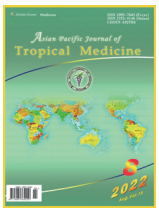

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Burkholderia cepacia outbreak in immunocompetent children in a tertiary hospital in Turkey: A case series

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ABSTRACT

Objective: To report an outbreak of *Burkholderia* (*B.*) *cepacia* related to contaminated surface cleaner in the pediatric ward of a tertiary hospital in Turkey.

Methods: This study retrospectively reported the outbreak occurred between January 16, 2018 and January 23, 2018. Twelve immunocompetent patients who developed a bloodstream infection a few days after the hospitalization and who were positive for *B. cepacia* were included. Environmental samples were collected from various areas in the hospital to find the source of the outbreak.

Results: All patients had clinical and biochemical evidence of sepsis. None of the patients had an underlying disease or had a central venous catheter as a risk factor. *B. cepacia* was isolated from the samples taken from the surface cleaners. The antibiotic susceptibilities of *B. cepacia* isolates were identical in the surface cleaners with the isolates from the patients' blood cultures. The outbreak was controlled after removing the surface cleaners from use. None of the infected patients died during the outbreak.

Conclusions: Nosocomial *B. cepacia* outbreak may occur in immunocompetent children as well. Rapid identification of the outbreak, defining the source and taking appropriate measures to control the outbreak are the key points in the management.

KEYWORDS: *Burkholderia cepacia*; Bacteremia; Immunocompetent; Outbreak; Infection control

1. Introduction

Burkholderia (*B.*) *cepacia* complex (BCC) is considered a group comprising a minimum of 20 *Burkholeria* species; some of them can be distinguished phenotypically, whereas others require genotype identification. BCC is a group of aerobic, non-spore forming, catalase producing, lactose non-fermenting, and Gram-negative bacteria. It is usually found in soil and aquatic environments[1,2]. *B. cepacia* is an opportunistic pathogen that rarely infects normal tissue, and often leads to infection in cystic fibrosis patients with whose respiratory epithelium was damaged previously or in individuals with immune dysfunction, including chronic granulomatous disease[1].

Certain *Burkholderia* species may colonize in the hospital environment. Although the immunocompetent individuals are generally unaffected, *B. cepacia* may induce infections in the respiratory system, blood stream, and urinary tract in immunosuppressed patients, in patients with underlying diseases, in children admitted to the pediatric intensive care unit (ICU), as well as in infants admitted to the neonatal ICU[1]. It is reported that hospital outbreaks have occurred through contaminated intravenous drugs/fluids, medical devices and skin disinfectants[3-5]. Identifying

Significance

Burkholderia cepacia may cause outbreak in immunocompromised children and in neonatal/pediatric intensive care units. However, in this study, *Burkholderia cepacia* is also shown to cause outbreak in immunocompetent children. Surface cleaners may be the source of these outbreaks. Rapid identification of the outbreak, defining the source and taking appropriate measures to control the outbreak are the key points in the management.

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the source of a *B. cepacia* outbreak might be difficult, therefore, it is imperative to immediately take measures to control and eliminate the outbreak[1].

To the best of our knowledge, this is the first reported outbreak of bloodstream infection caused by *B. cepacia*, particularly in immunocompetent children. This article not only retrospectively analyzes the demographic, clinical characteristics, and outcomes of the patients, but also addresses the infection control measures to control the outbreak.

2. Subjects and methods

This study was approved by the Medical Research Ethics Committee of Kocaeli Derince Training and Research Hospital (No. 2022-12).

In January 2018, we identified a cluster of three patients whose blood cultures were reported to be positive for *B. cepacia* in a 60-bed pediatric ward of Kocaeli Derince Training and Research Hospital in Turkey. At that time, *B. cepacia* was an uncommon microorganism and it had not been previously detected in our pediatric clinic. In the present study, we included 12 patients who were hospitalized in the pediatric ward between January 16, 2018 and January 23, 2018 and those who developed a bloodstream infection a few days after hospitalization and whose blood cultures were reported to be positive for *B. cepacia*.

