Outbreak of catheter-related *Burkholderia cepacia* sepsis acquired from contaminated ultrasonography gel: the importance of strengthening hospital infection control measures in low resourced settings

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SUMMARY

This article reports the largest nosocomial outbreak of *B. cepacia*-related hospital acquired infections (HAIs) and the epidemiological investigations leading to identification of ultrasound gel as a direct means of infection transmission. Multiple environmental sampling was conducted to identify the source and route of infection. The samples were collected from all sources considered to be potential reservoirs of *B. cepacia*. Standard methods for pathogen isolation and antibiotic sensitivity testing were used. Overall, 61 patients developed *B. cepacia*-related sepsis and this agent was isolated only from ultrasonography gel. All patients required the placement of a central venous line to receive the chemotherapy for the underlying hematologic disease. The hospital outbreak persisted after identification of the source of infection and it took more than four months to be completely eradicated after the first cases. *B. cepacia* is a serious threat for hospitalized patients needing invasive procedures, including the central line placement for chemotherapy, regardless of the need of any intensive care. Implementation of protocols for active surveillance of HAIs should also target this opportunistic agent and include periodic sterility control of commonly used medical materials, including ultrasonography gel and equipment.

Keywords: *Burkholderia cepacia,* hospital-acquired infections, catheter-related sepsis, ultrasonography gel.

INTRODUCTION

Burkholderia cepacia is a Gram-negative, catalase-positive, non-fermentative rod-shaped bacterium, which is commonly found in water and soil and, in particular, it can survive for long time in moist environments [1]. *B. cepacia* represents an important clinical problem in patients affected with cystic fibrosis, who can develop severe and drug-resistant pulmonary infections [2]. Indeed, *B. cepacia* can resist most hospital disinfectants and antiseptics, which increases the risk of dissemination in the clinical departments, leading to the occurrence of hospital-acquired infections (HAIs) [3]. Chronic diseases (such as cancer, diabetes mellitus, chronic heart failure, etc.) as

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well as invasive procedures (such as tracheal intubation, central vein catheterization, hemodialysis, indwelling urinary catheters etc.) and, in general, being admitted and staying in the intensive care units (ICUs), are all risk factors for *B. cepacia* infections [4-7].

HAIs caused by *B. cepacia* can derive from the contamination of a wide range of products for medical use, such as solutions for infusion and nebulization, eye drops, chlorhexidine disinfectants, blood-gas analyzers and even ultrasonography gel [8-10]. However, most reports about *B. cepacia*-related HAIs refer to patients admitted in the ICU and/or affected with cystic fibrosis. Here, we report the largest nosocomial outbreak of severe HAIs (catheter-related sepsis) due to *B. cepacia* so far, whose origin was connected to the use of contaminated ultrasonography gel, based on the epidemiological investigation in the hospital.

MATERIALS AND METHODS

Clinical setting

This report and the related epidemiological investigations refer to a tertiary care center, including also clinical departments of oncology, hematology, solid organ and stem cell transplantation for adults. These clinical activities are supported by specialized ICUs for surgery and hematological patients, respectively.

All patients of both genders who met the following inclusion criteria were included in this analysis:

1) age ≥18 years;
2) patients treated in hematology ICU;
3) presence of clinical or laboratory criteria of sepsis (in accordance with Surviving Sepsis Guidelines' Criteria for Sepsis Diagnosis);
4) confirmed *B. cepacia* isolation (blood culture).

Sixty-one cases of central line-related sepsis (among patients with hematological malignancies receiving bone marrow transplantation) were attributed to *B. cepacia*-related HAI, from March 2018 till August 2018. All patients developed fever, lethargy and hypotension.

Initial outbreak investigation and management

After the first case of *B. cepacia*-related sepsis was confirmed, the hospital infection control department was alerted. Epidemiological and environmental investigations were conducted to identify the source and route of infection dissemination: sets of samples were collected from all sources considered to be potential reservoirs of *B. cepacia*, including water reservoirs, antiseptic products, respiratory devices and sink drains. All the devices and equipment used in the department (mechanical ventilators, syringes, infusion systems, pumps) and potentially contaminated surfaces were considered. Of course, even samples of gel used for ultrasound-guided central line placement were analyzed.

