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Original Article

Successful management of a *Bacillus cereus* catheter-related bloodstream infection outbreak in the pediatric ward of our facility☆

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ABSTRACT

Bacillus cereus can spread easily in various environments and can contaminate medical environments, such as ventilator equipment, intravascular catheters, and linen. *B. cereus* is known to infect immunocompromised patients. Although nosocomial *B. cereus* outbreaks are often reported, effective preventive measures are not clarified. We report an outbreak of *B. cereus* catheter-related bloodstream infection (CRBSI) in the pediatric ward and aim at identifying risk factors and effective infection control measures for the outbreak. The nurse station at the pediatric ward and blood cultures were assessed. Sterilization of devices has been ensured thereafter. We identified common risk factors including catheter placement for liquid nutrition, use of high-caloric amino-acid-containing infusion fluid, immunocompromised patients, and contact of the catheter route with the floor. Intervention by the Infection Control Team and educating the medical staff regarding methods of disinfection, including scrubbing the facility, helped terminate the outbreak. We discuss a pre-emptive intervention to terminate the outbreak of CRBSI.

1. Introduction

B. cereus is a gram-positive sporulating bacillus that grows extensively in naïve environments, such as soil, water, and in mammals including humans [1]. Furthermore, it colonizes in medical environments, including linen, towels, and on the skin of patients and healthcare professionals [2].

B. cereus causes nosocomial infections especially in immunocompromised patients [3–5]. Healthcare-associated infections are inevitable in hospitalized immunocompromised hosts in the absence of complete preventive and control measures. Although nosocomial *B. cereus* outbreaks are often detected [6,7], effective preventive measures have not been developed.

Current preventive measures against nosocomial infections include prevention of contact with the source(s) of infection [8]. In this context, ensuring thorough hand hygiene in daily operations, improvement of the environment for intravenous drip equipment, thorough sterilization of the connection device of the drip route, and monitoring of the cleanliness of the drip route are essential to prevent catheter-related bloodstream infection (CRBSI).

In the spring of 2016, three patients with *B. cereus* CRBSI manifested at two-week intervals in the Pediatric ward. Infection Control Team (ICT) members educated the medical staff in the Pediatric ward and investigated the causes of this outbreak. On detecting the pathogens, prompt measures were taken; hence, these infections did not expand to severe nosocomial infections. Our investigation evaluated the size of the outbreak and also identified the risk factors for disease development; lastly, we aimed to implement appropriate control measures.

2. Methods

2.1. Epidemiological investigation

A case was defined as a patient who were hospitalized at the Pediatric ward of our facility during two months of spring in 2016,

Abbreviations: CVC, central venous catheter; CRBSI, catheter-related blood stream infection; ICT, Infection Control Team; PICC, peripheral inserted into central venous catheter; PVC, peripheral venous catheter.

☆ Authorship statement: All authors meet the ICMJE authorship criteria.

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had an indwelling infusion route, has shown feverish, resulting in positive *B. cereus* in blood culture.

CRBSI was defined as positive simultaneous blood cultures from intravenously sampled blood using catheters and peripheral blood yielding the same organism in the presence of at least one of the following: 1) simultaneous quantitative blood cultures with the CFU/mL of intravenous catheter-sampled blood ≥3 folds that of organisms isolated from peripheral blood, 2) positive semiquantitative (≥15 CFU/catheter segment) or quantitative (≥100 CFU/catheter segment) catheter tip cultures or 3) simultaneous blood cultures of equal volume wherein the central blood culture displays bacterial growth in an automated system ≥ 2 h earlier than peripheral blood culture.

2.2. Laboratory evaluation

We usually collect two sets of blood samples for culture via peripheral venipuncture and through catheters. Blood cultures are generally processed using BACTEC™ FX systems (Becton, Dickinson and Company, MD, USA) with either BACTEC™ PEDS Plus™/F or BACTEC™ Plus™ aerobic/F and anaerobic/F vials.

2.3. Devices and disinfection

A closed flush system, SurePlug® (Terumo Corporation, Tokyo, Japan), equipped with needleless connectors is used in our hospital. Before CVC or PICC insertion, we use maximal sterile barrier precautions, including povidone-iodine in alcohol to surface-sterilize the skin before insertion. Catheter site dressing is replaced once a week and disinfected with povidone-iodine. Before the procedure, we always surface-sterilize needleless connectors with individually packaged alcohol prep pads (containing 76.9–81.4% [v/v] ethanol; Hakujuji Co., Ltd. Tokyo, Japan) for antisepsis. Only sterile devices are used to access the needleless hubs.

