ORIGINAL ARTICLE

pISSN 2384-1079 · eISSN 2384-1087
Pediatr Infect Vaccine 2016;23:172-179
DOI: https://doi.org/10.14776/piv.2016.23.3.172

PIV PEDIATRIC INFECTION & VACCINE

소아 암 환자에서 발생한 *Bacillus cereus* 균혈증의 분자역학 분석에 관한 연구

김종민[1,2*] · 박기섭[3*] · 이병기[4] · 김수진[3] · 강지만[2] · 김양현[3] · 유건희[2] · 성기웅[2] · 구홍회[2] · 이남용[5] · 김예진[2]

서남대학교 의과대학 명지병원 소아청소년과[1], 성균관대학교 의과대학 삼성서울병원 소아청소년과[2], 삼성생명과학연구소 임상의학연구센터[3], 좋은강안병원 소아청소년과[4], 성균관대학교 의과대학 삼성서울병원 진단검사의학과[5]

Molecular Epidemiology of *Bacillus cereus* in a Pediatric Cancer Center

Jong Min Kim[1,2*], Ki-Sup Park[3*], Byung-Kee Lee[4], Soo Jin Kim[3], Ji-Man Kang[2], Yanghyun Kim[3], Keon Hee Yoo[2], Ki Woong Sung[2] Hong Hoe Koo[2], Nam Yong Lee[5], Yae-Jean Kim[2]

[1]Department of Pediatrics, Myongji Hospital, Seonam University College of Medicine, Goyang, [2]Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, [3]Center for Clinical Research, Samsung Biomedical Research Institute, Seoul, [4]Department of Pediatrics, Good Gang-An Hospital, Busan, [5]Department of Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Purpose: *Bacillus cereus* has been reported as the cause of nosocomial infections in cancer patients. In our pediatric cancer ward, a sudden rise in the number of patients with *B. cereus* bacteremia was observed in 2013 to 2014. This study was performed to investigate the molecular epidemiology of increased *B. cereus* bacteremia cases in our center.

Methods: Pediatric cancer patients who developed *B. cereus* bacteremia were identified from January 2001 to June 2014. The *B. cereus* bacteremia in this study was defined as a case in which at least one *B. cereus* identified in blood cultures, regardless of true bacteremia. Available isolates were further tested by multilocus sequence typing (MLST) analysis. A retrospective chart review was performed.

Results: Nineteen patients developed *B. cereus* bacteremia during the study period. However, in 2013, a sudden increase in the number of patients with *B. cereus* bacteremia was observed. In addition, three patients developed *B. cereus* bacteremia within 1 week in July and the other three patients within 1 week in October, respectively, during emergency room renovation. However, MLST analysis revealed different sequence types without consistent patterns. Before 2013, five tested isolates were ST18, ST26, ST177, and ST147-like type, and ST219-like type. Isolates from 2013 were ST18, ST73, ST90, ST427, ST784, ST34-like type, and ST130-like type.

Conclusions: MLST analyses showed variable ST distribution of *B. cereus* isolates. Based on this study, there was no significant evidence suggesting a true outbreak caused by a single ST among patients who developed *B. cereus* bacteremia.

Key Words: Bacillus cereus; Disease outbreaks; Multilocus sequence typing; Pediatrics; Neoplasms

*Jong Min Kim and Ki-Sup Park contributed equally to this study as first authors.

Received: 26 April 2016
Revised: 13 May 2016
Accepted: 13 May 2016

Correspondence: Yae-Jean Kim
Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
Tel: +82-2-3410-3539, Fax: +82-2-3410-0043
E-mail: yaejeankim@skku.edu

Introduction

Bacillus cereus is a gram-positive, spore-forming rod. Endospores from *Bacillus* species are resistant to advers environmental conditions, which enable *B. cereus* to be ubiquitous in nature[1)]. *B. cereus* is a major bacterium that causes food poisoning[2,3)]. In addition,

this species has been reported as a cause of nosocomial infection, especially in immunocompromised patients[4-11], and several nosocomial outbreaks of *B. cereus* have been reported[4,12-14]. We experienced a sudden increase of *B. cereus* bacteremia episodes in 2013. More importantly, there were two clusters of *B. cereus* bacteremia episodes in July and October, where three patients developed bacteremia within 1 week in July and another three patients also had bacteremia within 1 week in October. This observation prompted us to investigate the molecular epidemiology of *B. cereus* bacteremia that occurred in our pediatric cancer center and to examine whether the bacteremia episodes were linked by a common strain.