Laboratory diagnosis

Blood samples from central venous catheters and catheter tips were taken for microbiological analysis from all patients who developed clinical manifestations consistent with sepsis. These biological samples were analyzed by using standard microbiological methods (such as Gram staining, study of colony morphology and biochemical properties); then, isolated bacterial strains were tested for antibiotic susceptibility through the Kirby-Bauer disk-diffusion technique, according to Clinical and Laboratory Standards Institute (CLSI) specifications.

Data extraction and analysis

After the microbiological diagnosis of the first cases was established, an epidemiological investigation was initiated by the Department of infection control. Patients' clinical and demographic data (including admission dates into the hematology department and/or hematology ICU, age, gender, hematological diagnoses, dates and types of central line catheterization, blood cultures, medications - including chemotherapy, antimicrobial resistance, clinical outcomes) were extracted from the electronic hospital information system (EHIS). All these data were retrospectively analyzed.

Ethical clearance

The Ethical clearance for this study was obtained from the Ethics committee of the Institutional Review Board of Nazarbayev University (Nazarbayev University Institutional Research Ethics Committee, NU-IREC, approval of June 20th, 2019) and, additionally, an authorization letter for publication was obtained from the medical direction of the hospital.

RESULTS

Patients' demographic and clinical characteristics

During the period from March to August 2019, 61 cases of *B. cepacia*-related sepsis were recorded. All patients were either from hematological department or hematological ICU. There were no case of *B. cepacia* HAIs identified in other departments. The main demographic and clinical characteristics of these patients are shown in Table 1. Overall, the patients' mean age was 35 year (range 18-60 years); 31 patients were males and 30 were females. As mentioned, all patients were affected with hematological diseases (hematological malignancies: 70.6%; lymphomas: 27.8%; aplastic anemia: 1.6%) undergoing bone marrow transplant.

The most common manifestations of *B. cepacia*-related sepsis were fever > 38°C, elevated C-reactive protein level, sinus tachycardia (heart rate >100 per minute), tachypnea (respiratory rate >20) and hypotension (blood pressure <90/60 mmHg). Importantly, all 61 patients were neutropenic.

All patients received a combination of intra-venous (IV) sulfamethoxazole (100 mg/kg/day) and meropenem (1500 mg/day), in addition to the supportive therapy (*e.g.*, intravenous fluids, electrolytes, blood products), as outlined in Table 2. Six patients developed sepsis-induced hypotension/shock and multiple organ dysfunction/failure syndrome and, thus, received vasopressors (norepinephrine, epinephrine) and dexmedetomidine (for sedation), in order to provide them mechanical ventilation after tracheal intubation.

Table 1 - Baseline characteristics, demographics, diagnosis and outcomes.

Hematological disease	*Values*	
	n	%
Acute lymphoblastic leukemia	6	9.8
Acute myeloblastic leukemia	26	42.7
Hodgkin lymphoma	16	26.2
Acute promyelocytic leukemia	4	6.6
Chronic myeloid leukemia	1	1.6
Extra-nodal NK/T-cellular lymphoma	1	1.6
Myelodysplastic anemia	2	3.3
Multiple myeloma	4	6.6
Aplastic anemia	1	1.6

Table 2 - Main treatments received by patients developing *B. cepacia* sepsis.

Clinical characteristics	*Values*	
	n	%
Patients receiving blood products	61	(100)
Patients developing septic shock	6	(9.8)
Patients receiving vasopressors	6	(9.8)
Patients developing multiple organ failure syndrome	6	(9.8)
Lethal outcomes	6	(9.8)

Microbiological findings

All *B. cepacia* isolates resulted to be sensitive to sulfamethoxazole and meropenem. As regards further tested antibiotics, all isolates were sensitive to levofloxacin, ceftazidime, but they were resistant to ticarcillin-clavulanate and chloramphenicol. These results derived from the analysis of two sets of blood samples and central catheter tips.

