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## ***Bacillus cereus* Sepsis in the Treatment of Acute Myeloid Leukemia**

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### **1. Introduction**

Fatal sepsis during chemotherapy-induced neutropenia is the most severe complication of which physicians must be keenly aware. Common bacterial pathogens in neutropenic patients usually include gram-positive cocci such as coagulase-negative staphylococci, *Staphylococcus aureus*, *Enterococcus* species, and gram-negative rods such as *Escherichia coli*, *Klebsiella* species, *Enterobacter* species, and *Pseudomonas aeruginosa* (Wisplinghoff, *et al* 2003). Thus, clinical practice guidelines for the use of antibiotics are likely to be aimed at targeting these pathogens including antibiotic-resistant strains (Freifeld, *et al* 2011). In the absence of effector cells for these pathogens, the rapid progression of invasive bacterial infections may occur; therefore, antibiotics are a life-saving measure during severe neutropenia.

*Bacillus cereus* (*B. cereus*) is an aerobic gram-positive, spore-forming, and rod-shaped bacterium that is widely distributed in the environment. Although *B. cereus* is a common cause of food-poisoning, abdominal distress such as vomiting and diarrhea is usually mild and self-limiting unless the host is immunocompromised. Some patients that undergo prolonged hospitalization have *Bacillus* species as a part of the normal flora in their intestine (Drobniewski 1993). Therefore, identification of this microorganism in clinical cultures has usually been considered to be due to contamination. For example, 78 patients were found to have cultures positive for *B. cereus* in a single center in the United States; however, only 6% of them resulted in clinically significant infections (Weber, *et al* 1989). On the other hand, *B. cereus* is a growing concern as a cause of life-threatening infections in patients with hematologic malignancies, including septic shock, brain abscess, meningitis, colitis, respiratory infections, endocarditis, and infection-related coagulopathy and hemolysis. The risk factors for patients with unfavorable outcomes, however, have not been totally elucidated. In addition, *B. cereus* sepsis generally does not respond to any antibiotics in spite of their *in vitro* efficacy (Drobniewski 1993). Akiyama *et al.* reviewed 16 case reports of *B. cereus* sepsis in patients with leukemia, and consequently reported only 3 survivors (Akiyama, *et al* 1997). Therefore, physicians should identify specific risk factors of *B. cereus* sepsis during chemotherapy for leukemia patients and establish a proper strategy to overcome this life-threatening sepsis.

## 2. *B. cereus* sepsis in patients with hematologic malignancies

In recent years, we encountered several cases of *B. cereus* sepsis including 4 fatal cases with acute leukemia in our hospital. These episodes prompted us to review all cases of *B. cereus* sepsis especially in hematologic malignancies. In the present study, we collected the data and the clinical features of these patients with *B. cereus* sepsis in a retrospective fashion, and identified risk factors for a fatal prognosis in these patients (Inoue, *et al* 2010). Based on these data, we also put forward a proposal for the rapid diagnosis of *B. cereus* sepsis and earlier therapeutic intervention for this infection.

### 2.1 Patients and methods

We reviewed the microbiology records of all patients who produced a positive blood culture for *B. cereus* from September 2002 to November 2009 in our hospital. We routinely took at least two sets of blood culture samples from all patients with hematologic malignancies who developed a high-grade fever of over 38°C. Each set consisted of two blood culture vials for both aerobic and anaerobic cultures. Identification of *B. cereus* was made on the basis of Gram-staining, colony morphology, and analysis with NGKG agar (Nissui, Tokyo, Japan). Antimicrobial disk susceptibility tests were performed using Sensi-Disc (Beckton Dickinson).

We defined a case as sepsis when more than two blood culture sets were positive for *B. cereus* or only a single set was positive in the absence of other microorganisms in patients who had definite infectious lesions, such as brain or liver abscesses. Instead, febrile cases that did not satisfy the above criteria were defined as an unknown pathogen or contaminated culture.

With regard to sepsis patients, we also reviewed their charts to obtain clinical information, including the underlying disease, insertion of a central venous (CV) catheter, nutrition route, neutrophil count, and prior chemotherapy or steroid treatment. Oral nutrition was defined only when patients were eating a regular diet without high-calorie parenteral nutrition support. We also documented clinical signs at febrile events, such as gastrointestinal (GI) and central nervous system (CNS) symptoms, antibiotic use, and the drug sensitivity of *B. cereus*. Then, we assessed the risk factors for a fatal prognosis; i.e., whether the underlying disease was acute leukemia, whether a CV catheter was inserted, whether the patient was receiving oral or parenteral nutrition, whether their neutrophil count was 0/mm<sup>3</sup> or above 0/mm<sup>3</sup>, and whether characteristic clinical signs were present at the time of febrile events. We also reviewed the charts of patients without hematologic malignancies who had cultures positive for *B. cereus* in the same period. Furthermore, we assessed the above data in conjunction with those from previously reported patients with *B. cereus* sepsis, who had hematologic malignancies.

Statistical tests included  $\chi^2$  and Fisher's exact tests. All calculations were made using the program JMP 8.0 (SAS Institute, Cary, NC, US). All P-values of <0.05 were considered significant.

