MAJOR ARTICLE

Epidemiologic Investigation of a Cluster of Neuroinvasive *Bacillus cereus* Infections in 5 Patients With Acute Myelogenous Leukemia

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Background. Five neuroinvasive *Bacillus cereus* infections (4 fatal) occurred in hospitalized patients with acute myelogenous leukemia (AML) during a 9-month period, prompting an investigation by infection control and public health officials.

Methods. Medical records of case-patients were reviewed and a matched case-control study was performed. Infection control practices were observed. Multiple environmental, food, and medication samples common to AML patients were cultured. Multilocus sequence typing was performed for case and environmental *B cereus* isolates.

Results. All 5 case-patients received chemotherapy and had early-onset neutropenic fevers that resolved with empiric antibiotics. Fever recurred at a median of 17 days (range, 9–20) with headaches and abrupt neurological deterioration. Case-patients had *B cereus* identified in central nervous system (CNS) samples by (1) polymerase chain reaction or culture or (2) bacilli seen on CNS pathology stains with high-grade *B cereus* bacteremia. Two case-patients also had colonic ulcers with abundant bacilli on autopsy. No infection control breaches were observed. On case-control analysis, bananas were the only significant exposure shared by all 5 case-patients (odds ratio, 9.3; $P = .04$). Five environmental or food isolates tested positive for *B cereus*, including a homogenized banana peel isolate and the shelf of a kitchen cart where bananas were stored. Multilocus sequence typing confirmed that all case and environmental strains were genetically distinct. Multilocus sequence typing-based phylogenetic analysis revealed that the organisms clustered in 2 separate clades.

Conclusions. The investigation of this neuroinvasive *B cereus* cluster did not identify a single point source but was suggestive of a possible dietary exposure. Our experience underscores the potential virulence of *B cereus* in immunocompromised hosts.

Keywords. acute myelogenous leukemia; *Bacillus cereus*; central nervous system infection; infection control investigation.

Bacillus cereus is an unusual cause of nosocomial outbreaks and central nervous system (CNS) infections in immunocompromised patients [1, 2]. Five patients receiving chemotherapy for acute myelogenous leukemia

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(AML) developed neuroinvasive *B cereus* infection between May 2013 and February 2014 at Brigham and Women's Hospital (BWH) in Boston, Massachusetts. Four of the infections were fatal. We summarize the cases and investigation by the BWH infection control department, Boston Public Health Commission, Massachusetts Department of Public Health (MDPH), and the Centers for Disease Control and Prevention (CDC).

METHODS

Brigham and Women's Hospital is a 779-bed academic hospital with general medical and surgical services and a large oncology patient population. Cases were defined as *B cereus* blood or CNS isolates obtained from an AML patient with fever, neurological symptoms, and radiological evidence of acute CNS disease occurring >48 hours after admission. After the initial 5 cases were identified, we reviewed medical records of patients with *B cereus* isolated from any source from January 2011 through February 2014 and AML patients with unexpected deaths in 2013 to assess for other potential cases. We reviewed records of case-patients to collect information relevant to possible risk factors including room locations, medical staff contacts, procedures, medications, blood products, and dietary exposures. Multiple medication samples, environmental swabs, and air samples from areas shared by AML patients were sent for microbiologic culture. Pharmacy, interventional radiology, blood bank, nursing, and kitchen practices were observed.

A matched case-control study was performed to assess risk factors, including medications, procedures, and dietary exposures. Controls were randomly selected among patients hospitalized for AML treatment within the same month for an equal or longer duration than the time to onset of illness for each case (defined as the start of recurrent fever before *B cereus* bacteremia and/or neurological deterioration). The number of controls per case depended upon the availability of medication (4 controls), procedures (4 controls), and dietary (1–4 controls) exposure data. Odds ratios and *P* values were calculated using Fisher's exact test. Due to the small number of cases, the analysis focused only on exposures that were common to 4 or more case-patients. Some 2-by-2 tables contained cells with a value of zero; for these exposures, odds ratios and *P* values were calculated by adding .5 to each cell. There were too few case-patients to construct a multivariable regression model.