2.4. Ethical considerations

The Research Ethics Committee of the University of Fukui approved this research (No. 20180035), and informed consent was obtained from the patients or their legal representatives.

3. Results

3.1. Descriptions of outbreak cases of B. cereus CRBSI

As shown in Table 1, this outbreak occurred during two months of spring 2016 and affected three patients. *B. cereus* CRBSI manifested in each patient at two-week intervals. They were hospitalized in individual rooms without connected air-conditioning ducts. During this outbreak period, three patients did not come into contact with each other. Patient 1's room was next to the Patient 3's room. Standard precautions were undertaken during that period.

3.1.1. Case 1

A 19-year-old woman with minimally differentiated acute myeloid leukemia was administered chemotherapy and an amino-acid-containing infusion through PICC. On the first day of the outbreak in this report, in 2016, she developed sepsis under the neutropenic state without any focal infectious. Meropenem (6 g/day) and vancomycin (3 g/day) were administered after harvesting certain specimens for microbiological culturing. PICC, catheterized for 81 days was removed because *B. cereus* was isolated from a couple of blood cultures. Although she recovered from sepsis after 3 days, brain abscess was detected. Hence, meropenem and vancomycin administration was continued for 12 and 9 weeks, respectively, until the abscess was obliterated. Finally, she recovered without any neurologic sequelae (Fig. 1).

3.1.2. Case 2

An 8-month-old boy with a hepatic malignant vascular tumor was also administered chemotherapy and an amino-acid-

Table 1
Cases of catheter-related blood stream infection due to *Bacillus cereus*.

	Case 1	Case 2	Case 3
Age	19 Y	8 Mo	12 Y
gender	female	male	female
Reason for admission	AML	hepatic malignant vascular tumor	anorexia nervosa
Treatment	chemotherapy, amino-acid containing infusion	chemotherapy, amino-acid containing infusion	amino-acid containing infusion
State of patient	neutropenia	neutropenia	malnutrition
Device (indwelling days)	PICC (81)	CVC (57)	PVC (9)
Onset of CRBSI[a]	1st day	14th day	28th day
Blood Culture	*B. cereus*	*B. cereus*	*B. cereus*
Antimicrobial Treatment	1) Meropenem, Vancomycin	1) Cefepime 2) Meropenem, Vancomycin	1) Meropenem, Vancomycin
Complications	brain abscess	none	none
Sensitivities of *B. cereus* isolated from cases			
Penicillin G	R	R	R
Ampicillin	S	R	R
Cefotaxime	I	R	I
Erythromycin	I	S	I
Clindamycin	S	S	S
Chloramphenicol	S	S	S
Vancomycin	S	S	S
Levofloxacin	I	S	S
Meropenem	–	–	S
Teicoplanin	–	–	S

AML: acute myeloid leukemia, PICC: peripherally inserted into the central venous catheter, CVC: central venous catheter, PVC: peripheral venous catheter, S: susceptible, I: intermediate, R: resistant.

[a] The date of onset in Case 1 was set as the first day of the outbreak.