Infection course and control measures

After the first 3 cases of *B. cepacia* sepsis were confirmed in the first two weeks of March, the hospital medical direction and the department of infection control started the procedures to monitor and control the situation. However, despite this general alert, around 3 cases per week occurred during the following 19 weeks, until the first week of August, when the last case was recorded. The incidence of these cases of *B. cepacia* sepsis was not constant during the outbreak period but showed an irregular course with 3 peaks (week-4: 6 cases; week-9: 7 cases; week-12: 11 cases). Anyway, most cases (n=40, 65.5%) occurred over a 9-week period, between the first week of April (week-5) and the second week of June (week-14). In the remaining 7-week outbreak period, the weekly incidence was 1-2 cases until the end. The outbreak timeline is graphically summarized in Figure 1.

Potential sources of infection were extensively searched: samples were collected from all sources considered or known as potential reservoirs of *B. cepacia*, as described previously, but only the gel used for ultrasound guided central line placement provided positive microbiological results for the presence of *B. cepacia*. Accordingly, all invasive procedures were carefully reviewed,

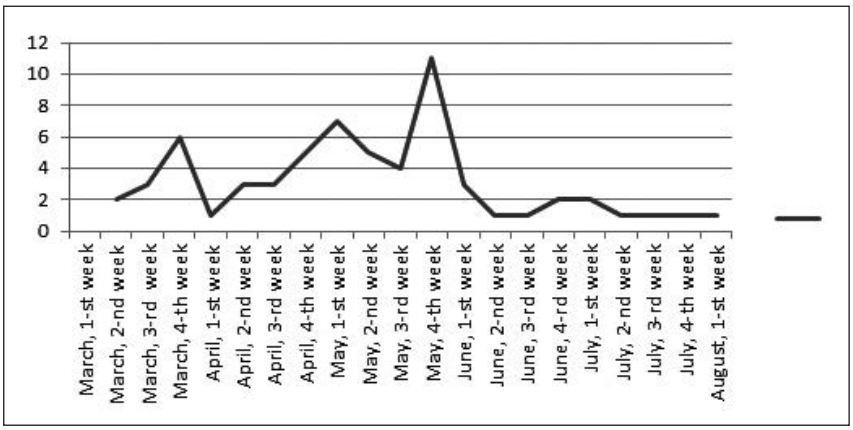

Figure 1 - Outbreak timeline (cases per week).

even though the central line catheterization was always performed by trained intensivists taking advantage of ultrasound guide for central vein catheterization. The procedures were performed in sterile conditions (documented) using standard technique. The dispensers and detergents were substituted and the hands cleansing technique was reviewed and monitored. Maintenance of the catheters was managed by trained and dedicated intensive care nurses. The entry points of catheters were cleaned with cotton balls soaked in 0.5% chlorhexidine gluconate solution on the daily basis. *B. cepacia* was identified in the gel on March 20th and the contaminated gel was immediately replaced with new batches. However, during the period from April to August, 55 new cases were identified, despite all efforts to control the infection and the implementation of procedures for hospital decontamination. During a two-year follow-up period starting from August 2018, there were no new cases of *B. cepacia* sepsis detected.

DISCUSSION

ICU-related HAIs result in prolonged ICU and hospital stay, increase morbidity, mortality and cost of treatment [11]. The incidence of HAIs in developing countries can reach 15% among hospitalized patients and up to 50% in ICU patients, which poses a significant burden on healthcare [12]. Additionally, pathogens that cause HAIs frequently develop multidrug and, in some cases, pandrug-resistance making the process of antibiotic selection and treatment extremely challenging [13].