Materials and Methods

We retrospectively reviewed the medical records of pediatric cancer patients who developed *B. cereus* bacteremia between January 2001 and June 2014. The Institutional Review Board of Samsung Medical Center (IRB File No. 2015-04-031) approved this study.

1. The definitions of *B. cereus* bacteremia and catheter-related bloodstream infection

The *B. cereus* bacteremia in this study was defined as a case in which at least one *B. cereus* identified in blood cultures, regardless of true bacteremia. As regards that all patients in this study had central venous catheters, catheter-related bloodstream infection (CRBSI) was defined when growth of microbes from blood drawn from a catheter hub at least 2 hours before microbial growth is detected in blood samples obtained from a peripheral vein. The true bacteremia was defined when both one peripheral blood culture and every catheter blood cultures, are positive for *B. cereus* without time-to-positivity. The contamination or colonization were defined if it did not met the criteria of CRBSI or true bacteremia.

2. Bacterial isolates, media, and bacterial growth

The isolates of *B. cereus* bacteremia obtained in blood cultures, which had been stored in a freezer, were subcultured by inoculating them on blood agar plates and incubating at 37℃ for 18 hours.

3. DNA extraction

A loopful of isolates of each *B. cereus* strain was suspended in phosphate-buffered saline and centrifuged for 10 minutes at 7,500 rpm. After removing the supernatant, the pellet was suspended in 480 μL of 50 mM ethylenediaminetetraacetic acid, and 60 μL 10 mg/mL lysozyme and 60 μL of 10 mg/mL lysostaphin (Sigma-Aldrich, St. Louis, MO, USA) were added. The solution was incubated for 30 minutes at 37℃. Next, extraction of genomic DNA from *B. cereus* was performed using the QIAamp DNA mini kit (Qiagen, Hilden, Germany).

4. Multilocus sequence typing analysis

Seven genes chosen for multilocus sequence typing (MLST) analysis included glpF (glycerol uptake facilitator protein), gmk (guanylate kinase, putative), ilvD (dihydroxy-acid dehydratase), pta (phosphate acetyltransferase), pur (phosphoribosylaminoimidazolecarboxamide), pycA (pyruvate carboxylase), and tpi (triosephosphate isomerase) (http://pubmlst.org).

The polymerase chain reaction (PCR) conditions used for amplification were as follows. A PCR was performed for 35 cycles with a 25 μL PCR mixture containing each deoxynucleoside triphosphate at a concentration of 10 mM, each primer at a concentration of 40 pmol, 500 ng of genomic DNA, and 1 U of Taq polymerase. An initial denaturation at 94℃ for 5 minutes was followed by 94℃ for 30 seconds. The primers and annealing temperatures for each primer set are shown in Table 1. The annealing time was 30 seconds, which was followed by extension for 30 seconds at 72℃. After 35 cycles, the reaction was completed by a final extension at 72℃ for 7 minutes. Nucleotide sequencing data was obtained.

The sequencing data was analyzed using the MLST website (http://pubmlst.org)[15-17].

Table 1. Primers Used for Polymerase Chain Reaction Amplification and Sequencing of *Bacillus cereus* Group Housekeeping Genes (http://pubmlst.org)

Gene	Gene length (bp)	Forward primer 5'-3' sequence	Reverse primer 5'-3' sequence	Annealing temperature (℃)
glpF	549	GCGTTTGTGCTGGTGTAAGT	CTGCAATCGGAAGGAAGAAG	59
gmk	600	ATTTAAGTGAGGAAGGGTAGG	GCAATGTTCACCAACCACAA	56
ilvD	556	CGGGGCAAACATTAAGAGAA	GGTTCTGGTCGTTTCCATTC	58
pta	579	GCAGAGCGTTTAGCAAAAGAA	TGCAATGCGAGTTGCTTCTA	56
pur	536	CTGCTGCGAAAAATCACAAA	CTCACGATTCGCTGCAATAA	56
pycA	550	GCGTTAGGTGGAAACGAAAG	CGCGTCCAAGTTTATGGAAT	57
tpi	558	GCCCAGTAGCACTTAGCGAC	CCGAAACCGTCAAGAATGAT	58