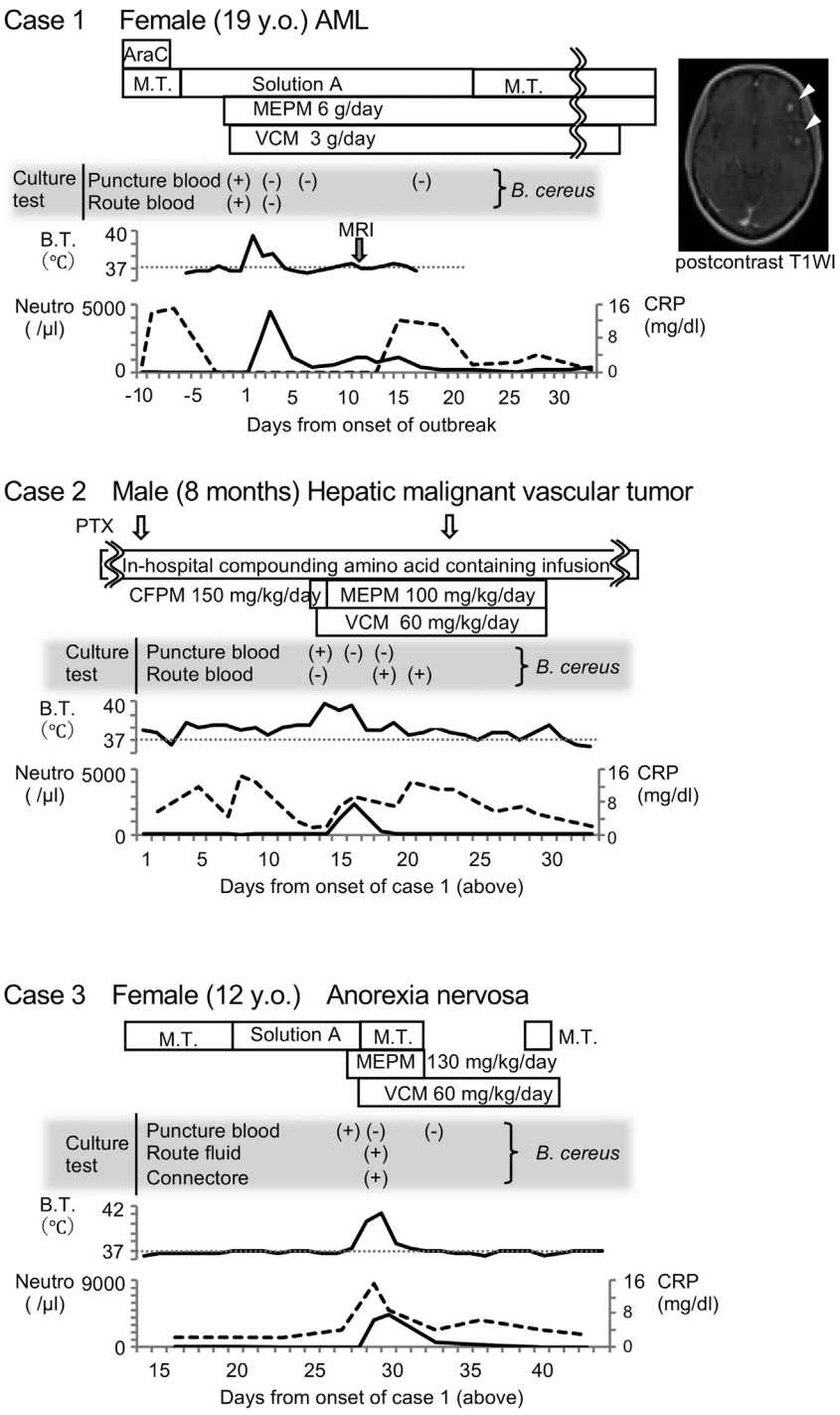

Fig. 1. Clinical course of each patient. MRI revealed brain abscesses on day 11 (arrowheads). Ara-C: cytarabine, Solution A: amino-acid containing infusion (composition is shown in Table 4), B.T.: body temperature, CRP: C-reactive protein, MEPM: meropenem hydrate, MRI: magnetic resonance imaging, M.T.: maintenance transfusion, PTX: paclitaxel, VCM: vancomycin hydrochloride.

containing infusion through CVC (Hickman Catheter, Medicon, Inc. Osaka, Japan). On the 14th day (since the first outbreak day in case 1), sepsis occurred under the neutropenic state without any focal infectious, and cefepime (150 mg/kg/day) was administered empirically. On the next day, *B. cereus* was isolated from a couple of blood cultures, meropenem (100 mg/kg/day) and vancomycin (60 mg/kg/day) were administered instead of cefepime, and CVC indwelled for 57 days was removed. He recovered from sepsis after 3 days without any sequelae (Fig. 1).

