

Burkholderia Sepsis in Children as a Hospital-Acquired Infection

Kyu Yeun Kim¹, Dongeun Yong², Kyungwon Lee², Ho-Seong Kim¹, and Dong Soo Kim¹

¹Department of Pediatrics, Severance Children's Hospital, Yonsei University College of Medicine, Seoul;

²Department of Laboratory Medicine and Research Institute of Bacterial Resistance, Yonsei University College of Medicine, Seoul, Korea.

Purpose: Hospital-acquired *Burkholderia cepacia* (*B. cepacia*) infection are not commonly recorded in patients without underlying lung disease, such as cystic fibrosis and chronic granulomatous disease. However, in 2014, *B. cepacia* appeared more frequently in pediatric blood samples than in any other year. In order to access this situation, we analyzed the clinical characteristics of *B. cepacia* infections in pediatric patients at our hospital.

Materials and Methods: We conducted a retrospective study of blood isolates of *B. cepacia* taken at our hospital between January 2004 and December 2014. Patient clinical data were obtained by retrospective review of electronic medical records. We constructed a dendrogram for *B. cepacia* isolates from two children and five adult patients.

Results: A total of 14 pediatric patients and 69 adult patients were identified as having *B. cepacia* bacteremia. In 2014, higher rates of *B. cepacia* bacteremia were observed in children. Most of them required Intensive Care Unit (ICU) care (12/14). In eleven children, sputum cultures were examined, and five of these children had the same strain of *B. cepacia* that grew out from their blood samples. Antibiotics were administered based on antibiotic sensitivity results. Four children expired despite treatment. Compared to children, there were no demonstrative differences in adults, except for history of ICU care.

Conclusion: Although there were not many pediatric cases at our hospital, awareness of colonization through hospital-acquired infection and effective therapy for infection of *B. cepacia* is needed, as it can cause mortality and morbidity.

Key Words: *Burkholderia cepacia*, sepsis, hospital infection, child

INTRODUCTION

Knowledge of infection, hygiene, and nutrition has improved tremendously in comparison to the past, and antibiotics have developed remarkably. Nevertheless, hospital-acquired infections remain an issue, especially for patients in the Intensive Care Unit (ICU) and those under prolonged hospitalization. Pathogens resistant to antimicrobial agents are another emerging issue. According to the Centers for Disease Control

and Prevention, gram negative bacteria accounted for the most urgent and serious microorganisms, such as carbapenem-resistant *Enterobacteriaceae*, *Acinetobacter*, and *Pseudomonas aeruginosa*.¹⁻³

Burkholderia cepacia (*B. cepacia*) has emerged as another important bacterium cause of hospital-acquired infections. The bacterium is known formerly as *Pseudomonas cepacia*, a gram negative aerobic, glucose, non-fermenting, motile bacillus. Immunocompromised and hospitalized patients are especially susceptible to this infection, leading to severe bacteremia that results in death.⁴ Studies also report its growth in endocarditis among drug addicts, in patients with prosthetic cardiac valves, in eye infections following surgical procedures, and in infections of the central nervous system. Once colonized with a specific strain, replacement of the original strain with another is infrequent.⁵ *B. cepacia* can cause severe disease in humans with underlying disease, such as cystic fibrosis and chronic granulomatous disease (CGD).^{5,6} Fortunately, since cystic fibrosis and CGD are very rare in Korea, *B. cepacia*

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Corresponding author: Dr. Dong Soo Kim, Department of Pediatrics, Severance Children's Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.

Tel: 82-2-2228-2050, Fax: 82-2-393-9118, E-mail: dskim6634@yuhs.ac

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infection is not usually a great concern.

B. cepacia infection is not a common source of infection in adult and pediatric patients. However, in 2014, *B. cepacia* growth was confirmed more frequently in pediatric blood samples than in any other year. Therefore, to assess the possibility that *B. cepacia* has become another important source of nosocomial infection, we analyzed clinical characteristics of *B. cepacia* infection in pediatric patients in our hospital over the course of the past ten years.

MATERIALS AND METHODS

A retrospective study was performed in patients with blood isolates of *B. cepacia* from January 2004 to December 2014 in our hospital.