Microbiologic, Pathologic, and Genomic Analysis

Standard histologic methods were used for perioperative or post mortem tissue samples, and standard microbiological methods were used in our laboratory to identify *Bacillus* species in blood and tissue cultures. Confirmatory support was performed by investigators at the CDC using pan-eubacterial 16S ribosomal DNA polymerase chain reaction (PCR) and a *Bacillus*-specific antibody for immunohistochemistry staining.

Genomic DNA was extracted from patient-derived (blood or CNS cultures) and environmental *B cereus* isolates using the QIAamp DNA mini kit (as per manufacturer's instructions) preceded by lysis with lysozyme. Multilocus sequence typing (MLST) was performed as previously described [3]. Barcoded sequencing libraries were prepared using the Nextera XT kit per manufacturer's instructions (Illumina, San Diego, CA), and paired-end whole genome sequencing (WGS) was performed (minimum sequencing coverage was 195 million bases per organism). Sequencing reads were computationally assembled using SPAdes, a graph theory-based assembly tool (http://bioinf.spbau.ru/spades) using paired-end default parameters. Multilocus sequence typing sequences were identified from these assembled sequences, by homology, using the BLASTn aligner. Multilocus sequence typing sequences were extracted and concatenated. The concatenated MLST sequences were aligned using MUSCLE (http://www.ebi.ac.uk/Tools/msa/muscle/), and a phylogenetic tree was generated using FastTree (http://www.microbesonline.org/fasttree/). This tree was generated using the neighbor joining method with 1000 resamplings.

Per discussion with the Partners Human Research Committee, Institutional Review Board approval was not sought because this study was done as part of a public health and infection control investigation.

RESULTS

Case-Patient Description and Clinical Investigation

No additional case-patients were found after reviewing records of patients with *B cereus* isolates and AML patients with unexpected deaths. The clinical characteristics, hospital courses, and relevant neuroimaging and pathology findings for the 5 case-patients are summarized in Table 1. All 5 case-patients were hospitalized to receive induction or salvage chemotherapy for AML and developed severe neutropenia with an absolute neutrophil count <100/mm^3. The median age was 49 years (range, 32–58), and 4 of the case-patients were female. All developed neutropenic fevers early on that rapidly resolved with empiric antibiotics (typically cefepime). All had either abdominal pain or significant nausea with vomiting. Fevers recurred in all patients more than 1 week later (median time of onset, 17 days; range, 9–20) with concurrent headaches and neurological changes. Abnormalities on neuroimaging included abscesses, infarctions, intraparenchymal and subarachnoid hemorrhages, leptomeningeal enhancement, cerebral edema, and brainstem herniation. Vancomycin was initiated around the time of neurologic decompensation in all cases.

Case-patient 1, the sole survivor, underwent neurosurgical drainage of her brain abscess on hospital day 28, 8 days after developing fever, headache, and blurry vision; intraoperative cultures were negative, but samples sent to the CDC were

Table 1. Clinical Characteristics of Five Neuroinvasive *Bacillus cereus* Case-Patients