## 2.2 Results

### 2.2.1 Characteristics of *B. cereus* sepsis patients

A total of 68 febrile patients that produced positive blood cultures for *B. cereus* were identified from September 2002 to November 2009 in our institute. Twenty-three of these patients had hematologic malignancies, including 4 patients who died of fatal sepsis.

Although 11 of the 23 patients showed signs of infection such as a high-grade fever, we classified them with an unknown pathogen or contaminated culture, since other causes of fever could not be totally excluded. With respect to underlying diseases, 2 of 5 cases of non-Hodgkin lymphoma (NHL), 3 of 5 cases of acute lymphoblastic leukemia (ALL), 5 of 6 cases of acute myeloid leukemia (AML), 1 of 4 cases of myelodysplastic syndrome (MDS), and 1 of 3 cases of multiple myeloma (MM) were diagnosed with *B. cereus* sepsis. Thus, we determined as many as 12 (patients 1 to 12) of 23 patients with hematologic malignancies as having *B. cereus* sepsis; whereas, only 10 of 45 patients without hematologic malignancies were similarly diagnosed on the basis of the same criteria ( $P=0.012$ ). All of these 10 patients recovered from *B. cereus* sepsis after treatment with appropriate antimicrobials including carbapenems, vancomycin, or fluoroquinolones. None of the 10 patients received chemotherapy. Their underlying diseases were as follows: chronic obstructive pulmonary disease, congestive heart failure, bronchial asthma, acute hepatitis, malnutrition, subarachnoid hemorrhage, ovarian cancer, gastric cancer, and cerebral infarction in 2 patients.

As shown in Table 1, we analyzed the profiles of the 12 patients with hematologic malignancies: 6 men and 6 women with a median age of 53.5 ranging from 20 to 85 years; 8 patients with acute leukemia, 5 who were treated with a CV catheter and 12 who received oral nutrition; 5 patients with a neutrophil count of  $0/\text{mm}^3$ ; all patients, except for patients 5, 10, and 12, had undergone prior steroid treatment within 2 weeks; and 8 patients exhibited GI symptoms including nausea, vomiting, diarrhea, and abdominal pain, and 6 patients displayed CNS symptoms ranging from disorientation to deep coma at the time of febrile episodes. Although CV catheters were removed in patients 2, 4, 6, and 12 as a part of the management for their febrile status, none of these catheters were found to be positive for *B. cereus*. In one patient (patient 6), postmortem cultures from CSF samples were performed, with positive results for *B. cereus*. Among 5 patients with CNS symptoms, lumbar puncture was only performed in patient 8, without *B. cereus* isolation. Lumbar puncture was not conducted for the remaining 4 patients because of their unstable conditions. No patient demonstrated other organisms as co-isolates in their initial blood cultures.

Patients 1 and 2, who had ALL, and patients 6 and 12, who had AML, developed consciousness disturbance, which resulted in a deep coma and brain stem dysfunction 3 days, 6 hours, 18 hours, and 8 hours after their febrile episode and they died 12 days, 7 days, 20 hours, and 15 hours after their febrile event, respectively, despite intensive antimicrobial therapy and supportive care (Table 1). All 4 patients had received intensive chemotherapy for acute leukemia, and febrile events occurred on day 13 after re-induction chemotherapy in patient 1; on day 18 after induction therapy in patient 2; on day 14 after consolidation in patient 6; and day 13 after induction therapy in patient 12. On the other hand, patient 7, who had received high-dose etoposide for the collection of peripheral blood stem cells, similarly developed a deep coma but recovered without sequela 28 hours after the onset of consciousness disturbance. Patients 8, 9, 10, and 11 also received intensive chemotherapy prior to *B. cereus* sepsis, as shown in Table 1. Patient 4 received methylprednisolone treatment (20 mg/day) for chronic graft-versus-host disease when the sepsis developed. The characteristics of the remaining patients are also shown in Table 1. In addition to patients 1, 2, 6, and 12, patient 8 died of underlying refractory AML 6 months after the onset of *B. cereus* brain abscesses despite successful treatment of the abscesses with long-term vancomycin administration, and patient 4 died of multiple organ failure caused by another bacterial infection 11 months later. No sequela or death occurred in the remaining patients, including

Table 1. Clinical features of patients with *Bacillus cereus* sepsis in our cohort

