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CLINICAL AND EPIDEMIOLOGICAL STUDY

An outbreak of *Burkholderia cenocepacia* bacteremia in immunocompromised oncology patients

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Abstract
Background *Burkholderia cepacia* is a common environmental bacterium that is resistant to disinfectants, and therefore is often encountered as a hospital-acquired pathogen. We describe an outbreak of *B. cenocepacia* bacteremia among hospitalized oncology patients.
Methods A matched case–control study and an extensive environmental investigation were conducted. Species were identified by RFLP of the amplified *recA* gene. DNA was fingerprinted by pulsed-field gel electrophoresis (PFGE).
Results Between November 2005 and September 2006, *B. cenocepacia* bacteremia developed in 17 patients with underlying malignancy of whom 14 had tunneled central venous catheters. All patients had fever and chills which subsided following removal of the central catheter and administration of ceftazidime. Extensive epidemiological investigation could not find a common source for the outbreak. Patients were hospitalized in three different buildings with different health care personnel. Medications were prepared in different sites by different personnel. A multivariate analysis demonstrated that the independent risk factors for developing nosocomial *B. cenocepacia* bacteremia were hospitalization at the center for long-term support (OR 28.8; 95% CI 1.83–453.4) and reduced use of antibiotics during the last month (OR 0.07; 95% CI 0.01–0.40). All isolates had identical antimicrobial susceptibility; PFGE indicated that a complex of closely related strains was involved in the outbreak. All isolates were identified as *B. cenocepacia*, known to infect cystic fibrosis patients. Strict infection control measures terminated the outbreak.
Conclusions *B. cenocepacia* is an emerging nosocomial pathogen among oncology patients.

Keywords *Burkholderia cenocepacia* · Immunocompromised patients · Bacteremia

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Introduction

Burkholderia cepacia complex (Bcc) are environmental bacteria, commonly found in moist environments [1]. Bcc are emerging pathogens among cystic fibrosis (CF) patients [2], and their resistance to disinfectants and antiseptics is blamed for them becoming hospital-acquired pathogens [3–20]. The clinical syndromes of Bcc infection range from asymptomatic carriage to necrotizing granulomatous

pneumonia in CF patients [2], and bacteremia or pneumonia among hospitalized patients [3–20]. Most patients acquiring Bcc bacteremia have serious co-morbidities such as chronic hemodialysis, diabetes mellitus, congestive heart failure, and malignancy. Risk factors for contracting the bacteria in-hospital include hemodialysis, intensive care admission, central venous catheters, indwelling urinary catheters, and endotracheal tubes [3–23]. Nosocomial outbreaks due to Bcc have been recognized on at least a few occasions and were traced to contaminated products in the hospital, mainly water and various disinfectants and antiseptics. *B. cepacia* was isolated in 0.2% of all ventilator-associated pneumonias reported to the National Nosocomial Infections Surveillance System (NNIS) in the United States between 1998 and 2004 [15], and accounted for 0.7% of all nosocomial isolates in Turkey [24]. Bcc infections in Israel are very rare, even among CF patients [25].

Recent taxonomic studies have shown that analysis of the *recA* gene of Bcc provides a rapid approach to identify and classify this taxonomically complex group of opportunistic pathogens [26, 27]. Organisms presumptively identified as *B. cepacia* constitute at least nine species (genomovars), collectively known as the *Bcc* which comprises: *B. cepacia* (I), *B. multivorans* (II), *B. cenocepacia* (III-A, III-B), *B. stabilis* (IV), *B. vietnamiensis* (V), *B. dolosa* (VI), *B. ambifaria* (VII), *B. anthina* (VIII), and *B. pyrrocinia* (IX). Although all species have been associated with infections in humans, *B. cenocepacia* and *B. multivorans* are the most common isolated Bcc species among CF patients [28, 29]. Most Bcc isolates from nosocomial infections and outbreaks are described as Bcc without further differentiation to species. However, *B. cenocepacia* [9, 12, 17], *B. cepacia* [18], and *B. stabilis* [19] were identified in a few nosocomial outbreaks.