Inclusion criteria were based on hospital-acquired infection as per the US Centers for Disease Control and Prevention (CDC) guidelines[6]. Outbreak cases were defined as patients with a clinical suspicion of sepsis (fever, tachycardia, tachypnoea, leukocytosis, or leukopenia, with or without hypotension) and who were reported to be positive for *B. cepacia*. An outbreak was defined as the simultaneous presence of more than two patients with positive blood cultures for *B. cepacia*. We thoroughly examined all cases, with special attention on diagnosis of hospitalized patients, underlying diseases of the patients, drugs used in the treatment, and interventional procedures performed.

When the outbreak occurred, the hospital infection control committee launched an investigation. Epidemic site visits were organized to identify the source and the transmission process of the infection. Contact precautions were taken in all cases and patients were cohorted in the pediatric ward. To determine the source of the outbreak, environmental cultures were collected from the sinks, faucets, tap water, hand soaps, surface cleaners, and oxygen outputs. In addition, samples were collected from various fluids and medications, including hypertonic saline solutions, total parenteral nutrition fluids, intravenous fluids, sterile distilled water, antiseptic, and antibiotic solutions.

All the blood cultures were collected in BacT/ALERT aerobic blood culture bottles (bioMérieux, France). They were incubated and monitored regularly using the BacT/ALERT system (bioMérieux, France). All bottles with a positive signal were Gram stained and cultured on blood agar and Eosin Methylene Blue agar. Phenotypic identification was confirmed with a VITEK® 2 (bioMérieux, France). The VITEK® 2 Compact device was used to determine the antibiotic susceptibility of trimethoprim-sulfamethoxazole, where Kirby-Bauer Disk Diffusion Susceptibility Test was used to test other antibiotic susceptibility occurrences.

Normally distributed quantitative variables were expressed as mean±standard deviation, whereas non-normally distributed quantitative variables were expressed as median with interquartile ranges. All analyses were conducted using SPSS 20 software (IBM SPSS Statistics, New York).

3. Results

Twelve cases were identified between January 16 to January 23, 2018 (Figure 1). The patients were located on two different wards, pediatric ward and pediatric surgery ward. The index cases were a 2-year-old boy and a 3-year-old girl hospitalized for pneumonia. Among the 12 patients, 7 were girls and 5 were boys. The patients' median age was 6.5 years (ranged from 2-14 years). Furthermore, 10 of the patients were diagnosed with pneumonia, 1 with bronchiolitis, and 1 with acute appendicitis. Respiratory panels were examined in patients hospitalized due to acute lower respiratory tract infection. H1N1 influenza, respiratory syncytial virus, and rhinovirus were detected in 5, 1, and 1 patients, respectively. None of the patients had an underlying disease or a central venous catheter. The median duration of hospitalization before the onset of bacteremia was 4.1 days (ranged from 3-7 days). The primary diagnosis and main characteristics of the patients are shown in Table 1.

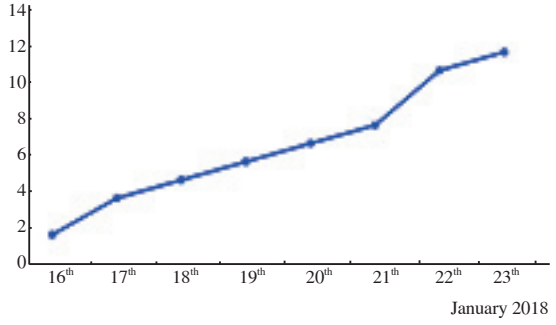

Figure 1. Cumulative number of patients with *Burkholderia cepacia* bacteremia from 16th January 2018 to 23th January 2018.

All patients had clinical symptoms of bacteremia and the median values of C-reactive protein and procalcitonin levels were 100.1 mg/L (ranged from 62.6-213.0 mg/L, reference range 0.68-3 mg/L) and 11.6 ng/mL (ranged from 3.43-138.7 ng/mL, reference range 0.15-2.0 ng/mL), respectively. Six patients developed thrombocytopenia. The day of hospitalization when *B. cepacia* bacteremia developed

Table 1. Demographic and clinical features of patients who developed *Burkholderia cepecia* bacteremia.