Patient	Age, y	Sex	Month Year	Primary diagnosis	CV catheter	Oral nutrition	ANC, cells/ $\mu$ l	Chemotherapy	Corticosteroid within 14 days	GI symptoms	CNS symptoms
1	40	F	Jun-03	ALL	(+)	(+)	0	Reinduction (doxorubicin, methotrexate, and vindesine )	(+)	Vomiting	(+)
2	42	F	May-07	ALL	(+)	(+)	0	Induction	(+)	Abdominal pain, diarrhea	(+)
3	58	F	May-07	MM	(-)	(+)	15200	(-)	(+)	Vomiting	(-)
4	49	M	Jun-07	MDS	(+)	(+)	4200	Allogeneic BMT 11 months before	(+)	Diarrhea	(-)
5	85	F	Sep-07	NHL	(-)	(+)	8340	(-)	(-)	(-)	(-)
6	67	M	Apr-08	AML	(+)	(+)	0	Consolidation (cytarabine and mitoxantrone )	(+)	Vomiting, diarrhea	(+)
7	67	M	Jun-08	NHL	(-)	(+)	2	High-dose etoposide	(+)	Abdominal pain, vomiting	(+)
8	45	M	Oct-08	AML	(-)	(+)	8	Consolidation (high-dose cytarabine)	(+)	(-)	(+)
9	31	F	Dec-08	ALL	(-)	(+)	0	Consolidation (cyclophosphamide, vincristine, and dexamethasone)	(+)	(-)	(-)
10	61	F	May-09	AML	(-)	(+)	6	Reinduction (cytarabine and idarubicin)	(-)	Diarrhea	(-)
11	20	M	Aug-09	AML	(-)	(+)	1	Consolidation (high-dose cytarabine)	(+)	Abdominal pain	(-)
12	74	M	Nov-09	AML	(+)	(+)	0	Induction (cytarabine, etoposide, and mitoxantrone )	(-)	(-)	(+)

CV catheter, central venous catheter; ANC, absolute neutrophil count; GI symptoms, gastrointestinal symptoms; CNS, central nervous system; ALL, acute lymphoblastic leukemia; NHL, non-Hodgkin lymphoma; MM, multiple myeloma; MDS, myelodysplastic syndrome; JALSG, Japan Adult Leukemia Study Group; BMT, bone marrow transplantation; M, male; F, female; (+), present; (-), absent; CAZ, ceftazidime; CFPM, cefepime; ISP, isepamicin.

patient 9, in whom the long-term administration of vancomycin was required for liver abscesses. Patients 9 and 10 successfully received allogeneic bone marrow transplantation (BMT) after recovering from severe *B. cereus* sepsis.

### 2.2.2 Results of autopsies

Of the 4 fatal cases, we performed autopsy in 3 patients. Autopsy of patient 2 demonstrated the presence of a small number of *B. cereus* in the subarachnoid space and venous thrombosis in the Vein of Galen and the superior sagittal sinus. In contrast, coagulation necrosis with bacterial infiltration in the liver and necrotizing leptomeningitis with subarachnoid hemorrhage (SAH) were observed in patient 6, and coagulation necrosis accompanied by *B. cereus* infiltration in the colon could be seen in patient 12. Histologic analyses of organs obtained in the autopsies of patients 2 and 6 are shown in Figure 1. Large venous thromboses in the vein of Gallen and superior sagittal sinus can be seen in patient 2 (A and B, H.E. staining,  $\times 40$ ). On the other hand, in patient 6, numerous gram-positive rods are present in the subarachnoid space (D, Gram staining,  $\times 400$ ) and outside of the subarachnoid membrane (E, H.E. staining,  $\times 100$ , in the circle), which may have caused the coagulation necrosis of the vessels in the subarachnoid membrane (arrows). The coagulation necrosis is also seen without the infiltration of inflammatory cells in the surface area of the cerebrum (arrowheads), which is distant from the *B. cereus* clusters. Extensive coagulation necrosis with bacterial infiltration stands out without an inflammatory response in the liver of patient 6 (C, H.E. staining,  $\times 100$ ). A number of gram-positive rods can be seen clustering in the circle. In patient 12, coagulation necrosis with bacterial infiltration could be similarly seen in the liver in addition to *B. cereus* infiltration in the colon, although we could not obtain pathological analysis in CNS.

### 2.2.3 Risk factors for a fatal prognosis, which were identified in patients in our institution

As shown in Table 1, all 4 fatal cases shared common factors, that is, acute leukemia, insertion of a CV catheter, an extremely low neutrophil count, and CNS symptoms at febrile episodes. We then statistically analyzed clinical parameters of 12 patients listed in Table 1, and identified the following risk factors for death due to *B. cereus* sepsis: CV catheter insertion ( $P=0.010$ ), a neutrophil count of  $0/\text{mm}^3$  ( $P=0.010$ ), and CNS symptoms at the time of febrile events ( $P=0.010$ ). While acute leukemia ( $P=0.141$ ), GI symptoms ( $P=0.594$ ), and prior steroid treatment within 2 weeks ( $P=0.764$ ) did not show a close relationship with a fatal course of *B. cereus* sepsis.

### 2.2.4 Antibiotic susceptibility

The antibiotics employed in the present study included meropenem or doripenem for 8 patients (patients 2, 6-12) and vancomycin for 7 patients (patients 2, 6, 8-12). All of the isolated *B. cereus* strains were susceptible to imipenem, vancomycin, levofloxacin, and gentamicin; whereas, no isolated *B. cereus* strains, except for that from patient 5, were sensitive to penicillins or cephalosporins *in vitro*.