Abbreviations: *glpF*, glycerol uptake facilitator protein; *gmk*, guanylate kinase, putative; *ilvD*, dihydroxy-acid dehydratase; *pta*, phosphate acetyltransferase; *pur*, phosphoribosyl aminoimidazolecarboxamide; *pycA*, pyruvate carboxylase; *tpi*, triosephosphate isomerase.

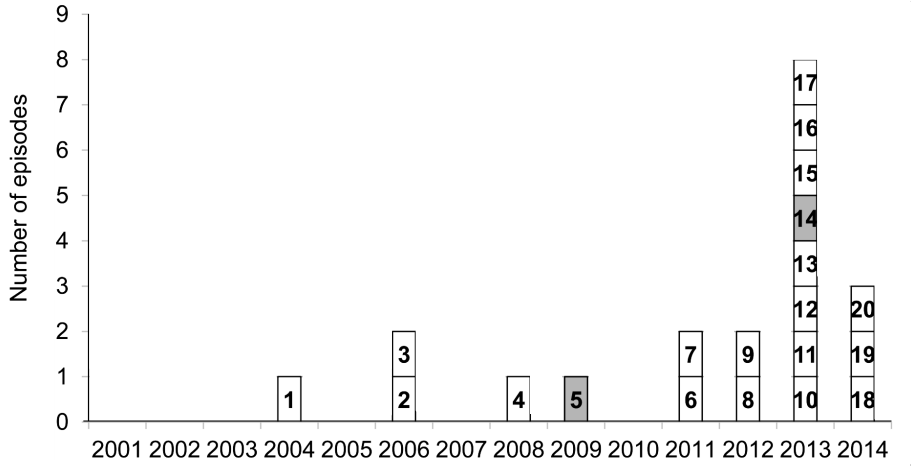

Fig. 1. Distribution of *Bacillus cereus* bacteremia episodes by year. Number in the bar indicates each bacteremia episode. No. 5 and 14 are two episodes from the same patient.

Table 2. Patient Characteristics

Characteristic	Value (n=19)
Male sex	7 (36.8)
Underlying disease	
Acute lymphoblastic leukemia	4
Acute myeloid leukemia	2
Hemophagocytic lymphohistiocytosis	1
Neuroblastoma	7
Wilms tumor	2
Other solid tumors*	3
Age at *Bacillus cereus* bacteremia (yr)	4.5 (1.5–18.2)
Hematopoietic stem cell transplantation recipients	6 (31.5)
Catheter-related infection	13 (68.4)
Neutropenia	12 (63.1)

Values are presented as number (%) or median (range).
*Medulloblastoma (n=1), ependymoma (n=1), and glioma (n=1).

Results

1. Characteristics of patients with *B. cereus* bacteremia

A total of 20 episodes of *B. cereus* bacteremia occurred in 19 patients during the study period. One patient had two episodes of *B. cereus* bacteremia in September 2009 and October 2013, respectively. Eleven episodes (11/20, 55%) occurred between January 2013 and June 2014 (Fig. 1). The characteristics of study patients are shown in Table 2. Bacteremia in three patients (isolates 10, 11, and 12) were clustered within 1 week in July 2013 and in another three patients (isolates 14, 15, and 16) were clustered within 1 week in October 2013.

In the cluster cases of July 2013, blood cultures from two patients were collected in an emergency room

(ER; isolates 10 and 12) and one patient (isolate 11) developed bacteremia while staying in the pediatric cancer ward. The patient with isolate 10 underwent a second autologous peripheral blood stem cell transplantation for medulloblastoma and the patient with isolate 12 had glioma. Both patients developed fever during radiotherapy and were diagnosed to have CRBSI caused by *B. cereus*. Of note, the patient with isolate 12 continued to have positive culture results from the second blood culture, which was collected in the pediatric cancer ward. The patient with isolate 11 developed bacteremia in the cancer ward during the induction treatment for leukemia.