Patient No.	Age (years)	Sex	Clinical diagnosis	Date of bloodstream infection	Length of stay before bloodstream infection (day)	Treatment received	Underlying disease	Coexistence of viral pathogen
1	2	Male	Pneumonia	January 16, 2018	4	Meropenem	No	Influenza A (H1N1)
2	3	Female	Pneumonia	January 16, 2018	4	Meropenem	No	Influenza A (H1N1)
3	5	Female	Pneumonia	January 17, 2018	5	Meropenem	No	No
4	2	Female	Pneumonia	January 17, 2018	4	Meropenem	No	No
5	4	Female	Pneumonia	January 18, 2018	3	Meropenem TMP-SMX	No	No
6	2	Female	Bronchiolitis	January 19, 2018	4	Meropenem	No	RSV
7	4	Female	Pneumonia	January 20, 2018	4	Meropenem	No	No
8	3	Female	Pneumonia	January 21, 2018	4	Meropenem TMP-SMX	No	Influenza A (H1N1)
9	13	Male	Pneumonia	January 22, 2018	3	Meropenem	No	Rhinovirus
10	14	Male	Acute appendicitis	January 22, 2018	3	Meropenem	No	Influenza A (H1N1)
11	2	Male	Pneumonia	January 22, 2018	7	Meropenem	No	Influenza A (H1N1)
12	2	Male	Pneumonia	January 23, 2018	4	Meropenem	No	No

TMP-SMX: Trimethoprim-sulfamethoxazole, RSV: Respiratory syncytial virus.

Table 2. Laboratory values of patients and hospital stay day who developed *Burkholderia cepecia* bacteremia.

Patient No.	Leukocyte (mm^3)	Platelet (mm^3)	CRP (mg/L)	Procalcitonin (ng/mL)	Hospitalization day
1	6 900	72 000	62.6	10.9	18
2	4 800	162 000	73.0	46.1	19
3	6 800	90 000	176.6	12.2	21
4	11 700	138 000	100.1	8.9	20
5	11 200	346 000	113.2	16.3	18
6	12 000	90 000	81.3	13.6	19
7	19 000	500 000	71.5	11.0	19
8	10 500	92 000	73.3	3.4	19
9	9 100	253 000	213.0	17.2	18
10	3 600	165 000	137.5	14.6	18
11	10 800	164 000	114.2	12.9	22
12	18 400	51 000	145.3	138.7	19

CRP: C-reactive protein.

and the laboratory values at that time are shown in Table 2.

The results of antimicrobial susceptibility tests revealed that all *B. cepacia* isolates associated with the outbreak showed a similar antibiogram, and they were sensitive to ciprofloxacin, meropenem, and trimethoprim-sulfamethoxazole and were resistant to ceftazidime. A total of 10 patients (83.3%) received meropenem treatment and 2 (16.7%) received meropenem and trimethoprim-sulfamethoxazole treatment. The mean hospitalization duration of the patients was (19.25±1.26) days.

Environmental-source cultures from tap water, alcohol-free soap, disinfectants containing chlorhexidine, povidone iodine, ethanol, bed rails, nebulization medication, and drug samples containing water were negative. However, ground surface cleaners showed the presence of *B. cepacia* cultures. The cultures of the unopened ground surface cleaning drums belonging to the same batch repeatedly showed positive culture results. The antibiotic susceptibilities of Burkholderia isolates were identical to each other and to those isolated from patients. This indicates that this outbreak was caused by the contamination of ground surface cleaners. The results were communicated to the manufacturer and products of that brand were withdrawn from the hospital.

Hospital infection control procedures were immediately implemented to prevent further spread of the outbreak following the four consecutive cases. Hospital staff, nurses, and doctors received recurrent training on hand hygiene compliance and disinfection of the environment. General ambient disinfection was performed twice consecutively. The cultures collected from the infected patients and the recollected ambient sample cultures did not show colonization. The outbreak was terminated and no new cases occurred as a result of the efforts aimed to control the outbreak. No complications were observed in the patients infected with *B. cepacia*. No patients died and they were discharged in good health.