### 2.2.5 Risk factors for a fatal prognosis in previously reported patients and ours

To our knowledge, 46 *B. cereus* sepsis patients with hematologic malignancies have been previously reported (Akiyama, *et al* 1997, Arnaout, *et al* 1999, Christenson, *et al* 1999, Colpin,

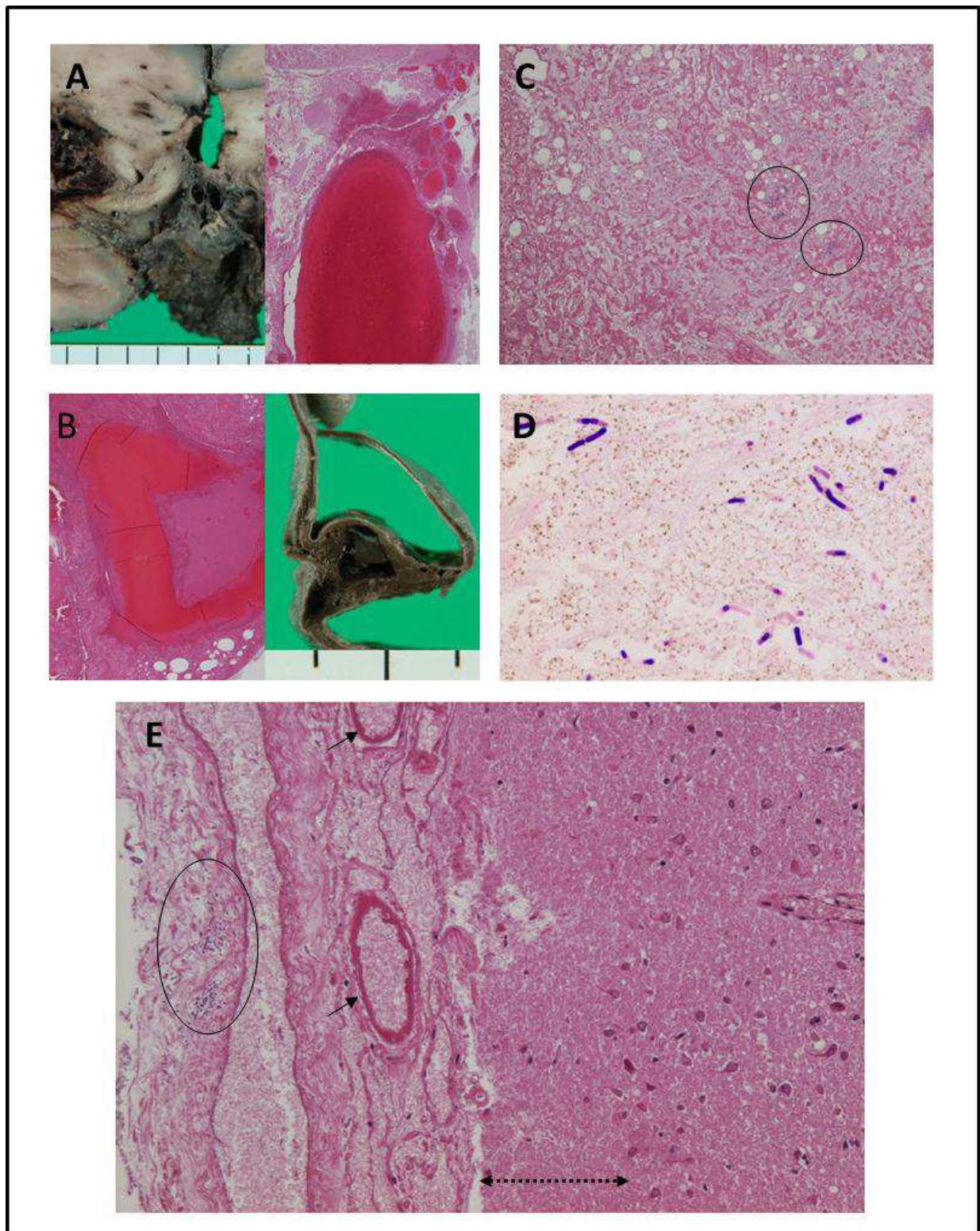


Fig. 1. Histologic analyses of organ specimens obtained in the autopsies of patients 2 and 6

*et al 1981, Cone, et al 2005, Coonrod, et al 1971, Dohmae, et al 2008, Feldman and Pearson 1974, Frankard, et al 2004, Funada, et al 1988, Garcia, et al 1984, Gaur, et al 2001, Ginsburg, et al 2003, Ihde and Armstrong 1973, Jenson, et al 1989, Katsuya, et al 2009, Kawatani, et al 2009, Kiyomizu, et al 2008, Kobayashi, et al 2005, Kuwabara, et al 2006, Le Scanff, et al 2006, Leff, et*

al 1977, Marley, et al 1995, Motoi, et al 1997, Musa, et al 1999, Nishikawa, et al 2009, Ozkocaman, et al 2006, Sakai, et al 2001, Strittmatter, et al 1995, Tomiyama, et al 1989, Trager and Panwalker 1979, Yoshida, et al 1993). On analyses of the clinical parameters of these patients, as in shown in Table 2, patients with acute leukemia, a neutrophil count of  $0/\text{mm}^3$  or below the lower limit of each institute, or CNS symptoms at febrile episodes were identified as risk factors closely correlated with a fatal prognosis ( $P=0.044$ ,  $0.004$ , and  $0.002$ , respectively). Patients younger than 15 years old had a tendency to show a more favorable prognosis in comparison with older patients. ( $P=0.063$ ). Male, GI symptom, corticosteroid administration, CV catheter insertion, and antimicrobial therapy except for that with vancomycin did not have a significant impact on the prognosis.