Case no., Age/Sex, Admit Date	Chemo Regimen	Preceding GI Symptoms	Timing of Illness	Symptoms at Time of Illness	Abxs Prior to Illness	Positive *B cereus* Blood Cultures?	Neuroimaging	Outcome	Pathology
Case 1, 32F, May 2013	Induction (7 + 3)	(+) Abd pain, n/v, diarrhea	HD20	HA, blurry vision	VM, CP CZ, CT	No	Occipital lobe abscess	Survived	Surgical pathology: Brain abscess with *B cereus* detected by PCR and IHC.
Case 2, 58F, May 2013	Induction (7 + 3)	(+) n/v; no abd pain or diarrhea	HD17	HA, AMS, seizures	CP, CZ, AM	No	Multifocal infarction	Expired	Autopsy: Brain abscess with *B cereus* isolated from cultures and consistent histopathology. Ascending colon ulceration with *Bacillus* species identified by IHC.
Case 3, 54F, Sept 2013	Salvage (Ara-C + CAFdA)	(+) Abd pain; no n/v or diarrhea	HD13	HA, AMS, seizures	CP, CZ	Yes	Leptomeningeal enhancement, multifocal infarcts, right basal ganglia enhancing lesion	Expired	Autopsy: Multifocal infarcts and abscess in putamen with negative cultures. Rare bacilli seen on GMS stain of abscess (CDC). No lesions in GI tract.
Case 4, 50F, Sept 2013	Induction (7 + 3)	(+) Abd pain; no n/v or diarrhea	HD20	HA, AMS, septic shock	CP, CZ	Yes	Diffuse SAH, cerebral edema, herniation	Expired	Autopsy: Edema and tonsillar herniation, patchy areas of SAH. Rare bacilli in subarachnoid space. Cultures, stains, IHC negative. GI tract unremarkable except a single flat lesion in colon with mixed bacteria.
Case 5, 52M, Feb 2014	Induction (AraC + Ida)	(+) Abd pain and diarrhea	HD9	Abd pain, AMS, septic shock	PT, CP, VM, CT	Yes	Extensive petechial hemorrhages, large basal ganglia ICH, uncal herniation	Expired	Autopsy: Brain with cerebral edema, hemorrhage, herniation, and multiple bacilli; cultures (+) for *B cereus*. GI tract with multiple colonic ulcerative lesions with surrounding erythema and abundant bacilli (identified as *B cereus* by PCR). Liver with subcapsular necrosis with sinusoids filled with bacilli.

Abbreviations: 7 + 3, cytarabine + daunorubicin; Abxs, antibiotics; Abd, abdominal; AM, amoxicillin; AMS, altered mental status; Ara-C, cytarabine; CAFdA, clofarabine; CDC, Centers for Disease Control and Prevention; Chemo, chemotherapy; CP, cefepime; CT, ceftazidime; CZ, cefazolin; GI, gastrointestinal; GMS, Gomori methenamine silver; HA, headache; HD, hospital day; ICH, intracerebral hemorrhage; Ida, idarubicin; IHC, immunohistochemistry; MZ, metronidazole; n/v, nausea/vomiting; PCR, polymerase chain reaction; PT, piperacillin/tazobactam; SAH, subarachnoid hemorrhage; VM, vancomycin.

ultimately identified as *B cereus* by PCR and immunohistochemistry. The patient was treated with a prolonged course of parenteral vancomycin with resolution of her brain abscess. Case-patients 2, 4, and 5 were transitioned to comfort measures and expired within 2–3 days after the onset of neurologic symptoms and had catastrophic findings on neuroimaging as described above. Case-patient 3 had progressively worsening neurological status and recurrent seizures over the ensuing 3 weeks before expiring.

Case-patients 1 and 2 had negative blood cultures, and *B cereus* was detected later only on CNS tissue examination. Case-patients 3–5 had documented *B cereus* bacteremia in multiple blood culture sets with the organism also identified on CNS pathological stains. Only case-patient 3 had a lumbar puncture after onset of neurologic symptoms, and cerebrospinal fluid (CSF) analysis revealed an elevated opening pressure (32 mmHg), elevated total protein (239 mg/dL), normal glucose (63 mg/dL), elevated red blood cells (620 in tube 1, 530 in tube 4), a normal number of total nucleated cells (4 in tube 1, 3 in tube 4), and no organisms on Gram stain or culture. Autopsies performed on the 4 patients who expired were notable for colonic ulcers with abundant bacilli in 2 cases (identified as *Bacillus* species by immunohistochemistry for case 2 and *B cereus* by PCR in case 5). Susceptibility testing (E-test method) done on 4 available isolates showed a minimum inhibitory concentration of 32 μg/mL or more for cefepime, 2 μg/mL or more for vancomycin, and 0.125 μg/mL or less for ciprofloxacin for all isolates.