From November 2005 to September 2006, we observed an outbreak of *B. cenocepacia* bacteremia involving 17 immunocompromised patients. In this report, we describe the epidemic and its investigation.

Patients and methods

Setting

Sheba Medical Center is a 1,470-bed tertiary care medical center in Israel. The hospital has 80–90 beds for immunocompromised patients distributed in the departments of bone marrow transplantation, hematology, oncology, internal medicine, HIV, pediatric heamto-oncology, and the Long Term Support Center which serves as a children center for palliative care (hospice). The medical center also has a large outpatient unit for patients with CF.

Study design

A matched case–control study was conducted in order to determine the risk factors for developing *B. cenocepacia* bacteremia in non-CF immunocompromised hospitalized patients. Cases were patients hospitalized between November 1, 2005 and September 30, 2006 who had a blood culture positive for *B. cenocepacia* ($n = 17$). Matched controls were defined from patients admitted to the same department during the same period without contracting *B. cenocepacia* bacteremia ($n = 44$). Risk analysis included age, gender, cause for admission, underlying malignancy, co-morbidities using the Charlson score, date and duration of hospitalization, departments in which patient was hospitalized during the month preceding the bacteremia, type of bone marrow transplantation (allogeneic, autologous), presence of neutropenia, type of intravenous line (peripheral, Hickman, Port-A-Cath, peripheral inserted central line), presence of indwelling urinary catheter or other foreign body, and medication administered before the bacteremia. The severity of bacteremia was evaluated according the Pitts bacteremia score [30]. Mortality was assessed during hospitalization and during the subsequent 30 days. Exposure variables before the date of onset of *B. cenocepacia* bacteremia were measured for cases and controls. All data were abstracted from the medical records and electronic databases of the patients using a standardized questionnaire and then entered into a database (Microsoft Access). The local institutional review board approved the study.

Infection control practices

The work schedules of healthcare workers, including physicians, nurses, respiratory therapists, radiology personnel, and pharmacists was reviewed. They were interviewed, and their execution of different procedures, including catheters insertion, preparation, and administration of medication were observed.

Environmental investigation

Environmental samples were collected from the water supply, sinks, drains, air conditioning systems, shower heads, ice and coffee machines, cleaning and disinfection solutions, distilled water, sterile saline, intravenous fluids, vials of lidocaine and epinephrine, various drugs administered in the departments, dressings, cotton wool, inhaled

medications, ventilators, anesthesia equipment, hand lotion, mouthwash, and other liquid reservoirs in patients' rooms. Samples were obtained from the blood bank (blood products, centrifuge, refrigerator, collection bags, and environmental surfaces), the radiology department (solutions, topical anesthetic agents, environmental surfaces), and the pharmacy (solutions, environmental surfaces). Sputum samples were obtained from pharmacy personnel with persistent cough.

Laboratory methods

All microbiology laboratory records from October 1, 2005 through September 30, 2006 were reviewed for both blood and non-blood isolates of Bcc. Blood cultures were carried out using the Bactec 9240 (Becton, Dickinson, Sparks, MD, USA). Blood isolates of Bcc were prospectively collected and processed according to standard practice. Fluid was passed through a 0.45-μm filter (Pall, Ann Arbor, MI, USA). Disinfectants containing alcohol, aldehydes, chlorine compounds or phenolic ingredients were first diluted in nutrient broth (Brain heart infusion broth). Environmental cultures were collected on several days during the outbreak, and were placed in enrichment broth overnight and then streaked for isolated colonies on MacConkey agar and TSA plus 5% sheep blood [31]. Suspicious bacterial colonies were then identified by Vitek I (Biomerieux, France). Antibiotic susceptibility was determined by the disc diffusion method according to the recommendation of the Clinical and Laboratory Standards Institute [32].