3.1.3. Case 3

A 12-year-old girl with anorexia nervosa was nasogastrically administered enteral nutrients and an amino-acid-containing infusion through PVC. On the 28th day (since the first outbreak day in case 1), she developed symptoms of sepsis without any focal infectious, and meropenem (130 mg/kg/day) was administered after obtaining microbiological cultures. When *B. cereus* was detected in blood cultures of Patient 2, ICT alerted the ward staff regarding the extraordinary rate of *B. cereus* CRBSI incidence. They

Infusion fluid	Electrolyte	Glucose (%)	Amino acid (g/L)	Relative Osmolality	pH
Solution A	Na^+, K^+, Cl^-, Ca^{2+}, Mg^{2+}, Zn^{2+}, lactate, phosphate, citrate, acetate, sulfate	7.5	30	3	6.7
Solution B (Saline)	Na^+ , Cl^-	0	0	1	3.5~6.5
Solution C (5% Glucose)	-	5	0	1	3.5~6.5
Solution D (10% Glucose)	-	10	0	2	4.0~6.0
Solution E	Na^+, K^+, Cl^-, $Lactate^-$, Phosphate	5	0	2	4.0~6.0
Solution F	Na^+, K^+, Cl^-, lactate, phosphate, acetate	10	0	3	4.0~6.0
Solution G	Na^+, K^+, Cl^-, lactate, phosphate, acetate, sulfate	17.5	30	5	5.3

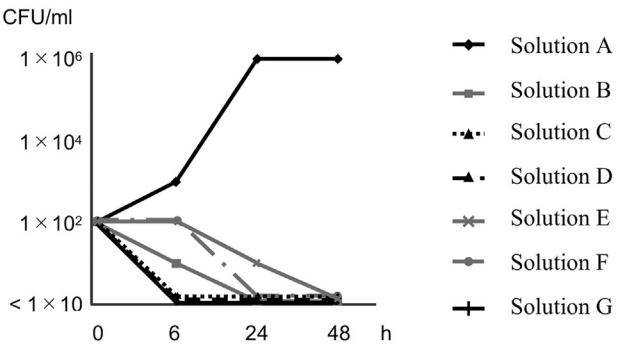

Fig. 2. Growth of *B. cereus* in various infusion fluids, based on their constituents. Reproduced with the author's permission (Sakai et al. Shimane J Med Technol 2012 [11]).

immediately implemented interventions. Next day, therefore, PVC was replaced with vancomycin (60 mg/kg/day) because *B. cereus* was isolated from two blood cultures. After 2 days, *B. cereus* was detected from the catheter hub and the internal fluid. She had received meropenem and vancomycin for 7 and 15 days, respectively. Finally, she recovered from the infection after 3 days without any complications (Fig. 1).

3.2. Assessment result of the outbreak

When *B. cereus* was detected in blood cultures of Patient 2, ICT alerted the ward staff regarding the extraordinary rate of *B. cereus* CRBSI incidence. They immediately implemented interventions, and Patient 3 was immediately treated with antibiotics to which *B. cereus* displays susceptibility. Finally, this outbreak was terminated after the infection was reported in Patient 3. Because microbiological examination revealed differences in antibiotics susceptibilities of *B. cereus* isolated from the patients, no genetic screening was conducted. No new patients in the ward simultaneously developed *B. cereus*-induced bacteremia. Therefore, an environmental culture-based survey has not been performed.

At the time ICT intervened, containers for drip infusion bags, needles, route catheters, and other devices were scattered and in disorder on the medical treatment table and piled up carelessly (Fig. 3.1). Devices and medical instruments remained in disorder, without being returned from their designated spaces (Fig. 3.2). A drip infusion bag and other instruments and devices were hung around the drip stand (Fig. 3.3). The linen container was left beside the basin (Fig. 3.4).

3.3. Suspected risk factors for the outbreak of B. cereus CRBSI

In the present cases, common risk factors include the long length of catheter placement for liquid nutrition, the use of injection solution for high-calorie nutrition, immunocompromised patients, and contact of the catheter route with the floor. In general, long duration of catheterization is a risk factor for CRBSI [9]. In the present cases, detention lengths of the catheter were 81, 57, and 9 days, respectively (Table 1). An amino-acid-containing infusion (Solution A) containing characteristic elements, including 30 g/L amino acid, 7.5% glucose, and $NaHSO_3$ (50 ppm), thereby potentially enabling *B. cereus* growth in the catheter (Fig. 2, Tables 2 and 3). Malnutrition and/or chemotherapy for malignant cancers induce immunodeficiency. In all three cases, normal nutrition was not maintained, and immune perturbations were observed. Sometimes, it was necessary to extend their

Fig. 3. The nurse station. Containers on a medical treatment table (1), medical instruments on terminals (2), drip stand equipped with devices (3), and a linen container beside a basin (4).