## 2.3 Discussion and proposal

### 2.3.1 How do we efficiently select high-risk patients?

Our report contains 12 adult *B. cereus* sepsis cases of hematologic malignancy, which is, to our knowledge, the largest cohort of *B. cereus* sepsis in adult patients from a single center. Because of the serious outcomes of these patients with hematologic malignancies, the detection of *B. cereus* from blood culture samples at febrile events from these patients should not be regarded as contamination. In our cohort, patients with a neutrophil count of  $0/\text{mm}^3$ , with CNS symptoms, or who had undergone CV catheter insertion definitely had a poor prognosis. However, we had difficulties in identifying further precise prognostic factors because of the small number of *B. cereus* infection cases in our institution. Therefore, we assessed the data in conjunction with those from our 12 patients and from 46 previously reported patients, giving a total of 42 patients with acute leukemia, although reporting bias may have existed because severe cases with peculiar clinical features tend to be selectively reported and some reports did not refer all factors which we consider to be important. Consequently, patients who had acute leukemia, a neutrophil count of  $0/\text{mm}^3$  or a count below the lower limit of each institute, or CNS symptoms at febrile episodes were identified as being associated with a fatal prognosis. Interestingly, the relatively more favorable prognosis in younger patients implies the importance of appropriate evaluation in adult patients (Table 2).

Regarding the neutrophil count, patients 7, 8, 10, and 11 fully recovered from *B. cereus* sepsis complicated with coma, in clear contrast to patients 1, 2, 6, and 12 who had a neutrophil count of  $0/\text{mm}^3$  (Table 1), suggesting that both immediate therapeutic intervention and even a small number of neutrophils can effectively work against *B. cereus* sepsis. The poor outcomes in acute leukemia patients may have been an indirect consequence because of the greater immunosuppression following intensive chemotherapy, rather than due to the underlying disease. Regarding the relationship between *B. cereus* sepsis and the treatment process of acute leukemia in the combined clinical parameters, 35 patients developed sepsis during remission induction or reinduction therapy, 9 consolidation therapy, 4 post-transplantation, and 1 maintenance therapy in a total of 49 acute leukemia patients whose clinical data were available (Akiyama, et al 1997, Arnaout, et al 1999, Christenson, et al 1999, Colpin, et al 1981, Cone, et al 2005, Coonrod, et al 1971, Dohmae, et al 2008, Feldman and Pearson 1974, Frankard, et al 2004, Funada, et al 1988, Garcia, et al 1984, Gaur, et al 2001, Ginsburg, et al 2003, Ihde and Armstrong 1973, Jenson, et al 1989, Katsuya, et al 2009, Kawatani, et al 2009, Kiyomizu, et al 2008, Kobayashi, et al 2005, Kuwabara, et al 2006, Le Scanff, et al 2006, Leff, et al 1977, Marley, et al 1995, Motoi, et al 1997, Musa, et al 1999, Nishikawa, et al 2009, Ozkocaman, et al 2006, Sakai, et al 2001, Strittmatter, et al 1995,



		Number (Deaths)	Survival	
			Odds Ratio	<i>P</i>
Age, y	≥ 15	48(28)	5.600	0.063
	< 15	10(2)		
Sex	Male	34(21)	2.692	0.069
	Female	24(9)		
limited to ≥ 15 years old	Male	29(20)	3.056	0.122
	Female	19(8)		
GI symptom at febrile episodes	(+)	34(19)	1.497	0.451
	(-)	24(11)		
limited to ≥ 15 years old	(+)	27(18)	2.200	0.184
	(-)	21(10)		
CNS lesion or CNS symptoms	(+)	32(23)	6.937	<b>0.002</b>
	(-)	26(7)		
limited to ≥ 15 years old	(+)	27(21)	7.000	<b>0.005</b>
	(-)	21(7)		
Corticosteroid use within 14 days	(+)	31(17)	0.552	0.357
	(-)	16(11)		
limited to ≥ 15 years old	(+)	25(16)	0.808	0.754
	(-)	16(11)		
CV catheter	(+)	26(15)	1.273	0.863
	(-)	29(15)		
limited to ≥ 15 years old	(+)	18(14)	3.250	0.149
	(-)	27(14)		
VCM therapy	(-)	29(18)	1.964	0.238
	(+)	22(10)		
limited to ≥ 15 years old	(-)	26(17)	2.099	0.367
	(+)	19(9)		
Neutrophil count of 0 or less than the lower limit	(+)	22(18)	8.000	<b>0.004</b>
	(-)	25(9)		
limited to ≥ 15 years old	(+)	19(17)	13.222	<b>0.002</b>
	(-)	23(9)		
Underlying disease	Acute leukemia	50(29)	9.667	<b>0.044</b>
	Others	8(1)		
limited to ≥ 15 years old	Acute leukemia	41(27)	11.571	<b>0.032</b>
	Others	7(1)		

These data include both previous reports and our 12 sepsis patients. P-values were calculated using  $\chi^2$  and Fisher's exact tests. Odds ratios predict the possibility of death from *Bacillus cereus* sepsis. GI, gastrointestinal. CNS, central nervous system. CV, central vein. VCM, vancomycin.