The bacterial species was confirmed by 16S rDNA and *recA* species-specific polymerase chain-reaction analysis [26]. Discrimination between species was made by PCR of the *recA* gene obtained with primers BCR1 (5′ TGA CCG CCG AGA AGA GCA A 3′) and BCR2 (5′ CTC TTC TTC GTC CAT CGC CTC). In cases of positive PCR, the product was digested with 20 units of *Hae*III or *Mnl*I (Invitrogen Life Technologies, Milan, Italy) for 1 h, and electrophoresed on 2.5% agarose gel in TAE 1× buffer. Strain relationship was analyzed by pulsed-field gel electrophoresis (PFGE) following *Spe*I digestion [33]. Clonality was identified based on the recommendations of Tenover et al. [34].

Statistical analysis

Data was analyzed with SPSS version 14.0. Continuous variables were compared by the Student's t test. Odds ratios and their 95% confidence intervals were calculated for categorical variables using the Mantel–Haenszel χ^2 test for matched analyses or by the Fisher exact test. Variables with $p < 0.2$ were entered into a logistic regression model, where significance was set at $p < 0.05$.

Results

Description of cases

Seventeen patients developed *B. cenocepacia* bacteremia between November 2005 and September 2006 (Fig. 1). This was a significant increase from the baseline of zero Bcc isolates throughout the years 2000–2004. Furthermore, from 2000 to September 2006, Bcc was not isolated from any specimen except blood in the Sheba Medical Center.

Table 1 shows the demographic and clinical characteristics of cases. Thirteen were males and 4 females, 11 adults and 6 children, of median age 27 years (range 2–67). All patients had underlying malignancies: acute leukemia (6), lymphoma (3 non-Hodgkin's lymphoma, 1 Hodgkin's lymphoma) and multiple myeloma (3). Four patients had solid tumors (Wilms tumor, osteosarcoma, renal cell tumor, and neuroblastoma). Eight patients underwent bone marrow transplantation (6 allogeneic, 2 autologous). Ten patients were neutropenic.

The outbreak involved patients hospitalized in five different departments located in three different buildings of the medical center: the general hospital, the pediatric hospital and the Long Term Support Center for children, each located 500 m apart. Seven patients were hospitalized at the pediatric hematoncology department, five at the adult hematology department, two at the Long Term Support Center for children, and two at the adult oncology department. One patient was hospitalized at the bone marrow transplantation department. Sixteen patients were treated before the bacteremia with various

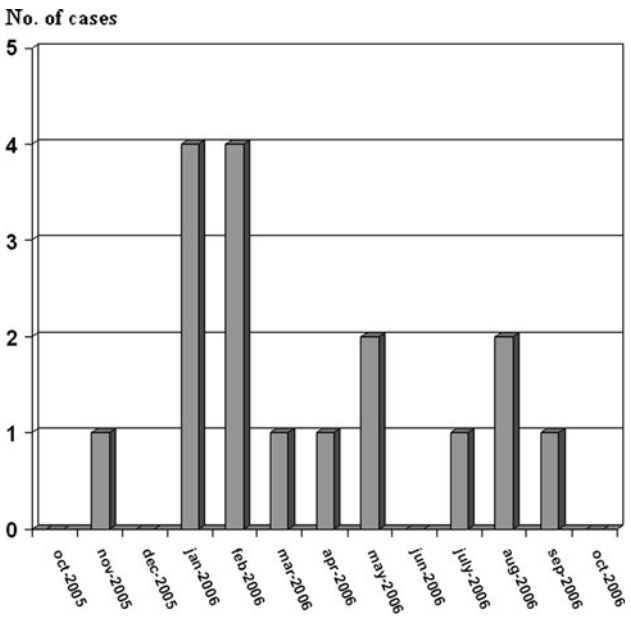

Fig. 1 *B. cenocepacia* bacteremia in the Sheba Medical Center from November 2005 to September 2006