Table 2
Constituent of infusion fluids used in the cases.

Solution	Case 1, 3	Case 2	Case 1, 3
	Solution A	In-hospital compounding amino acid containing infusion	Maintenance transfusion
Glucose	7.5%	26.1%	3.2%
Amino acid	30 g/L	24 g/L	0 g/L
Number of contained amino acids	18	19	0
Lipid	0 g/L	0 g/L	0 g/L
pH	6.7	–	3.5–6.5

Table 3
Composition of solutions.

	Composition (M/W%)	Electrolyte (mEq/L)	pH	Osmolarity Rate to saline
Solution B	Sodium chloride: 0.9	Na^+: 154, Cl^-: 154	4.5–8.0	1
Solution C	Glucose: 5.0	–	3.5–6.5	1
Solution D	Glucose: 10.0	–	3.5–6.5	2
Solution E	Sodium chloride: 0.117, Potassium chloride: 0.149, Dipotassium phosphate: 0.116, Potassium dihydrogen phosphate: 0.022, Glucose: 5.0	Na^+: 40, K^+: 35, Cl^-: 40, $Lactate^-$:20, Phosphate: 8 (mmol/L)	4.0–6.0	2
Solution F[a]	Sodium chloride: 0.117, Potassium chloride: 0.149, Dipotassium phosphate: 0.116, Potassium dihydrogen phosphate: 0.022, Glucose: 10	Na^+: 40, K^+: 35, Cl^-: 40, $Lactate^-$:20, Phosphate: 8 (mmol/L)	4.0–6.0	3

[a] Glacial acetic acid is added for pH adjustment.

catheter route when they moved. Medical staff including physicians often forgot to ensure the re-positioning of the catheter line. Furthermore, no precautions were taken to prevent the catheter route from contacting the floor.

3.4. Interventions for the outbreak and the outcome

Initially, we ensured that the medical staff scrubbed needleless connectors with alcohol pads before accessing the catheter hub by

Table 4
Composition of amino-acid-containing solutions.

Solution A[a]	
Essential Amino Acids (mg/dL)	
L-histidine	150
L-isoleucine	240
L-leucine	420
L-lysine	315
L-methionine	117
L-phenylalanine	210
L-threonine	171
L-tryptophan	60
L-valine	240
Non-Essential Amino Acids (mg/dL)	
L-alanine	240
L-arginine	315
L-aspartic acid	30
L-cysteine	30
L-glutamic acid	30
Glycine	177
L-proline	150
L-serine	90
L-tyrosine	15
Amino Acids (g/dL)	3
Total Nitrogen (mg/dL)	470
Glucose (g/dL)	7.5
Electrolytes (mg/dL)	
Potassium chloride	63.4
Calcium chloride hydrate	36.8
Magnesium sulfate hydrate	61.6
Zinc sulfate hydrate	0.14
Dipotassium phosphate	100
Dibasic sodium phosphate hydrate	154
Sodium citrate hydrate	57
Sodium lactate	229.0
Vitamins (mg/dL)	
Tiamine	0.15
Sodium hydrogensulfite (mg/dL)	5
Trace elements (μmol/L)	–

Solution G[a]	
Essential Amino Acids (mg/dL)	
L-histidine	300
L-isoleucine	480
L-leucine	840
L-lysine	629
L-methionine	2.34
L-phenylalanine	420
L-threonine	342
L-tryptophan	120
L-valine	480
Non-Essential Amino Acids (mg/dL)	
L-alanine	480
L-arginine	630
L-aspartic acid	60
L-cysteine	60
L-glutamic acid	60
Glycine	354
L-proline	300
L-serine	180
L-tyrosine	30
Amino Acids (g/dL)	3
Total Nitrogen (mg/dL)	470
Glucose (g/dL)	17.5
Electrolytes (mg/dL)	
Potassium chloride	74.6
Sodium lactate	165
Sodium chloride	205
Potassium dihydrogenphosphate	82.1
Calcium chloride hydrate	37
Magnesium sulfate hydrate	62
Potassium acetate	108
Vitamins (mg/dL)	
Thiamine	0.153
Riboflavin	0.36
Pyridoxine	0.202
Cyanocobalamine	0.25 μg/dL
Nicotinic acid amide	2
Panthenol	0.7
Folic acid	0.02
Biotin	3 μg/dL
Ascorbic acid	5
Vitamin A oil	165 IU
Cholecalciferol	0.25 μg/dL
Tocopherol acetate	0.5
Phytonadione	0.1
Sodium hydrogensulfite	3
Trace elements (μmol/L)	
Iron	17.5
Manganese	0.5
Zinc	30
Copper	2.5
Iodine	0.5