Table 2. Univariate analysis of prognostic factors of *B. cereus* sepsis

Tomiyama, *et al* 1989, Trager and Panwalker 1979, Yoshida, *et al* 1993). Therefore, patients under induction or reinduction therapy may be more likely to be susceptible to *B. cereus* sepsis. Also, previous studies have shown that variations in toxins and enzymes, which were produced by *B. cereus*, such as cereolysin, enterotoxin, emetic toxin, phospholipase C, and sphingomyelinase, between isolates of *B. cereus* were correlated with the reversibility of clinical courses (Turnbull, *et al* 1979, Turnbull and Kramer 1983). With respect to clinical symptoms related to *B. cereus* sepsis, patients with CNS disturbance mostly had a fatal outcome ( $P=0.005$ , in adult patients) (Table 2). Gaur *et al.* reported that patients with possible CNS involvement had a tendency to exhibit severe neutropenia at the onset of sepsis and to have an unfavorable outcome, although their study was conducted in a children's hospital (Gaur, *et al* 2001). Given that most of the patients with a fatal prognosis had GI symptoms at the time of febrile episodes (Table 2), clinicians must be cautious of the early signs of CNS in addition to GI symptoms. Although GI symptoms were not significantly correlated with a fatal prognosis, we consider that the symptoms are very important in terms of early clues to the diagnosis of *B. cereus* sepsis. CV catheter insertion did not have a significant impact on the prognosis ( $P=0.149$ , in adult patients), although the result was opposite to that found in our cohort.

### **2.3.2 We have a very limited time to avoid CNS damage in the face of *B. cereus* sepsis**

With respect to the results of autopsy, the findings observed in patient 2 have not been reported elsewhere, although coagulation necrosis with *B. cereus* infiltration of the liver and the GI tract may not be rare in *B. cereus* sepsis, as demonstrated in patients 6 and 12, respectively. In any case, the patients' condition rapidly deteriorated in spite of intensive antibiotic coverage, including carbapenems and vancomycin, which were effective against *B. cereus in vitro*, although these agents (especially meropenem and vancomycin) are still recommended because of the inherent ability of *B. cereus* to produce  $\beta$  lactamases and the presence of the blood brain barrier (Hasbun, *et al* 1999, Zinner 1999). The failure of apparently adequate therapy may have been due to inadequate tissue concentrations of antibiotics. However, we emphasize that delays in therapeutic intervention must be avoided even if the CNS may have already been damaged by *B. cereus* before the administration of adequate antibiotics, as seen in our fatal cases. Patient 7 (Table 1), with a neutrophil count of near 0, had consciousness disturbance at the febrile event. We started to treat this patient very quickly based on information from Patient 2 and 6 with antibiotics effective for *B. cereus*, with the successful recovery from sepsis including CNS symptoms. This experience may be very important in terms of the necessity of very early therapeutic intervention.

### **2.3.3 Proposal: Initial management of fever and neutropenia in AML patients in view of fatal *B. cereus* sepsis**

According to the Infectious Diseases Society of America (IDSA) guideline for neutropenic patients with cancer, 'high-risk' patients are considered to be those with anticipated sustaining (>7-day duration) and profound neutropenia (absolute neutrophil count (ANC) <100 cells/mm<sup>3</sup>) and/or significant medical co-morbid conditions, including hypotension, pneumonia, new-onset abdominal pain, or neurologic changes (Freifeld, *et al* 2011). It is generally assumed that all AML patients during intensive chemotherapy meet the high-risk criteria.

In the face of febrile AML patients, physicians should evaluate a complete blood count including a differential leukocyte count, although therapeutic intervention must be performed without delay in cases when the neutrophil count is expected to be 0/mm<sup>3</sup> or below the lower limit of each institute. At least 2 sets of blood culture are recommended, with a set collected simultaneously from each lumen of an existing CV catheter and from a peripheral vein. Without a CV catheter, 2 sets of blood culture should be obtained from different peripheral sites. The number of blood cultures has been described as correlated with the detectability of circulating pathogens, that is, only a single blood culture may cause misevaluation regarding underlying pathogens (Lee, *et al* 2007).

In the IDSA guideline, high-risk patients require initial antibiotic therapy that covers *Pseudomonas aeruginosa* and other serious gram-negative pathogens (Freifeld, *et al* 2011). Although the isolation of gram-positive organisms, such as coagulase-negative staphylococci, is more common than that of gram-negative pathogens, gram-negative bacteremias, especially those caused by *Pseudomonas aeruginosa*, are generally associated with greater mortality (Schimpff 1986). Thus, empirical monotherapy with an anti-pseudomonal  $\beta$ -lactam agent, such as cefepime, carbapenem (meropenem or imipenem-cilastatin), or piperacillin-tazobactam, is recommended and vancomycin should be considered only for clinically special indications, including suspected catheter-related infection, skin or soft tissue infection, pneumonia or hemodynamic instability (Freifeld, *et al* 2011). Coagulase-negative staphylococci, the most commonly identified microorganisms in septic patients with neutropenia, are clinically weak pathogens that rarely cause rapid deterioration; therefore, for many physicians, there is no urgent need to treat such infections with vancomycin at the time of a febrile event.