Table 1 Clinical and demographic data of 17 cases with *B. cenocepacia* bacteremia

No.	Age (years)	Gender	Date of bacteremia	Diagnosing department	Underlying disease	Prior chemo-therapy (days)	BMT/ neutropenia[a]	Line/interval from line insertion (days)	Pitts score	Duration of bacteremia (days)
1	67	M	07/11/2005	Adult hematology	MM	240	Autologous/+	Hickman/14	3	2
2	2	M	04/01/2006	PHO	ALL	18	No/+	Hickman/22	0	5
3	17	M	05/01/2006	PHO	Lymphoma	150	No/−	PICL/127	2	5
4	24	M	08/01/2006	PHO	Lymphoma	510	Allogeneic/+	Hickman/8	0	1
5	31	M	30/01/2006	Adult hematology	Lymphoma	210	Allogeneic/+	Peripheral/7	2	1
6	51	M	12/02/2006	Adult hematology	MM	150	Allogeneic/+	Permacath/7	3	8
7	52	F	12/02/2006	Adult hematology	AML	6	No/+	Peripheral/9	0	6
8	41	M	15/02/2006	Adult hematology	ALL	30	No/−	Hickman/7	1	3
9	6	F	21/02/2006	LTSC	Solid tumor	540	Autologous/−	PICL/102	2	3
10	65	F	08/03/2006	Adult oncology	Solid tumor	0	No/−	Peripheral/19	1	8
11	25	M	29/04/2006	PHO	Lymphoma	30	No/−	PICL/27	3	2
12	19	M	16/05/2006	PHO	AML	180	Allogeneic/+	Hickman/12	0	5
13	66	M	30/05/2006	BMT	AML	200	Allogeneic/+	Hickman/8	2	10
14	56	F	11/07/2006	Adult oncology	MM	120	No/−	Peripheral/1	0	1
15	12	M	20/08/2006	PHO	Solid tumor	30	No/−	PICL/6	0	11
16	3	M	21/08/2006	LTSC	Solid tumor	150	No/+	Hickman/38	0	3
17	8	M	06/09/2006	PHO	ALL	1,400	Allogeneic/+	PICL/65	1	7

PHO Pediatric hemato-oncology, *LTSC* Long Term Support Center, *BMT* bone marrow transplantation, *ALL* acute lymphatic leukemia, *AML* acute myelocytic leukemia, *MM* multiple myeloma, *PICL* peripheral inserted central line

[a] + Yes, − no

chemotherapeutic agents for 6–1,400 days (median 150 days). Six patients had bacteremia on admission, while in 11 patients the bacteremia developed after 6–17 days (median 7 days) of hospital stay. Thirteen patients had central venous catheters including Hickman catheters (7), peripheral inserted central line (5), and Port-A-Cath (1). Four patients had peripheral venous access. The mean interval between the insertion of a central line and the diagnosis of bacteremia was 32 days (range 7–127 days). The bacteremia was associated with the venous access in six patients: in five, the bacteremia developed immediately following flushing the central line with saline; another patient developed an exit-site infection. The catheters were removed and cultured in all patients; however, *B. cenocepacia* grew only in one patient with exit-site infection. All patients had fever and chills, one developed septic shock. The mean Pitts bacteremia score was 1.18 (Table 1). Mean duration of bacteremia was 3 days (range 1–11 days). Sixteen patients were treated for a mean of 3.5 days (range 1–10 days) with empiric antibiotics that were inappropriate for *B. cenocepacia.* All patients recovered following ceftazidime therapy, together with removal of the central catheter.

All patients received intravenous fluids, 15 received various chemotherapeutic agents, 13 received granisetron, and 9 received blood products.

Case control study

Matched univariate analysis demonstrated that cases were treated with antimicrobial therapy in the month prior the admission significantly less than the controls ($p < 0.001$). Control patients were treated with chemotherapeutic agents significantly longer than case patients ($p = 0.05$), as detailed in Table 2.