In the cluster cases of October 2013, blood cultures from two patients were collected in the ER (isolates 14 and 16) and one patient (isolate 15) developed bacteremia while staying in the pediatric cancer ward. The patient with isolate 14 visited the ER with neutropenic fever and blood cultures grew *B. cereus* only from the third lumen of a Hickman catheter. The follow-up blood cultures collected in the cancer ward before initiation of appropriate antibiotic therapy showed no further bacteremia in any Hickman catheter lumens. The patient with isolate 16 visited the ER with neutropenic fever and the blood cultures grew *B. cereus* only from a peripherally inserted central catheter. Meanwhile, the case with isolate 15 developed CRBSI in the transplantation unit, where the patient was undergoing peripheral blood stem cell collection for transplantation.

In the cluster cases of July 2013, all three cases of *B. cereus* infection appeared to be true bacteremia. However, in the cluster cases of October 2013, two cases (isolates 14 and 16) appeared to be contamination or colonization, and only one case with isolate 15 appeared to be true bacteremia. All six patients had a central catheter. Three of the patients were in a neutropenic state. In relation to stem cell transplantation, one patient was 113 days post second autologous peripheral blood stem cell transplantation. Co-infection was observed in one patient (isolate 11) with parainfluenza infection.

Overall mortality at 28 days from *B. cereus* bacteremia onset was 10.5% (2/19). One patient died of suspected septic shock without any identified microorganism while the other patient died of *Enterobacter aerogenes* sepsis.

2. MLST analysis

Of the 20 episodes of *B. cereus* bacteremia, 15 isolates were available for MLST analysis. The analysis showed 12 sequence types (ST18, ST24, ST26, ST34-like type, ST73, ST90, ST130-like type, ST147-like type, ST177, ST219-like type, ST427, and ST784) (Tables 3, 4). The phylogenetic relationship of the 15 isolates according to MLST analysis using seven genes concatenately is shown in Fig. 2. All available five isolates from the July 2013 and October 2013 clusters had different STs, respectively (Table 4).

There are three STs that were identified in two or more isolates. ST18 was identified in isolate 7 (year 2011) and 12 (year 2013). ST73 was identified in isolates 10 (year 2013) and 20 (year 2014). ST177 was observed in isolates 5 (year 2009) and 19 (year 2014). Even though these isolates share the same STs, there were no epidemiological links. Except for these three

Table 3. Results of Seven Genes and Sequence Types of Each Isolates

ID	glp	gmk	ilv	pta	pur	pyc	tpi	ST
5	13	47	9	11	68	12	10	177
6	74	22	85	62	66	66	75	Nearest match 219
7	11	9	14	12	12	14	7	18
8	1	1	122	1	18	33	3	Nearest match 147
9	3	2	31	5	16	3	4	26
10	13	8	9	14	9	12	31	73
11	6	4	41	5	43	46	3	90
12	11	9	14	12	12	14	7	18
13	122	8	8	11	9	12	10	427
14	201	36	229	210	196	176	32	784
15	33	8	146	19	2	17	7	Nearest match 34
17	65	1	83	1	1	37	43	Nearest match 130
18	12	8	9	14	11	12	10	24
19	13	47	9	11	68	12	10	177
20	13	8	9	14	9	12	31	73

Abbreviations: ID, identification; glp, glycerol uptake facilitator protein; gmk, guanylate kinase, putative; ilv, dihydroxy-acid dehydratase; pta, phosphate acetyltransferase; pur, phosphoribosylaminoimidazolecarboxamide; pyc, pyruvate carboxylase; tpi, triosephosphate isomerase; ST, multilocus sequence type.