The BacT/ALERT 3D (bioMérieux, Inc., Durham, NC, USA) blood culture system was used. Isolates were identified using the VITEK 2 system with GP and GN cards. An antimicrobial susceptibility test (AST) was performed via a broth microdilution test using the VITEK 2 system with P625, N211, and N212 cards. AST interpretation was determined using Clinical and Laboratory Standard Institute (CLSI) guidelines; CLSI recommended testing with ceftazidime, minocycline, meropenem, and cotrimoxazole in 2010.⁷

Since not all samples were available, we constructed a dendrogram for *B. cepacia* from the sputum of three children and four adults only. The main spectrum profile (MSP) showing the highest score was selected from each isolate and was included to construct the dendrogram using the statistical toolbox in MATLAB 7.1 integrated in the matrix-assisted laser desorption/ionization (MALDI) Biotyper 2.0 software (Bruker Daltonics GmbH, Leipzig, Germany). Based on the principle that identification score reflects the agreement of the spectra with the standard *Acinetobacter baumannii* database entry, the MSP profile showing the highest score implies that the specific spectra represents the most typical aspects of a certain strain from the database. This selection of the highest score marking spectra was necessary, especially when highly similar strains were studied because several mass spectral features related to limited reproducibility of the method might eclipse mass spectral differences between the strains. Test strain clonality was determined with cut-off values at a distance of 250.⁸ Instead of pulsed-field gel electrophoresis or whole genome sequencing, the gold standard for confirming clonality, we used the MALDI TOF Mass Spectrometry method.⁹

Patient clinical data were obtained retrospectively from electronic medical records. This study was approved by the Institutional Review Board (IRB) in our hospital (IRB No. 4-2015-0540).

RESULTS

Over the 10-year period, a total of 14 pediatric patients and 55 adult patients were identified as having *B. cepacia* bacteremia (Table 1). In the years 2005, 2009 and especially in 2014, higher rates of *B. cepacia* bacteremia were observed in pediatric patients (Fig. 1). Although the increasing patterns in 2009, 2013, and 2014 were similar, there were few differences in annual incidence between adults and children. The overall incidence of *B. cepacia* bacteremia in pediatric patients was lower than that in adult patients.

There was no difference between genders in children. Most children had underlying disease except for one patient. Underlying diseases included cancer (4/14), congenital heart disease (4/14), immunodeficiency, such as CGD (1/14), and prematurity (2/14). One previously healthy pediatric patient who had pneumonia and a history of treatment in the ICU also had *B. cepacia* bacteremia. Three out of 14 pediatric patients had positive *B. cepacia* intravenous catheter tip cultures simultaneously with blood culture.

Among adults, more male than female patients had *B. cepacia* bacteremia (1.72:1). Almost all adult patients had underlying disease. They were mostly oncology patients (40/55) and patients with cardiovascular problems (13/55). Only two had a history of simple surgery.

Most of the pediatric patients had undergone ICU care (12/14). Twelve of the patients with ICU care were initially due to underlying disease or right after cardiac surgery, not due to *B. cepacia* infection. In adult patients, 47% underwent ICU care (26/29), fewer than for the children.

Eleven pediatric patients had their sputum cultures examined, of which five children had the same strain of *B. cepacia* grown from the blood samples; the other six children had other strains but not *B. cepacia*. Three did not get sputum cultures because there was no pneumonia. Among the adult patients, only five patients had the same strain of *B. cepacia* grown from the blood samples. Two patients had multidrug resistance who stayed in the oncologic general ward without history of ICU care. Though they are isolated in the same month, the sensitivity patterns of antibiotics were different, and thus, they were thought to be different pathogens. Antibiotics were used properly based on the antibiotics sensitivity results (Table 2). Only one patient was administered cotrimoxazole for treatment, and 11 patients including the previously mentioned patients used meropenem. Four children expired despite treatment. Only two of the patients were thought to have expired by direct effect of *B. cepacia* bacteremia. Another one patient had multiple gram negative bacterial growth in their blood samples, and could not predicate *B. cepacia* as the direct cause of death. The remaining patient expired due to underlying cardiac disease after cardiac surgery. Among the adults, 20 patients expired, 13 due to the direct effect of *B. cepacia*.