[a] Glacial acetic acid is added for pH adjustment.

the recommendations of the guidelines for the Prevention of Intravascular Catheter-Related Infections [10]. To physically eliminate *B. cereus* spores, we recommend scrubbing for 15 s. As additional measures, re-education was provided to the medical staff regarding hand hygiene, and new protocols were established regarding the exchange of PVC every 72 h on having established the administration of an amino-acid-containing infusion. Furthermore, protocols regarding the environmental arrangement around the drip preparation table have been established. After intervention by ICT, we terminated the outbreak and thereafter no *B. cereus* CRBSI occurred for more than two years.

4. Discussion

We realized the possibility of a healthcare-associated outbreak of *B. cereus* CRBSI and conducted the survey immediately. Because microbiological examination revealed differences in antibiotics susceptibilities of *B. cereus* isolated from the patients, no genetic screening was conducted. None of the new patients in the ward simultaneously developed *B. cereus*-induced bacteremia. *B. cereus* is known to colonize in medical environments. Therefore, an environmental culture-based survey has not been conducted. We hypothesized that the outbreak was caused by contamination of infusion fluids with *B. cereus* through inadequate disinfection of catheter hubs and handling of infusion lines. We developed pivotal methods to eliminate bacterial contamination from the catheter device and educated medical staff regarding standard precautions for preventing the outbreak. Consequently, we could terminate the chain of infections without allowing its expansion.

Sakai et al. [11] analyzed the effects of the components of infusion fluids on *B. cereus* growth *in vitro*. As shown in Fig. 3, among the examined infusion fluids, *B. cereus* grew only in an amino-acid-containing infusion (Solution A, Table 4). It was supposed that the optimum growth factors for *B. cereus* were two or more amino acids and pH approaching 7.0. Thus, the infusion fluid used for Patients 1 and 3 may have favored the growth of *B. cereus*. When Solution A or similar amino-acid-containing infusions are intravenously administered, care should be taken to not contaminate the interior of the catheter.

According to the CDC guidelines for the Prevention of Intravascular Catheter-Related Infections 2011, disinfection of swiping devices with 70% alcohol for only 3–5 s is inadequate [12]. However, it is unknown which disinfection method is optimal for catheter devices [13]. To physically eliminate *B. cereus* spores, we referred to a previous report on the effect of scrub duration to disinfect contaminated catheter hubs with fluorescent powder [14]. Disinfection of devices for less than 10 s is inefficient. We supposed

that a period exceeding 15 s is an inconvenience to most healthcare professionals. Therefore, we recommend a 15-s scrubbing period.

Standard precaution to respect the five moments of hand hygiene is fundamental to measures against Healthcare-associated infections. Sasahara et al. [15] described that alcohol-based hand-rubbing is not effective for removing *B. cereus* spores from hands, and handwashing with soap is appropriate. Although washing hands with soap and water might be important when manipulate connectors of catheters, it was not essential for termination of the present outbreak.

ICT members lectured all of medical staff in our ward about the following: 1) 15-s scrubbing, 2) compliance with five moments of hand hygiene, and washing hands with soap and water before handling connectors, 3) wiping the supplies thoroughly, which was carried into the patient's zone, and 4) appropriate measure of environmental management should be adopted. These norms ware necessary to improve the prevention and control infection. Shimoyama et al. [16] generated an educational program for decreasing catheter-related bloodstream infections in intensive care units and reported that educational lectures held every 3 months significantly decreased the rate of primary systemic infections. Thus, the implementation of the educational program as part of mandatory training is useful in preventing CRBSI.

5. Conclusions

In conclusion, recognition of the possibility of a healthcare-associated outbreak of *B. cereus* systemic infection and early intervention by the ICT are essential for early termination of the outbreak. The use of high-caloric amino-acid-containing infusion fluid would be a risk factor of *B. cereus* bacteremia. Management of the intravenous infusion route, including needless hubs, and hand hygiene practices are critical in preventing CRBSI.

Conflict of interest statement

None.

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