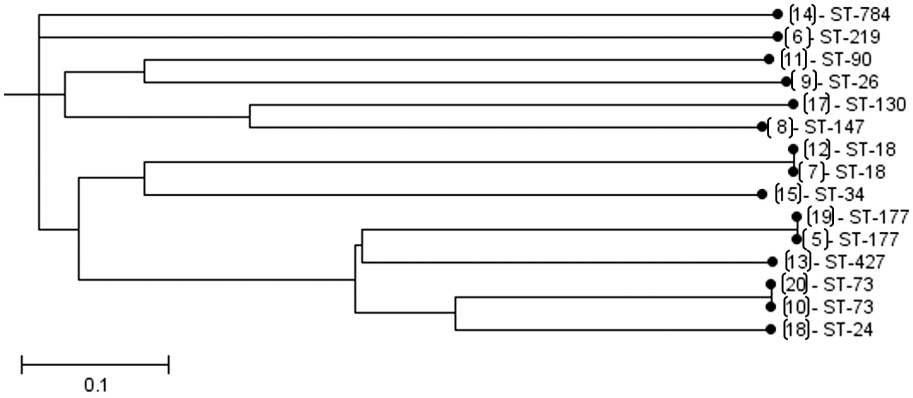

Fig. 2. Phylogenetic tree of 15 tested isolates. Numbers in parentheses indicate each isolate ID. Isolates from episodes 1, 2, 3, 4, and 16: not available. The scale at the bottom represents genetic distances in nucleotide substitutions per site.

Table 4. Comparison of STs according to Time Period (2001 to 2012 vs. 2013 to April 2014)

2001–2012		2013–April 2014	
Isolate ID	ST	Isolate ID	ST
1	NA	10	73
2	NA	11	90
3	NA	12	18
4	NA	13	427
5	177	14	784
6	Nearest 219	15	Nearest 34
7	18	16	NA
8	Nearest 147	17	Nearest 130
9	26	18	24
		19	177
		20	73

No. 5 and 14 are two episodes from the same patient.
Abbreviations: ST, multilocus sequence type; ID, identification; NA, not available.

STs, there was no common ST among the rest of the 9 isolates (Fig. 2).

Discussion

B. cereus is well known as a common cause of bacteremia in immunocompromised patients[4-11] and nosocomial infection has been reported in previous studies[4,12-14]. In this study, there was also a suspicion for nosocomial infection of *B. cereus* bacteremia in our pediatric cancer center because of a sudden increase of *B. cereus* bacteremia episodes in 2013 to 2014. However, further investigation for molecular epidemiology by MLST revealed little possibility of nosocomial transmission of a single strain of bacteria.

Nosocomial infection of *B. cereus* is well known. Outbreaks that originated from common contaminant sources, such as linens and towels, were reported in some studies[12-14]. In those cases, similarity of *B. cereus* on MLST or pulsed-field gel electrophoresis analysis was reported between the *B. cereus* isolated from patient blood cultures and environment cultures. Since *B. cereus* endospores are known to be resistant to heat and alcohol[1,18], it was thought that endospores could have survived in the hospital environment, such as washing machines or hands, to cause the outbreak of *B. cereus* bacteremia. In those studies, control measures against the outbreak were implemented. It included sterilizing linens by autoclaving, cleansing washing machines with a powerful detergent, and washing hands with soap instead of alcohol[19], and promoting the use of gloves among the hospital staff during patient care. After implementation, the incidence of *B. cereus* nosocomial infection was decreased significantly[12,13].

On the contrary, pseudo-outbreaks are also possible in a situation where an organism is recovered from culture at a higher rate than usual and that cannot be clinically correlated with the supposed infection[20,21]. This situation may result from systemic extrinsic contamination during specimen collection or processing or intrinsic contamination at the time the culture medium

was manufactured or prepared[21,22].

In this study, the suspicion for outbreak caused by *B. cereus* from a common source began when we observed clusters of *B. cereus* bacteremia in three patients in 1 week in July and October, 2013. However, MLST analysis revealed a total of 12 different STs in 15 isolates (Table 3). In 12 STs, ST18, ST73, ST90, and ST147 were reported previously in human bacteremia cases (http://pubmlst.org)[23-25]. The ST24, ST34, ST177, and ST427 types are known to be found in food, feces, and the human body (http://pubmlst.org; http://cdc.go.kr)[25,26]. The remaining ST26, ST130, ST219, and ST784 types were reported in soil (http://mlstoslo.uio.no). Therefore, it appears that the possibility of a common infection source for B. cereus bacteremia was low in the current study.