Since not all samples were available for study, we only gath-

Table 1. Clinical Characteristics of *B. Cepacia* Infection in Pediatric Patients and Adult Patients

Patient ID	Year isolated	Age	Sex	Underlying disease	Isolation site	ICU care	<i>B. cepacia</i> in the sputum culture	Outcome	Used antibiotics
1	2003	0	M	None	Blood IV catheter tip	Yes	Yes	Treated	Imipenem
2	2005	0	M	Neuroblastoma	Blood IV catheter tip	Yes	No	Treated	Meropenem
3	2005	1	F	Large VSD	Blood	Yes	Sputum culture not done	Treated	Ceftriaxone
4	2006	1	F	Core pulmonale, vegetation on aortic valve	Blood	Yes	Sputum culture not done	Treated	Ceftazidime Meropenem Levofloxacin
5	2008	0	M	Prematurity, panperitonitis	Blood	Yes	No	Treated	Cefepime
6	2009	10	F	Medulloblastoma	Blood	Yes	Sputum culture not done	Treated	Carbenin Cefepime
7	2009	0	M	Atresia of pulmonary artery	Blood	Yes	No	Expired	Meropenem
8	2010	0	F	Prematurity, cystic hygroma	Blood Urine	Yes	Yes	Treated	Meropenem
9	2012	7	F	Chronic granulomatous disease	Blood	Yes	Yes	Expired	Meropenem
10	2014	6	M	Medulloblastoma	Blood	Yes	No	Expired	Meropenem Colistin
11	2014	0	M	HLHS	Blood IV catheter tip	Yes	Yes	Expired	Meropenem Cotrimoxazole
12	2014	0	F	Coarctation of aorta, DORV	Blood	Yes	Yes	Treated	Certazidime Meropenem
13	2014	12	M	ALL	Blood	No	No	Treated	Meropenem
14	2014	6	F	ATRT	Blood	No	No	Treated	Meropenem
Adult patients (55 cases)	2003–2014	18–87 (62.1)	M:F (1.72:1)	Oncology patients: 40 cases Patients with cardiovascular problems: 13 cases Simple surgery: 2 cases	Blood: 55 cases Catheter tip: 4 cases Urine: 4 cases Pleural fluid: 1 case	26 cases	5 cases	Treated: 35 cases	

ICU, Intensive Care Unit; *B. cepacia*, *Burkholderia cepacia*; VSD, ventricular septal defect; HLHS, hypoplastic left heart syndrome; ALL, acute lymphoblastic leukemia; ATRT, atypical teratoid rhabdoid tumor; IV, intra-venous.