There was no overlap of hospital location or in the medical staff who cared for case-patients. Transfusion records were examined and no common donors were identified, and there was no overlap in the technicians who drew blood from each of the relevant donors. On case-control analysis, no medication or procedure was significantly associated with *B cereus* infection. However, bananas were consumed by all 5 case-patients and were significantly associated with infection (odds ratio [OR], 9.3; $P = .04$) (Table 2). Cranberry juice was consumed by 4 case-patients and was the only other significant exposure (OR, 9.6; $P = .04$).

Medications and foods common among the patients (including cefepime, potassium chloride, magnesium sulfate, mouthwashes, body lotions, bananas, yogurt, eggplant, and various fruits) were sent to the MDPH laboratory for culture; *B cereus* was isolated from 1 sample of homogenized banana peels. The significance of this isolate was unclear at this early point in the investigation; thus, the isolate was not archived. Multilocus sequence typing was not pursued before discarding the isolate. Recent renovation and construction projects at the hospital were reviewed; there were 11 hospital renovation projects during the cluster period, but no breaches were identified in construction containment practices. No breaches in practice were observed in any of the other examined departments or observed procedures, including chemotherapy preparation and administration and central line care. Of the 47 environmental, food, and medication samples sent to the CDC, only 4 tested positive for *B cereus* at very low concentrations, including a kitchen cart

Table 2. Summary of Case-Control Analysis to Assess for Risk Factors for Neuroinvasive *Bacillus cereus* Infection in Hospitalized AML Patients

	Cases (n = 5)	Controls (n = 13 or 20)[a]	Odds Ratio	*P* Value
Medications				
Acetaminophen (PO)	5	16 of 20	1.0	>.99
Allopurinol (PO)	4	11 of 20	3.3	.63
Cefazolin (IV)	4	7 of 20	7.4	.19
Cefepime (IV)	5	12 of 20	7.5	.13
Chlorhexidine mouthwash	5	18 of 20	1.5	.91
Colace (PO)	4	14 of 20	1.7	>.99
Cytarabine (IV)	5	11 of 20	9.1	.08
Magnesium sulfate (IV)	4	18 of 20	0.44	>.99
Normal saline (IV)	5	17 of 20	2.2	.68
Nystatin swish and swallow	5	16 of 20	3.0	.50
Ondansetron (IV)	4	16 of 20	1.0	>.99
Potassium chloride (IV)	5	16 of 20	3.0	.50
Sarna (TP)	4	7 of 20	7.4	.19
Procedures				
Central venous catheter	5	14 of 20	4.9	.26
Bone marrow Biopsy	4	10 of 20	4.0	.49
Dietary Exposures				
1% Milk	4	5 of 13	4.6	.33
Aquafina	4	5 of 13	4.9	.16
Banana	5	4 of 13	9.3	.04[b]
Chicken noodle soup	4	8 of 13	2.1	.94
Chicken pot pie	4	5 of 13	8.4	.10
Cranberry juice	4	2 of 13	9.6	.04[b]
Fruit cup	4	5 of 13	4.9	.33
Ketchup	4	9 of 13	1.2	.9
Oatmeal	4	7 of 13	2.5	.78
Oatmeal raisin cookie	4	4 of 13	5.7	.15
Pepper	4	6 of 13	3.8	.24
Salt	4	9 of 13	2.2	>.99
Spring water	5	5 of 13	6.0	.09
Strawberry frappe	4	6 of 13	3.8	.58
Strawberry yogurt	4	6 of 13	3.1	.62

Abbreviations: PO, oral; IV, intravenous; TP, topical.

[a] Twenty controls were used for medications and procedures; only 13 controls were available for dietary exposures due to incomplete dietary records.

[b] Indicates statistically significant exposures.