Upon additional investigation, we found that a part of the ER was under remodeling construction between July 1 2013 and October 10 2013. Among a total of six cases of *B. cereus* bacteremia in July and October 2013, four cases of blood cultures were collected in the ER. The increase of *B. cereus* bacteremia following hospital construction was previously reported. Loeb et al.[27] reported pseudo-bacteremia, speculating that *Bacillus* species acting as airborne contaminants from the construction site likely seeded the plastic lids of the stored blood culture bottles. Another *Bacillus* outbreak after renovation work was reported by Ohsaki et al.[21]. They considered the case as an undetected *Bacillus* pseudo-outbreak after the hospital renovation work. They also considered that filters of the heating, ventilation, and air-conditioning systems and towels and gowns were probable sources of the outbreak[21]. However, we did not discover a definite correlation between ER renovation and the increase of *B. cereus* bacteremia.

Although there is a possibility that increased *B. cereus* bacteremia in our center were a part of a pseudo-outbreak, we could not prove it. It appears that the increase of *B. cereus* bacteremia came from temporary contamination with diverse *B. cereus* STs, which were distributed throughout various environments rather than from a common environmental source contaminated with a specific *B. cereus* ST.

Our study has several limitations. First, this study was performed retrospectively. We could not perform the environmental cultures at the time every *B. cereus* bacteremia case developed. We did not obtain a questionnaire from the patients and their parents to find a common exposure source such as food, specific behavior, and contact history to the person or materials. Second, except MLST analysis, additional studies, such as virulence gene analysis or antibiotic susceptibility tests, were not performed on these *B. cereus* isolates. Finally, because of the small sample number limited to pediatric cancer patients, we could not identify the risk factors for *B. cereus* bacteremia and the difference of clinical course according to *B. cereus* sequence type.

In conclusion, although a sudden increase in *B. cereus* bacteremia cases was observed in our pediatric cancer center, there was no significant evidence suggesting a true outbreak caused by a single ST based on molecular epidemiological links. However, there may be a possibility of a pseudo-outbreak caused by multiple STs in the process of the renovation work of the hospital. Continuous monitoring is needed and hospital environmental culture surveillance is required especially when increased *B. cereus* bacteremia cases are observed or possible environmental contamination is suspected. Furthermore, the intensified implementation of control measures should be maintained according to the comprehensive and effective infection control policy.

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요약

목적: *Bacillus cereus*는 암환자들에서 기회감염을 일으킬 수 있다. 2013년에서 2014년 기간 동안 삼성서울병원 소아 암 병동에서 *B. cereus* 균혈증의 급격한 증가가 관찰되었다. 이에 증가된 *B. cereus* 균혈증에 대해 분자역학적 연구를 시행하였다.

방법: 2001년 1월부터 2014년 6월까지의 기간 동안 *B. cereus* 균혈증이 발생한 소아 암 환자들을 확인하였다. 이번 연구에서 *B. cereus* 균혈증은, 오염여부와는 상관없이, 혈액배양검사에서 적어도 한 번 이상 *B. cereus*가 확인된 경우로 정의하였다. 획득 가능한 균주들에 대해 multilocus sequence typing (MLST) 분석을 시행하였고, 후향적 챠트 리뷰를 실시하였다.

결과: 연구 기간 동안 총 19명의 *B. cereus* 균혈증 환자가 확인되었다. 그러나, 2013년도에는 *B. cereus* 균혈증 환자가 급격하게 증가하였다. 또한, 응급실 공사 중이던 2013년 7월의 1주, 2013년 10월의 한 주 동안 각각 3명의 환자가 발생하였다. 그러나 MLST 분석상 일정한 패턴이 없는, 다양한 sequence types (STs)들로 확인되었다. 2013년 이전의 5개의 균주들의 ST는 ST18, ST26, ST177, ST147-like type, ST219-like type이었고, 2013년도의 균주들의 ST는 ST18, ST73, ST90, ST427, ST784, ST34-like type, ST130-like type으로 확인되었다.

고찰: MLST 분석상 *B. cereus* 균주들의 다양한 ST 분포가 확인되었다. 이번 연구에서 단일 ST의 *B. cereus*에 의한 균혈증 발생의 가능성은 낮아보인다.