Analysis of all departments in which patients were hospitalized during current admission found that 6/17 (35%) and 4/44 (9%) of cases and controls, respectively, were hospitalized in the Long Term Support Center for children ($p = 0.013$). Case and control patients were statistically similar with respect to age, gender, underlying disease, prior hospitalization, bone marrow transplantation, presence or type of central line, renal functions, mechanical ventilation, or history of bronchoscopy. No association was found between exposure to any particular group of medications and the development of *B. cenocepacia* bacteremia.

In multivariate analysis, the independent risk factors for developing nosocomial *B. cenocepacia* bacteremia were hospitalization at the Long Term Support Center for children (OR 27.65; 95% CI 1.66–460.69) and reduced use of antibiotics during the preceding month (OR 0.05; 95% CI 0.09–0.35).

Table 2 Risk factors for nosocomial bacteremia with *B. cenocepacia* (univariate and multivariate analysis)

Characteristic	Cases $n = 17$	Controls $n = 44$	*P*	Adjusted odds ratio[a]	95% confidence interval
Age	32 ± 23	33 ± 22	0.91		
Male gender	13 (77%)	27 (61%)	0.27		
Underlying disease (lymphoproliferative malignancy/solid tumor)	13/4	33/11	0.95		
BMT	8 (47%)	21 (48%)	0.96		
Previous hospitalization	13 (77%)	38 (86%)	0.35		
Chemotherapy	16 (94%)	37 (84%)	0.3		
Chemotherapy (days)	233 ± 340	502 ± 654	0.05	1	1.00–1.01
Antibiotic therapy during last month	3 (19%)	31 (70%)	<0.001	0.05	0.09–0.35
Central venous catheter	13 (77%)	34 (77%)	0.95		
Insertion of urinary catheter	2 (12%)	7 (16%)	0.68		
Hospitalization in the LTSC during last month	6 (35%)	4 (9%)	0.013	27.65	1.66–460.69
Creatinine	1.11 ± 0.9	0.85 ± 0.35	0.12		

LTSC Long Term Support Center, *BMT* bone marrow transplantation

[a] Data were analyzed for parameters with significant values

Significantly more episodes of severe hypotension developed during the current admission among the cases (11/17) than among controls (40/44; $p = 0.013$). None of the patients with *B. cenocepacia* bacteremia died, while 7/44 of the controls died ($p = 0.08$).

Review of work schedules of healthcare workers

Neither was any single healthcare worker common to all cases, nor was any single drug commonly administered to all bacteremic patients. The medical personnel in each unit did not work in the other departments where the outbreak occurred. Heparin, bicarbonate, and leukoverin were administered to patients from multidose bottles, but we did not find exposure to these medications to be more common among case patients than control patients. We identified a few common materials (non-sterile cotton-wool, dressings, IV fluids, etc.), but they did not grow *B. cenocepacia*.

Microbiological study

All isolates were resistant to all antibiotics except ceftazidime, meropenem, cotrimoxazole, and minocycline. *RecA–Hae*III analysis of strains identified as Bcc, found that all had a typical restriction profile of *B. cenocepacia* IIIB. Three closely related genotypes were identified on PFGE generated by *Spe*I digestion: the same genotype was demonstrated among strains 1–5, 7–9, 11, 13–17; deletion of one band in strains 6, 10; and an additional band in strain 12 (Fig. 2).

Environmental studies

All environmental cultures did not grow *B. cenocepacia*. Sputum obtained from one health care worker with chronic cough did not grow *B. cenocepacia.*

Epidemic-control measures

Investigation was initiated after the first two case patients were diagnosed, but the source of the outbreak could not be found. Following implementation of strict infection control measures, which included contact precautions for all patients with *B. cenocepacia* bacteremia and restricting the reuse of heparin ampoules and non-sterile cotton balls, the transmission chain was interrupted and the outbreak was terminated.