To our knowledge, here we reported the largest outbreak of *B. cepacia*-related HAIs. In details, we described 61 cases of sepsis in patients affected with hematological diseases requiring the placement of central venous lines. *B. cepacia* is an opportunistic microbe that usually colonizes the respiratory airways and, indeed, represents the major cause of morbidity and mortality in patients affected with cystic fibrosis [2]. However, due to its wide distribution in the environment, as mentioned in the introduction, *B. cepacia* is a serious threat for all immunocompromised patients, especially those needing intensive care treatments. In this clinical setting, systemic and severe infections associated with *B. cepacia* bacteremia have been widely described, due also to its resistance to commonly used skin disinfectants. However, this outbreak of *B. cepacia* HAIs was not caused by the contamination of disinfectants, IV drugs/fluids or other common medical devices (or specific components of them) directly used to provide the intensive care needed by these 61 patients. Moreover, the contamination of all water reservoirs and supplies was ruled out. The analysis of additional potential - even though less common - means of contamination have been performed, leading to the identification of the gel used for the ultrasound-guided placement of central catheters, as source of this hospital outbreak.

Not so many experiences of *B. cepacia* HAIs due to ultrasonography gel contamination have been reported in the medical literature so far. The first well-documented report was published by Hutchinson J et al. in 2004 [14]. They reported six unrelated cases from two hospitals in Canada, which occurred between 2000 and 2002. Among

them, only one was affected with hematological malignancy, whereas all the remaining patients were diagnosed with a bacteremia starting from urinary tract infection without any underlying comorbidity impairing the immune function. In 2010, the same group (Organ M et al.) published an article re-discussing some of the previous cases and they emphasized the relationship of *B. cepacia* infection with the invasive procedure of transrectal prostate biopsy [15]. Actually, the very first description about this kind of complication dated back to 1993, when Keizur JJ et al. reported the occurrence of "*Pseudomonas cepacia* cystoprostatitis" in 9 out of 110 patients undergoing transrectal ultrasound guided needle biopsy of the prostate [16]. In 2015, Nannini EC et al. reported the first hospital outbreak involving as many as 11 patients, most of them receiving intensive care, over a 3-month period [17]. Actually, seven patients were neonates hospitalized in the neonatal intensive care unit (NICU), whereas three were identified in the ICU and one in the general ward as well. Recently, two reports describing *B. cepacia* HAIs in the ICU because of contaminated gel, have been published (both in 2018). Abdelfattah R et al. described 14 cases occurred in 2016: like in the present study, these infections resulted from the contamination of the ultrasound gel used during the procedure of central line insertion [18]. Yamunadevi VR et al. observed 24 episodes of *B. cepacia* bacteremia in the ICU in a 6-month period between 2016 and 2017 [19].

Thus, the present article described the largest outbreak of ultrasonography gel-related *B. cepacia* HAIs, but the most significant (and concerning) point of this experience is the persistence of the outbreak even after the isolation of this primary source of infection and, thus, the elimination of all contaminated supplies.

Unfortunately, this report has several limitations. First, like several healthcare institutions in other developing countries, our medical center experienced the constraint of financial and laboratory resources needed for a precise and complete epidemiological investigation and microbiological genotyping. However, it is important to raise the attention on *B. cepacia* HAIs, which can be very difficult to be managed and controlled, especially in countries with limited resources. Actually, this experience underlines the importance of immediate actions and procedures for the environmental recovery in the hospital, which may have not been extensive and appropriate for the aforementioned reasons. Another limitation is that we performed several interventions for the eradication of *B. cepacia* but, unfortunately, we cannot precisely identify which one of them resulted in (or contributed to) the outbreak resolution.

In our opinion, two main practical messages derive from this experience. First, the hospital should implement an appropriate plan of HAIs surveillance, which must include the periodic control of medical supplies, such as ultrasonography gels. Indeed, after the identification of a cluster of multidrug-resistant Gram-negative bacteria in a general ward of an Italian hospital, Marigliano et al. implemented the extensive *B. cepacia* contamination of all gel bottles circulating at that time in the institution [20]. As a consequence, they suggested a routine sterility control of ultrasound gel, along with the implementation of guidelines for its appropriate management in the clinical practice, especially if any intensive care is provided. Indeed, no infections occurred in these hospitalized patients, because the gel was used in patients without immune and/or skin defects, probably. Previously, Jacobson M et al. investigated the contamination of ultrasound gel to explain the sustained endemicity with intermittent outbreaks of *B. cepacia* HAIs in the Hospital for Sick Children in Toronto. Here, *B. cepacia* resulted to be most frequent contaminant of ultrasonography gel by far [8].

