbreaks, environmental contamination is very diverse and extensive,[4,13,20,21] and some *A. baummanii* strains can live for several months on dry surfaces and survive even in anaerobic nutrient-depleted water for over 14 days.[3,22] Therefore, our infection-control strategy relied on six concepts where the most crucial ones were hand hygiene promotion, universal contact precautions, and environment management.

Hand hygiene is the most important and powerful defense to prevent the transmission of nosocomial pathogens. However, hand hygiene alone is not effective against pathogens such as MDRAB, which can live for extended periods in the environment. Mousa et al.[23] measured air samples from around ventilated patients and reported that *A. baumannii* disseminated as a form of aerosol during treatment, and activities such as endotracheal suctioning, changing bedsheets, and diapers were most likely to be associated with air contamination. The nature of patient care in intensive units is such that healthcare workers come into close contact with the patient and the patient's environment, and therefore wearing a plastic gown helps prevent pathogen spread through the clothes of healthcare-workers. In universal contact precautions, hand hygiene promotion and lowering healthcare worker-patient contact rates achieved remarkable results.[24] In endemic situations, we suggest that universal contact precautions is more effective in controlling an outbreak than contact precautions that are implemented only for the affected patients. However, some studies conducted in non-endemic intensive care units and focused on the acquisition rate of antibiotic resistance have questioned the effectiveness of universal contact precautions.[25-27] Given the staff burden and medical costs,[27] it should be noted that these strategies should be strictly implemented in a short period.

With regard to the host factor for bacterial transmission, we found that an open-heart surgery and a higher PRISM III score were associated with MDRAB colonization. The transmission route related to open-heart surgery was not identified, although the association can be deduced from the higher PRISM III score in the MDRAB group. Patients with higher PRISM III scores were more vulnerable to MDRAB colonization because they had invasive devices, such as central venous catheters, a urinary catheter, arterial lines, and multiple chest tubes, and required more contact with healthcare workers. In this regard, we believe that hand hygiene promotion and universal contact precautions played a key role in our infection-control strategy.

In this study, MDRAB colonization contributed to increased morbidity but did not affect mortality. The MDRAB-associated mortality rate exceeds 25%, and even reaches 75% depending on several factors.[10,28-30] Importantly, antibiotic susceptibility is the most fundamental factor when treating MRDAB infections.[6,9] Fortunately, the MDRAB strain was susceptible to colistin and intermediately susceptible to amoxicillin/sulbactam; otherwise, the outbreak would have resulted in several fatal cases due to the MDRAB infection. In the early period of the outbreak, PICU staff tried to prevent further spread but were very ineffective until the infection-control strategy devised by the multidisciplinary team was applied. Had the outbreak been recognized as a serious situation early and responded quickly to at this point, the affected patients and their morbidity would have been considerably lower. We demonstrated that early recognition of an outbreak and prompt intervention measures are the most important and effective control strategies to improve patient outcomes following environmental contamination with long-lived bacteria, such as *A. baumannii.*

Many factors are involved in developing MDRAB outbreaks, including the acquisition rate of antibiotic resistance.[11] However, we speculate that the outbreak we experienced was caused by environmental contamination with the major MDRAB strain derived from the index case and MDRAB transmission due to the poor hand hygiene among healthcare workers. Therefore, in this study, we focused on controlling the MDRAB outbreak, and the acquisition rate of antibiotic resistance is beyond the scope of our study.

This study has some limitations. We tried to statistically infer the association between patient characteristics and MDRAB colonization to identify risk factors for bacterial spread. However, statistical approaches may be inappropriate because the investigation began long after the outbreak had occurred. Furthermore, the reliability of the results is limited because of the small number of patients. In addition, due to the nature of the retrospective descriptive study design, unrecognized factors might have mediated the development of the outbreak.

In conclusion, we experienced an MDRAB outbreak that caused a significant morbidity increase, probably due to a contaminated environment and poor hand hygiene. The MDRAB outbreak was successfully controlled at our PICU by implementing a comprehensive infection-control strategy involving a multidisciplinary team. We believe that hand hygiene promotion, universal contact precautions, and environmental cleaning and disinfection are vital to control an MDRAB outbreak.

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