Table 3. Results of Multilocus Sequence Typing of *Bacillus cereus* Strains From Clinical Investigation[a]

Source	Sample ID	Multilocus Sequence Typing						
		glpF	gmk	ilvD	pta	pur	pycA	tpi
Case 1	Brain biopsy	*33*					*17*	*7*
Case 2	Brain	*65*	*1*	*93*	*1*	*51*	*37*	*24*
Case 3	Blood	*47*	*8*	*88*	*26*	*86*	*36*	*7*
Case 4	Blood	*94*	*2*	*232*	*5*	*32*	*156*	*143*
Case 5	Brain	*47*	*8*	*14*	*12*	*2*	*36*	*142*
Environmental sample 1	Blanket warmer	*37*	*28*	*14*	*12*	*37*	*157*	*144*
Environmental sample 2	Banana cart	*12*	*8*	*9*	*192*	*11*	*12*	*10*
Environmental sample 3	Air sample near construction site	*81*	*53*	*117*	*193*	*113*	*93*	*145*
Environmental sample 4	Beneprotein	*6*	*4*	*42*	*4*	*16*	*6*	*3*

Abbreviations: ID, identification; MLST, multilocus sequence typing; PCR, polymerase chain reaction.

[a] Bacterial isolates and, in 1 case, a pathological specimen from a brain biopsy were subjected to whole genome sequencing and targeted amplification of genes for MLST (http://www.pubmlst.org/bcereus). In cases in which PCR-based amplification of MLST locus was unsuccessful, the MLST genomic sequence was identified, by homology, from whole genome sequencing data. In all cases in which both PCR-based and whole genome sequencing-based MLST data were available, the results were concordant.

where bananas were stored, the shelf of a blanket warmer, an air sample near a construction site, and a beneprotein food sample.

Genomic Analysis

Multilocus sequence typing was performed using both Sanger sequencing of PCR-amplified amplicons and homology-based identification of MLST-genes from WGS. Multilocus sequence typing data were obtained for all *B cereus* isolates from BWH patients (n = 4) and swabs of environmental screening efforts (n = 4). Multilocus sequence typing confirmed that all strains were genetically distinct, and it suggested that the environmental strains were relatively divergent from the pathogenic strains (Table 3). Multilocus sequence typing-based phylogenetic analysis of all isolates revealed that the pathogenic organisms appeared to cluster in 2 separate clades and that MLST-based analysis does not phylogenetically distinguish environmental from case strains (Figure 1).

DISCUSSION

These 5 cases of *B cereus* infection highlight the risk of nosocomial infection from this organism and the potential for devastating neurologic sequelae in immunocompromised patients. Although there were few cases, the investigation was performed with urgency because of the high associated mortality (80% in our series) and the unusual nature of this cluster, as supported by the absence of other cases in the preceding 3 years at BWH. Clinical and pathologic review suggests gastrointestinal translocation as the likely route of infection for some or all of the case-patients, because all had notable gastrointestinal symptoms and 2 had colonic ulcers with evidence of *Bacillus* infection on autopsy.

Multilocus sequence typing demonstrated that the cluster was not the result of a single *B cereus* strain. Rather, the infections appear to have been attributable to multiple distinct strains within at least 2 distinct genotypic clusters. Although this is less consistent with a point-source outbreak, a common environmental or food exposure is still possible, particularly if the exposure was due to intermittent environmental contamination of a common food. All 5 case-patients had consumed bananas, 1 of only 2 dietary items significantly associated with infection in the case-control analysis. *Bacillus cereus* was recovered from the shelf where the bananas were stored in the kitchen, and *B cereus* was also cultured from a banana peel. The timing of the cluster with multiple hospital renovation and construction projects, some of which were proximate to the kitchen storage area, raises the possibility of environmental contamination of foods stored in the kitchen or direct inoculation of patients, although no breaches were identified in construction containment practices.