However, such a strategy as described above does not sufficiently satisfy appropriate treatment for fatal *B. cereus* sepsis, since *B. cereus* has an inherent ability to produce  $\beta$  lactamases (Hasbun, *et al* 1999, Zinner 1999). If neutropenic patients really suffer from *B. cereus* sepsis, it takes at least a few days to determine bacterial strains and, meanwhile, the patients' condition rapidly deteriorates. Although physicians should avoid the unnecessary administration of broad-spectrum antibiotics to prevent widely distributing resistant bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococcus (VRE), extended-spectrum  $\beta$  lactamase (ESBL)-producing gram-negative bacteria, and *Klebsiella pneumoniae* carbapenemase (KPC), therapeutic delays for *B. cereus* sepsis would result in a fatal outcome.

Therefore, as shown in Figure 2, at the first febrile event, we propose the prompt administration of both carbapenems and vancomycin for the following neutropenic AML patients with possible *B. cereus* sepsis, especially for patients with a neutrophil count of 0/mm<sup>3</sup> or below the lower limit of each institute, and CNS symptoms at febrile episodes. These 2 antibiotics are also desirable for febrile and neutropenic AML patients with CV catheter insertion or GI symptoms (Inoue, *et al* 2010). We consider that both agents are necessary as an initial management because of the presence of fulminant sepsis with *B. cereus* resistant to carbapenem (Kiyomizu, *et al* 2008). CV catheter removal is recommended if clinically possible. In patients with clinically and microbiologically documented infections other than *B. cereus*, appropriate agents should be started instead of carbapenems and vancomycin, and the duration of therapy depends on the species of pathogen and their infection site.

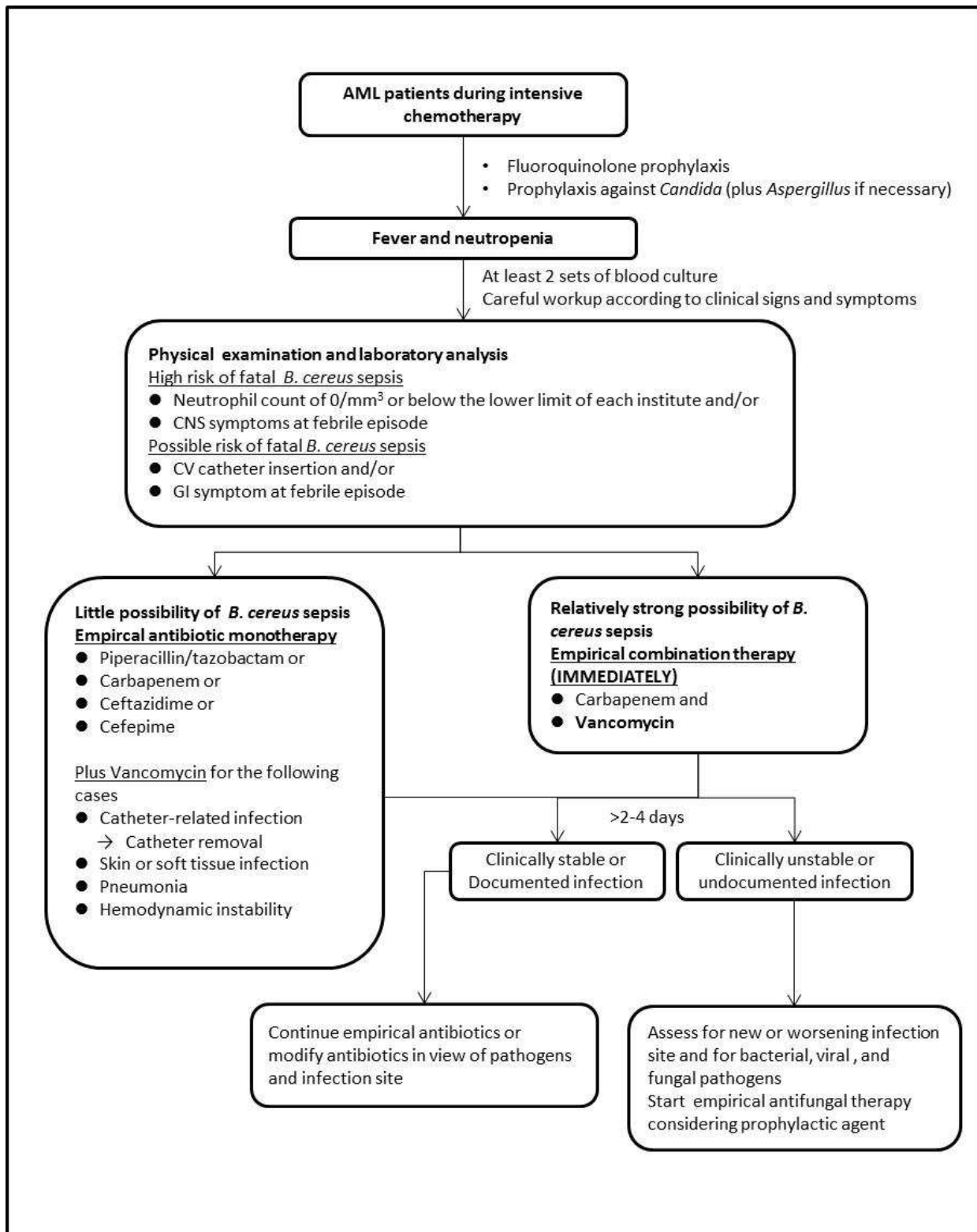


Fig. 2. Initial and urgent management for fever and severe neutropenia in AML patients in view of fatal *B. cereus* sepsis