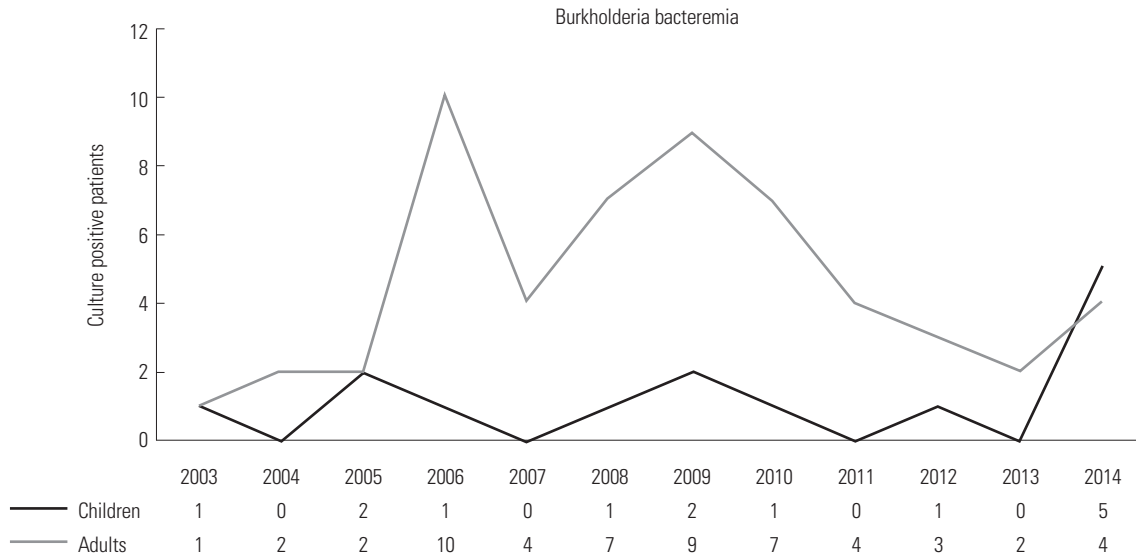


Fig. 1. Annual incidence of *B. cepacia* infection in our hospital. *B. cepacia*, *Burkholderia cepacia*.

Table 2. Microbial Sensitivity of *B. Cepacia* Isolated from 14 Patients

Patient ID	Ceftazidime	Levofloxacin	Meropenem	Minocycline	Tetracycline	Cotrimoxazole
1	S	R	S	Not done	R	I
2	S	R	S	Not done	R	I
3	S	S	S	Not done	R	S
4	I	I	R	Not done	R	S
5	S	S	S	Not done	S	S
6	S	S	S	S	Not done	S
7	I	I	S	I	Not done	S
8	S	I	S	S	Not done	R
9	S	S	S	S	Not done	S
10	S	S	S	S	Not done	S
11	S	S	S	S	Not done	S
12	I	S	S	S	Not done	S
13	R	I	R	R	Not done	S
14	I	I	R	R	Not done	R

B. cepacia, *Burkholderia cepacia*; S, susceptible; I, intermediate; R, resistant.

ered seven samples of *B. cepacia* from sputum, three from children and four from adults. Patients B, E, and F were children. Patients A, B, C, and G had a history of ICU care in March 2014, and patient D had a history of ICU care in August 2014. Patients E and F had a history of pediatric cardiovascular ICU (PCCU) care in March and August (Fig. 2). We were able to find two clonalities; those were each isolated in March and August in the ICU and PCCU.

DISCUSSION

Our hospital data showed that *B. cepacia* infection was not common over the past ten years. The total number of cases with *B. cepacia* bacteremia was 69, and of these, about 20% were pediatric cases with low incidence. As in adult patients,

pediatric patients continually showed *B. cepacia* infection in our hospital. We do not think *B. cepacia* infection is increasing in pediatric populations. However, in 2014, there were five cases of *B. cepacia* bacteremia in pediatric patients, which was unlike the rate in other years. We are unable to explain the reason for the increased incidence of *B. cepacia* in year 2014. However, physicians should be aware of this pathogen as a cause of the hospital infection in immunocompromised patients and in previously healthy pediatric patients with a history of ICU care.

According to other reports and studies, *B. cepacia* mainly causes problems in patients with cystic fibrosis or immunodeficient patients, such as CGD, rather than in immunocompetent patients. In our case, there was one patient with CGD and expired due to *B. cepacia* sepsis. It can cause mortality in over 90% of pediatric cystic fibrosis patients who have pulmo-

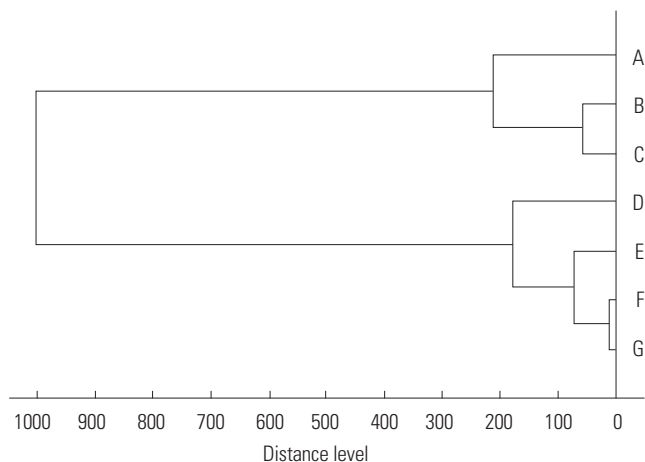


Fig. 2. Dendrogram of *B. cepacia* isolated in seven patients. Patients B, E, and F are pediatric patients; the others are adult patients. Patients A, B, C, D, and G were from the ICU, and Patients E and F were from the pediatric cardiovascular ICU. *B. cepacia*, *Burkholderia cepacia*; ICU, Intensive Care Unit.