Nosocomial *B cereus* outbreaks at other institutions have been reported with various suspected sources, including construction work, contaminated linen and towels, intravenous catheters, infusion fluids, ventilator equipment, air ventilation systems, tea bags, gloves, and hands of staff [4–10]. However, definitively establishing the source of an outbreak is complicated by the fact that *B cereus* is a ubiquitous organism (including in food), and so the significance of isolating low colony counts from environmental cultures is often unclear. When outbreaks do occur, obtaining control can be difficult because *Bacillus* is able to survive long periods in the environment and is resistant to many commonly used cleaning products [11].

Bacillus cereus is typically disregarded as a contaminant when isolated from blood cultures, but patients receiving chemotherapy for hematological malignancies have been noted to be at disproportionately high risk for CNS infection, with substantial associated mortality [12–15]. The pathogenicity of *B cereus*

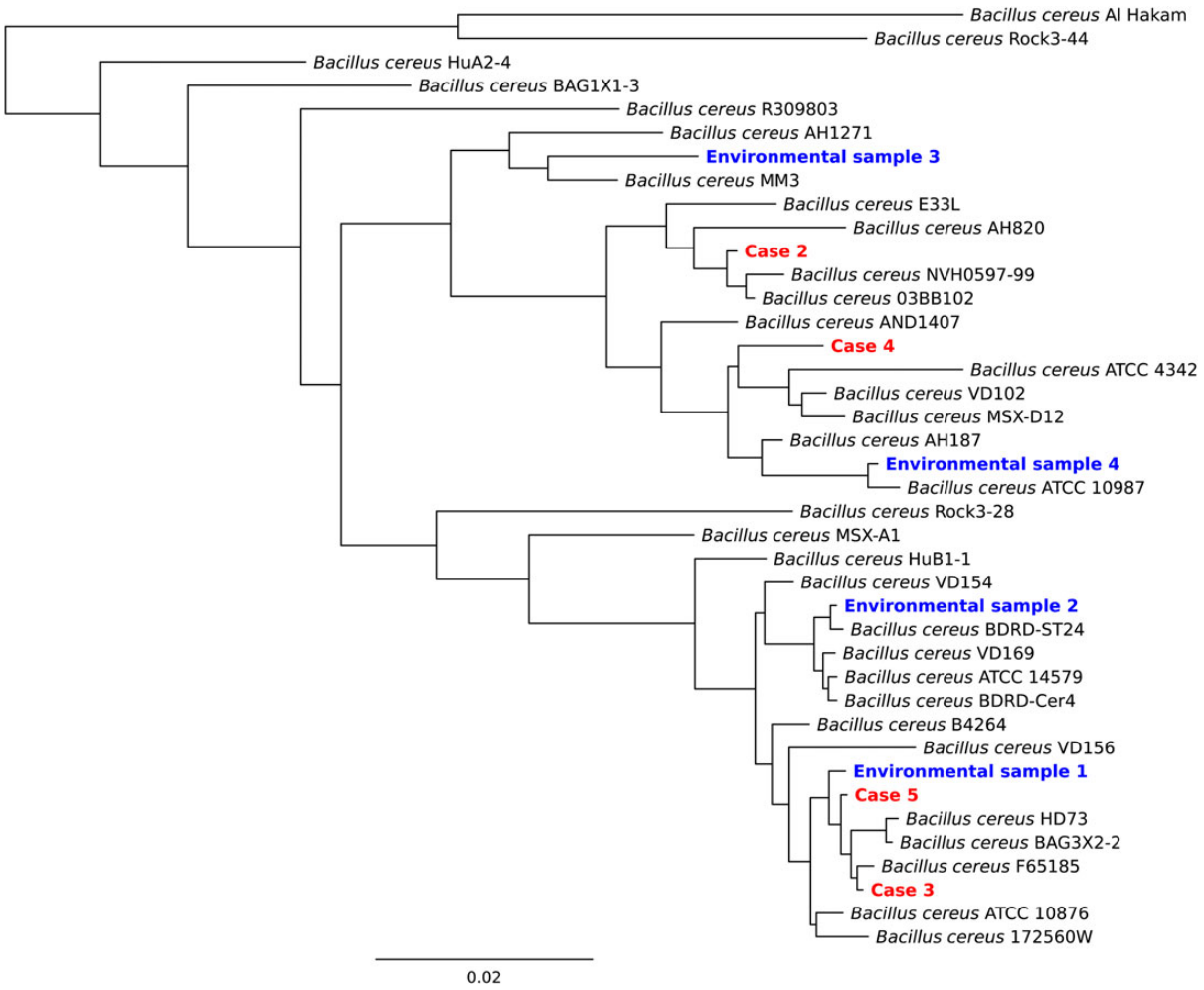

Figure 1. Phylogenetic tree of selected *Bacillus cereus* strains generated using multilocus sequence typing (MLST) results. A phylogenetic tree was constructed using MLST information from strains from cases 2–5 (because incomplete MLST information was available for case 1) in this study, as well previously published genome sequences of both environmental and pathogenic *B cereus* strains. This tree was constructed using the neighbor joining method with 1000 resamplings, as described in the Methods section of the manuscript. Of note, analysis of the sequences from the *B cereus* strains in cases 3 and 4, although temporally closely related, revealed that these strains were genetically very diverse from one another.

(both intestinal and extraintestinal) is associated with the production of a wide range of tissue-destructive exotoxins and enterotoxins [16–18]. Central nervous system infection in immunocompromised patients may result from bloodstream seeding from gastrointestinal infection (particularly in the setting of mucosal injury from chemotherapy), or from central venous catheters with subsequent CNS invasion, or possibly from direct introduction via intrathecal administration of chemotherapy [14, 19, 20]. It is important to note that our first 2 case-patients never had positive blood cultures, and none received lumbar punctures or intrathecal