4. Discussion

Clusters of infections should be investigated immediately because health care-associated infection (HCAI) outbreaks constitute an important cause of morbidity and mortality. Indications that urge investigation include detecting HCAI clusters caused by

an uncommon microorganism, a common microorganism with an unusual pattern of antimicrobial susceptibility, or a series of infections occurring in the same anatomical region[1]. *B. cepacia* is one of the major causes of HCAI outbreaks owing to its resistance to a number of antimicrobial agents and disinfectants[2]. Published research on outbreaks covers an invaluable resource because it provide insight into potential causes. In their compendium, Abdallah *et al.* summarized the 30 BCC outbreaks in patients without cystic fibrosis admitted to neonatal, pediatric, and adult ICU. The source of the outbreak was determined *via* genotyping in 16 of the 21 outbreaks and by similar antibiograms in isolates in 5 outbreaks without genotyping[7]. The contaminated products detected in the BCC outbreaks at the pediatric ICU and neonatal ICU were liquid docusate, skin antiseptic containing 0.5% chlorhexidine glucose, Ⅳ caffeine citrate, lipid emulsion stopper, Ⅳ fluids, Amikacin vial rubber stopper, and suction apparatus[4,7–11]. Two consecutive nosocomial *B. cepacia* outbreaks occurred in a Malaysian hospital neonatal unit, 1 year apart. These two outbreaks could have been taken under control by implementing general infection control measures; however, the sources of these two outbreaks could not be identified[12]. Antony *et al.* suggested that the source of the *B. cepacia* outbreak at the pediatric ICU was the distilled water on the grounds and that the insulates collected from the patients and distilled water had the same biotype and antibiogram[13]. Detailed epidemiological research and phenotypic identification methods may prove to be important components of epidemic management in cases, where molecular methods cannot be used to determine whether the isolates are of the same origin.

We did not detect *B. cepacia* in any of the ambient isolates tested except for the ground surface cleaner as a result of epidemiological investigation with regard to the *B. cepacia* bacteremia in children admitted to our pediatric service. We concluded that the *B. cepacia* outbreak was caused by contaminated ground surface cleaner. This conclusion was drawn on the basis of the following parameters: the clinical and ambient source isolates had similar antibiotic susceptibilities, a single common source was identified, and the outbreak was terminated upon removal of the source.

As with many opportunistic pathogens, although *B. cepacia* does not typically result in clinical infection when it colonizes immunocompetent individuals, it was reported as a source of HCAI in immunosuppressed patients and usually occurs in the form of a sepsis[2]. Bacteremia associated with *B. cepacia* was observed in 14 children over a 10-year period at a children's hospital in Korea. With an exception of one patient, most children had an underlying medical condition, such as cancer, congenital heart disease, chronic granulomatous disease, and prematurity, and 12 children had a history of intensive care admission[14].

Unlike other studies, none of our patients had a known underlying disease, or a history of intensive care admission, or central venous catheter. Most of the inpatients were admitted for lower respiratory tract infections.

It is difficult to treat the *B. cepacia* infections since these opportunistic pathogens are highly resistant to antibiotics. *B. cepacia* has intrinsic resistance to aminoglycosides, polymyxins, and β-lactam antibiotics, and variable resistance to chloramphenicol, fluoroquinolones, meropenem, and trimethoprim/sulfamethoxazole. Ceftazidime, minocycline, meropenem, levofloxacin, chloramphenicol, and cotrimoxazole are recommended in the treatment of bloodstream infections with *B. cepacia*. Treatment with two or more agents may prove to be necessary to control the infection and prevent the development of resistance[1,2]. The antibiotic sensitivity patterns of the clinical and source isolates were similar in our study. The isolates were susceptible to co-trimoxazole, levofloxacin, and meropenem, and were resistant to ceftazidime.

Epidemic investigation is absolutely necessary to control the nosocomial pathogens. A multidisciplinary approach is necessary to determine the source and adopt successful interventions. The source may not be found despite adequate supervision and investigation. Removal of the source upon identification therefore is an important step to limit the spread of the epidemic. In order to end the epidemic, infection control measures, including the implementation of hand hygiene policies, training, patient cohorting, contact measures, visitor restrictions, advanced ambient hygiene, and disinfection should be considered together.

The limitation of our study is that owing to technical deficiencies and lack of equipment in our hospital, genotypic molecular methods could not be employed. However, the same approach proved itself to be a valuable asset in epidemic analyses to determine that the microbial agents are the same.

In conclusion, it should be noticed that nosocomial *B. cepacia* outbreak may occur in immunocompetent children as well. It is necessary to quickly identify the source and implement strict hospital infection control measures and administer appropriate treatment to successfully manage the outbreak and achieve better clinical outcomes.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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Authors' contributions

CC developed the theoretical formalism, performed the analytic calculations and performed the numerical simulations. Both CC and UA authors contributed to the final version of the manuscript.

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