nary damage, after colonization and being transferred to the blood stream. In the ICU setting and in treatment with catheters or similar devices, this infection can lead to morbidity and mortality. In our study, mortality cases were suspected to have expired due to infection with *B. cepacia*. Fortunately, in Korea, as cystic fibrosis and CGD are rare conditions, *B. cepacia* is not much of a concern to physicians. However, as ICU care and catheter or device treatment is increasing, the importance of *B. cepacia* infection is also increasing. In 14 cases of *B. cepacia* bacteremia, 13 cases had underlying disease, and 12 had a history of ICU care. This is consistent with other reports.¹⁰⁻¹⁴ Although immune status was not assessed during the study period, cardiac surgery, chemotherapy, and prematurity can cause immunosuppressive conditions, and this may lead to sepsis.

When comparing data for the children and the adults, there were no significant differences, except for ICU care. As many of the adult patients had signed do not resuscitate (DNR) documents, patients were not admitted to the ICU and maintained treatment in the general ward.

Five of the 11 cases with sputum culture results showed the same strain of *B. cepacia* grown from blood samples. This suggests that colonization with *B. cepacia* in the airway can cause bacteremia and lead to morbidity and mortality, although there is no exact evidence that *B. cepacia* in the airway is a pathogen or not. Nevertheless, there is no effective method for eradication of colonized *B. cepacia*. Therefore, hospital environment and health care hygiene are still the most important issues.

Therapeutic options for *B. cepacia* are unfortunately limited because many strains of this organism exhibit high levels of resistance to many antimicrobial agents *in vitro*, which may be intrinsic to certain cases. Studies report up to 50.4% resistance to every antibiotic tested, indicating that multidrug resistant isolates are not uncommon.^{5,15} In our study, *B. cepacia*

isolated from five cases all reported sensitivity to antibiotic agents. Only one patient showed resistance to ceftazidime, three to meropenem, and two to co-trimoxazole.

The antimicrobial option most commonly used in *B. cepacia* infection is co-trimoxazole (trimethoprim/sulfamethoxazole). Co-trimoxazole is also the prophylactic drug of choice for CGD. There is some hurdle to the use of co-trimoxazole, since allergic or hypersensitivity reactions, intolerance, and resistance may be observed in patients receiving co-trimoxazole.¹⁵ Our CGD case was also using cefixime for prophylactic measure instead of co-trimoxazole due to a history of allergic reaction to co-trimoxazole.

In this study, many different antimicrobials were tested. Interestingly, patients who survived responded efficiently to the prescribed antibiotics. Even after removal of the catheter or device, we could not isolate *B. cepacia* from the blood of patients anymore, without changing antibiotics. This might suggest that *B. cepacia* infection in patients without underlying immunocompromised disease may be controlled well only with removal of contaminated catheters or devices. The prevailing thought has been that removal of a contaminated catheter or device should be essential for the control of *B. cepacia* infection, which is the principal treatment for catheter infections.

As *B. cepacia* bacteremia was increased in both adults and children, there was no obvious association between the two groups, though the trend seemed to be similar. According to the dendrogram results, we suspect that there may be a reservoir in our hospital. We do not know whether the pathogens isolated from children are from adult patients or contrary pathogens isolated from adults are from children. As we do not have a separate pediatric ICU and share the same space with adult patients, we can say that children can share the same hospital infection. Accordingly, this suggests the importance of sustainable infection control and hygiene.

The limitation of this study is that it was a retrospective study from a single center. The number of study subjects was also too small. The strength of this study is that we reviewed data for a ten-year period and *B. cepacia* bacteremia in pediatric patients. Since not much data exists regarding *B. cepacia* in Korea, especially in pediatric patients, more data should be collected and analyzed.

Although there were not many cases in our hospital, awareness of colonization and effective therapy of *B. cepacia* infection is needed, as such an infection can cause mortality and morbidity. Also, infection control and monitoring are important, especially in patients under prolonged hospital admission.

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