Discussion

Outbreaks or pseudo-outbreaks due to Gram-negative environmental species have been reported, and Bcc were recognized as the cause of nosocomial infections in at least a few occasions [3–20]. Most reports documented nosocomial transmission of Bcc in CF patients associated with contaminated respiratory equipment and via person-to-person [35]. In addition, Bcc were reportedly transmitted in CF summer camps [36]. However, in non-CF patients, some outbreaks were described among patients undergoing long-term dialysis [7, 13, 17, 20] and among patients hospitalized in intensive care units [8, 9, 14, 15, 23] as well as in oncology departments [3, 18, 19].

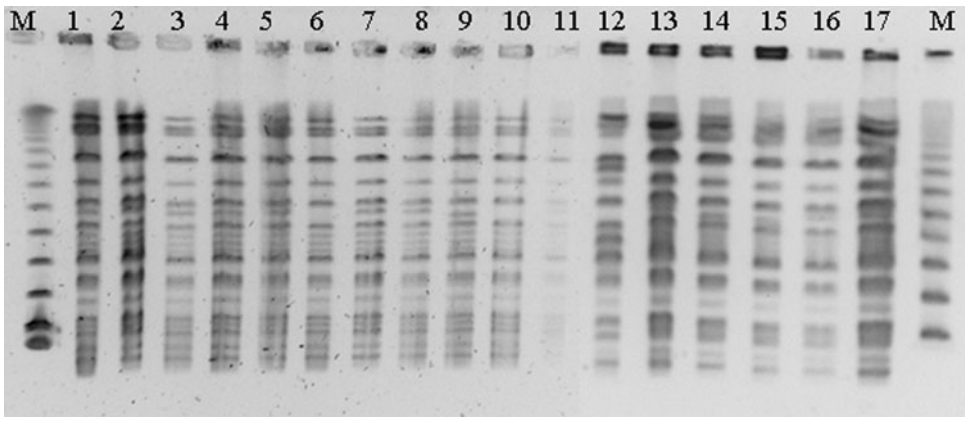

Fig. 2 Pulsed-field gel electrophoresis analysis of *Spe*I-digested genomic DNA of the studied *B. cenocepacia* isolates recovered from patients (*M* lambda ladder size marker, *lanes 1–17* isolates obtained from patients)

Bcc outbreaks were previously traced to contaminated products in the hospital, including tap, distilled, or deionized water [11], chlorhexidine [7, 19, 20], and quaternary ammonium solutions [17]. Other outbreaks were traced to mouthwash [8], albuterol nebulizer solution [5, 15], infusion solutions [3, 6, 16], blood-gas analyzers [4], capped rubber stoppers [10], and sterile napkins [17]. In two of the outbreaks among oncology patients reported in the literature, the source of the bacteremia was related to central venous catheters that were flushed with intravenous fluid from a multiple-use bag contaminated with Bcc [3, 18, 19]. In the current outbreak, only 13/17 patients had a central venous catheter, and in only 6 was the bacteremia associated with the venous access.

The clinical course of the bacteremia in our center was mild, with a mean Pitts bacteremia score of 1.18, despite inappropriate antibiotics administered for a mean of 3.5 days in 16 patients. All patients recovered following removal of the central catheter together with ceftazidime therapy. In contrast to our observation of no mortality, the overall case fatality rate of Bcc bacteremia reported in the literature is high (11–100%) [12, 14, 16–18]. Despite the tendency of certain Bcc species to cause severe disease among CF patients, a similar association could not be found in Bcc nosocomial infections; the mortality rate varied from 0 to 100% in two different outbreaks due to *B. stabilis* bacteremia [14, 19].