The second important message is that the eradication of the environmental contamination by *B. cepacia* can be extremely difficult, especially in clinical and social contexts with limited resources. Of course, all potential contaminated medical devices and products were eliminated and replaced, but the *B. cepacia* outbreak did not stop right after the identification of the ultrasound gel, as main source of infection, despite the measures implemented to recover the hospital setting. Therefore, the ultrasound gel was supposed to act as "direct" meant of infection transmission to the patients, but other sources of environmental persistence of *B. cepacia* must have been implicated. The survival of *B. cepacia* is possible on many environmental surfaces, but that is more likely when the bacterium is suspended in secretions and, thus, in clinical settings whereby patient with cystic fibrosis are managed [21]. Anyway, the medical and

nursing staff could be a potential carrier and repeatedly contaminate some equipment, including the ultrasound gel. Unfortunately, our investigation cannot address this specific aspect, because the limited technical/microbiological resources did not allow to establish the specific *B. cepacia* strain(s) involved in the hospital outbreak.

Indeed, the sampling of multiple environmental sources (*e.g.* bed rails, linen, stethoscopes, carts, ICU furniture, mechanical ventilators and its contours, walls) has been included among the strategies for the successful management of a hospital outbreak of *B. cepacia* infections in a neurotrauma ICU [22]. Furthermore, detergent and disinfectants were analyzed.

Recently, Santos-Cruz E et al. reported the eradication of an ICU outbreak by a Bundled Environmental Hygiene Approach (BEHA). The "pre-cleaning environmental samples revealed *B. cepacia* from multiple high-touch surfaces" [23]. Importantly, only two months after the terminal cleaning of the ICU and the implementation of all BEHA procedures, no further cases of *B. cepacia* infection were recorded. Moreover, the environmental sampling should include also the healthcare workers, which could be done at regular intervals [22]. Unfortunately, BEHA requires a significant effort in terms of organization and costs and, thus, could not be implemented - or not completely - in hospital settings with restricted resources. However, the appropriate management and storage of the ultrasound gel should be a feasible objective for future, along with the implementation of a "care bundles" approach for the prevention of central line-associated bloodstream infections (CLABSI), which include a set of evidence-based measures to create a safer patient care environment [24]. Such an approach has been demonstrated to be effective also in under-resourced settings of low- and middle-income countries (such as Kazakhstan), where HAIs and the related antimicrobial resistance are actual and important challenges [24, 25]. It was previously recommended that regular infection control audits, rational antibacterial therapy, and general hygiene maintenance should be the most important measures for preventing HAIs in developing countries [23]. In order to improve hospital infection control and patient-related outcomes, there is a need to continuously collect and analyze not only pathogen-related data but also patient related data (past medical and history of present illness, physiological data from monitoring systems, laboratory data, invasive and surgical procedures) [26]. This is only a single report of ICU-related HAIs (*B. cepacia* sepsis) in a tertiary Kazakhstani medical center, which does not allow to make any approximate conclusion about the situation in other regions of the country; therefore, organizing an integrated nation-wide monitoring center with and the hospital infection control departments in each medical center could be beneficial for systematically studying and controlling HAIs at the national level.

In conclusion, *B. cepacia* is a serious threat for hospitalized patients needing invasive procedures, including even a simple central line placement for chemotherapy, no matter if intensive care is needed. The implementation of protocols for active surveillance of HAIs should be addressed to this opportunistic agent as well, and include the periodic sterility control of commonly used medical materials, including the ultrasonography gel and equipment. This experience demonstrated that, in order to reduce or prevent HAIs outbreaks, it is essential to strengthen the infection control measures and to monitor the invasive procedures techniques, paying attention to appropriately maintain medical devices, equipment and consumables.

Conflict of interest

No conflict of interest to declare.

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Author contribution

DV contributed to design, DV, MK, VK and AZ contributed to data collection, DV conceived and drafted this article. DV and DP wrote the manuscript; DP provided significant intellectual contribution and reviewed the related medical literature. DV and DP contributed equally in writing.

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