The IDSA guideline recommends fluoroquinolone prophylaxis for high-risk patients with expected durations of prolonged and marked neutropenia ( $ANC \leq 100/mm^3$  for  $>7$  days) to reduce febrile events, documented infections, and infections involving the blood stream due to gram-positive or -negative bacteria (Bucaneve, *et al* 2005). Although fluoroquinolones, such as levofloxacin and ciprofloxacin, are usually efficacious against *B. cereus in vitro* and may prevent the rapid production of a large amount of bacterial toxins, there has been no report concerning the prophylactic efficacy of antibiotics against *B. cereus* sepsis (Bucaneve, *et al* 2005, Freifeld, *et al* 2011, Gafter-Gvili, *et al* 2005). The question of whether gut decontamination with oral fluoroquinolones can contribute to the reduction of *B. cereus*-related mortality remains to be addressed.

Fungal infections are encountered after the first week of prolonged neutropenia and empirical antibiotic therapy in the early phase of neutropenia, so that empirical antifungal therapy and investigation for invasive fungal infections should be considered for patients with persistent or recurrent fever after 2-4 days of antibiotics, including cases receiving prophylactic agents against *Candida* infections or invasive *Aspergillus* infection (Freifeld, *et al* 2011). Also, physicians should recurrently monitor possible fungal infection using the  $\beta$ -(1-3)-D glucan test, the galactomannan test, and high-resolution CT, leading to pre-emptive therapy if necessary.

### 2.3.4 What kind of environmental precautions should be taken?

It is reasonable to assume that *B. cereus*, which forms spores and is heat-resistant, in the environment or food passes through the GI tract or a CV catheter and enters into the circulation based on the results and information from our cases and previously reported patients (Banerjee, *et al* 1988, Terranova and Blake 1978). Especially, GI symptoms were present prior to the development of *B. cereus* sepsis in 8 cases, while no organism was grown from the tip of a CV catheter in any case (patients 2, 4, and 6) (Table 1). We regarded bananas, strawberries, and fried noodles as possibly causative foods in patients 1, 2, and 6, respectively. In these patients, the impairment of mucosal barriers due to intensive chemotherapy may have been an important factor; therefore, clinicians should pay strict attention to the foods consumed by such patients and prepared luncheon meats should be avoided, although Gardner *et al.* reported that avoidance of raw fruits and vegetables did not prevent major infection that led to death among AML patients in a randomized trial where cooked and noncooked food diets were compared (Gardner, *et al* 2008).

In previous reports, the inadequate sterilization of respiratory circuits (Bryce, *et al* 1993) and bacterial contamination of hospital linen (Barrie, *et al* 1994, Dohmae, *et al* 2008) were also considered to be major sources of nosocomial infection. *B. cereus* sepsis in patients 2 and 3 occurred in the same room and the same period (May, 2007). These facts prompted us to compare each *B. cereus* strain cultured from the blood samples of the 2 patients with *B. cereus* detected from hand towels, pajamas, a shared sink, and so on. However, each strain proved distinct from the other strains detected, suggesting little possibility of nosocomial infection. Although *B. cereus* is widely distributed in the environment, the bacterial burden should be minimized because the threshold of the burden might determine the frequency of *B. cereus* sepsis. From this point of view, the regular surveillance of *B. cereus* strains in the environment may also be important.

### 3. Conclusion

We encountered fatal *B. cereus* sepsis in patients with acute leukemia, in whom apparently appropriate antibiotics were not effective, while we also encountered reversible cases. This report has provided risk factors for a fatal prognosis in combination with previous data. It may be highly instructive for clinicians treating leukemia patients with several prognostic factors identified in this study for *B. cereus* sepsis with special relevance to patients with acute leukemia, and we strongly recommend the immediate initiation of treatment with carbapenems and vancomycin in such situations. Similar studies with a larger cohort are necessary to establish successful therapeutic interventions.

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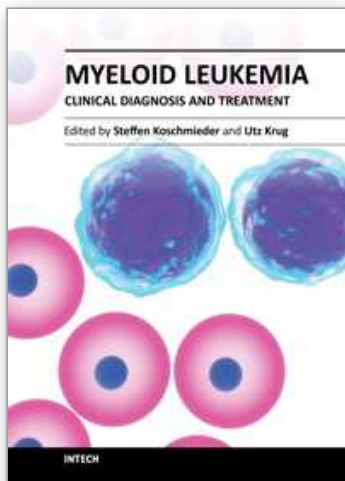
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