Despite our extensive investigation, the source of *B. cenocepacia* associated with the current outbreak was not found. A complex of three closely related strains was involved in this outbreak. The involvement of closely related strains among the patients is interesting and suggests a single source of contamination. Hospitalization at the Long Term Support Center for children in the month prior to the bacteremia was an independent risk factor for developing nosocomial *B. cenocepacia* bacteremia, although all environmental cultures from this center were negative for the bacterium; furthermore, not all cases were hospitalized there before the bacteremia. Antibiotic therapy during the month preceding the bacteremia was protective, probably reflecting the relative mild disease in the case patients; this is also evident from the low mortality. The finding that the outbreak strain in this study was a highly antibiotic-resistant *B. cenocepacia* raises the potential of a human source for this outbreak, but the possibility that a healthcare worker infected with *B. cenocepacia* was a potential source of this outbreak could not be documented. Furthermore, *B. cenocepacia* was not recovered from any CF patient who received care at our medical center. Although the environmental investigation in the current outbreak was performed according to routine published methods [31], we did not use an enrichment broth containing selected carbon sources and antimicrobials or O/F agar for the isolation of Bcc, as was suggested by Vermis et al. [37]. Furthermore, despite extensive epidemiologic investigation, the source of infection is often not identified [9, 12, 14].

Molecular diagnostic techniques based on PCR provide a rapid and highly discriminatory means of microbial identification. Nucleotide sequence polymorphism in the 16S rRNA gene is widely used for bacterial taxonomy; however, it has limited ability to differentiate the Bcc [38]. RecA is a protein essential for repair and recombination of DNA. Amplification of *recA* with primers BCR1 and BCR2 can be used as an initial means of placing an isolate within the Bcc; after successful amplification of *recA*, RFLP with *Hae*III and *Mnl*I may be used to place the isolate within a specific genomovar or *recA* group [26, 27, 39, 40]. Recently, it was found that MLST could identify Bcc isolates which were not identified by means of *recA* RFLP and species-specific PCR [41, 42]. Detection of *cblA*, the cable pilus gene [43], and a novel marker, *ecfB* [44], are new attractive targets for identification of undefined Bcc. However, in our study, *RecA–Hae*III analysis of strains demonstrated the same typical restriction profile of *B. cenocepacia*, so further studies were not necessary.

Despite their close relationship, Bcc species have a differential capacity for human infection. The majority of Bcc infections in CF patients in western countries are caused by *B. cenocepacia* (genomovar III), and many studies have shown that CF patients infected with this species suffer clinical complications and high mortality [28, 29, 39]. The genomovar III can be further classified into *III-A* and *III-B* based on the *recA* gene [26]. Genomovar *III-A* is currently the most prevalent and transmissible genomovar in CF patients, and is dominant in Canada, UK, and Italy [12]. The majority of reported Bcc nosocomial infections and outbreaks among non-CF patients were not characterized to the species level; however, *B. cenocepacia* was one of the most common reported species [9, 12, 17]. *B. cenocepacia* III-B, the causative agent of the present outbreak, was the species responsible for a napkin-associated outbreak of *B. cenocepacia* bacteraemia in haemodialysis in Italy [17]. The difference between Bcc species may be related to virulence factors or, alternatively, this could reflect differences in the prevalence of Bcc species in the natural environment. The ET12, PHDC, and the Midwest clone are *B. cenocepacia* strains, which were recently characterized among CF patients, and were found to be more transmissible or better adapted to human infection than other Bcc species [45].

Infection control is important in preventing Bcc infection among persons with CF [46]. The Centers for Disease Control and Prevention guidelines recommend the cohorting of Bcc colonized or infected CF patients and the placing of them in contact isolation [47]. Implementation of these measures has led to decreased nosocomial transmission [48]. The optimal infection control measures for management when non-CF patients are involved are still unknown. Our experience supports using barrier precautions for patient management, as these measures limited the extent of transmission among our patients. Furthermore, single-dose bottles of medication should be used when possible, especially when the medication is for patients with indwelling intravenous catheters. Appropriate aseptic technique and education of health care workers can decrease the risk of such outbreaks in the future.

Conflict of interest statement None.

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