chemotherapy before onset of disease. All 5 case-patients shared risk factors for poor prognosis, including acute leukemia, an absolute neutrophil count approaching zero, neurological symptoms at the time of febrile episodes, and active receipt of induction or reinduction chemotherapy [1]. It is interesting to note that the 1 case-patient who received a lumbar puncture had a normal number of total nucleated cells on CSF analysis. *Bacillus cereus* meningitis has been reported to be associated with a relatively bland CSF profile in patients with hematological malignancies. This may be a reflection of underlying host immunosuppression and possibly an intrinsic lack of inflammatory response by the organism [7, 13, 21]. Neuropathology in our cases demonstrated areas of acute infarction, cerebritis, abscesses, hemorrhage, and meningitis, reflecting the wide range of potential CNS manifestations of this organism [12–14, 20, 22–27].

Several control measures were instituted as a result of this investigation, including enhanced environmental cleaning and exclusion of bananas and fresh fruits, vegetables, and rice from the diets of AML patients undergoing induction chemotherapy.

Our hospital's empiric antibiotic recommendations were also modified to include the addition of ciprofloxacin for recurrent neutropenic fever to optimize *B cereus* coverage, given that susceptibility testing on the isolates revealed low minimum inhibitory concentrations for ciprofloxacin. No additional cases have been found in the year after the last case.

CONCLUSIONS

In summary, this cluster of neuroinvasive *B cereus* infections in 5 AML patients prompted an extensive epidemiologic and genomic investigation that ultimately did not support the hypothesis of a single point source, but it did suggest the possibility of a dietary exposure to *B cereus*. Our experience underscores the potential virulence of this organism in susceptible hosts. Clinicians should not automatically disregard *Bacillus* in blood cultures as being contaminants and *B cereus* should be considered in febrile immunocompromised patients with neurological symptoms, even without positive blood cultures. It is possible that the responsible organisms share a transferable virulence-conferring factor, and comparative microbial genomic and biological efforts are underway that may identify bacterial and host factors that induce heightened virulence.

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