Use of peripheral parenteral nutrition solutions as a risk factor for *Bacillus cereus* peripheral venous catheter-associated bloodstream infection at a Japanese tertiary care hospital: A case-control study

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PPN solutions as risk for *B. cereus* PVCBSI
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Summary

The risk factors are unclear for peripheral venous catheter-associated bloodstream infections (PVCBSI) by *Bacillus cereus* (*B. cereus*). Thus, we aimed to examine the risk factors in patients with *B. cereus* PVCBSI by conducting a 2-year case-control study in a large teaching hospital. We analyzed all adult cases of *B. cereus* PVCBSI (37 patients) and 180 controls, who were randomly selected from among patients who had a PVC in place for 2 days or longer. Multivariate analysis using the conditional logistic regression model indicated that independent risk factors were use of a peripheral parenteral nutrition (PPN) solution with adjusted odds ratio (OR) of 88.7 (95% confidence interval [CI], 17.4-451.9), and steroid therapy [adjusted OR, 5.7 (95% CI, 1.3-24.4)]. In conclusion, use of PPN solutions or steroids was independent risk factors for *B. cereus* PVCBSI. Appropriate use of PPN solutions may help prevent *B. cereus* PVCBSI. Prospective studies are needed to confirm these results.
"Bacillus cereus" is a ubiquitous aerobic spore-forming Gram-positive bacillus that is distributed over soil, water, or dust, and in hospital environments (1,2). The pathogenicity in cases of food-borne "B. cereus" infection commonly results from the enterotoxin produced by this organism, and central line-associated bloodstream infections, meningitis, ventilator-associated pneumonia have occurred in immunocompromised individuals (1-7).

Blood cultures that are positive for "B. cereus" usually result from a false-positive contaminant in the environment where the blood culture had been obtained (8). However, outbreaks of catheter-related bloodstream infection (CRBSI) have been sporadically reported in association with a specific hospital environment or linens (9-17). Multiple fatal cases with serious "B. cereus" CRBSI were recently reported (3, 6, 13-15, 17).

It is unclear what risk factors exist for the development of "B. cereus" CRBSI. Only small case series or studies on special subgroups such as patients with haematological cancers or patients with central lines have been conducted on this issue (14, 17). No studies have investigated risk factors of patients with "B. cereus" peripheral venous
catheter-associated bloodstream infections (PVCBSIs). Thus, we aimed to examine the risk factors in patients with \textit{B. cereus} PVCBSI by conducting a case-control study in a large teaching hospital.

This 2-year case-control study was conducted in an 802-bed acute care teaching hospital in the Kanto area of Japan between January 2005 and December 2006. Approval from the Human Subject Committee of this hospital was obtained. Patients were 18 years or older; had episodes of two-set or greater positive blood cultures for \textit{Bacillus cereus} 48 hours after admission; and were believed to have PVCBSI, based on the diagnostic criteria of laboratory-confirmed bloodstream infection (LCBSI) by the United States Centers for Disease Control and Prevention (CDC; Atlanta, GA, USA). The case identification and confirmation was performed \textit{via} two-step process: (1) all enrolled prospective patients with positive blood cultures were checked by a certified infection disease physician with regard to the PVCBSI criteria (these physicians are required to consult all patients with positive blood cultures) and (2) the patients were retrospectively double-checked in accordance with the PVCBSI criteria by a certified infection control nurse who was a principal investigator in this study. Patients who did not meet the diagnostic criteria were excluded. In patients with multiple episodes of
these infections, the first episode was used for analysis.

The control patients were 18 years or older and were admitted for more than 5 days during the 2-year study period. They had peripheral venous catheters in place for more than 48 consecutive hours. The department of clinical microbiology in this hospital cultured and identified \textit{B. cereus}. The department fulfilled the quality standard evaluation by the Japan Council for Quality Health Care (http://jcqhc.or.jp/).

A research nurse collected the case and control patient data by using electronic medical records. Based on previous study (1, 2, 9, 13, 17, 18), the data collected were demographics; admission diagnosis; nutritional status assessed by Mini Nutritional Assessment (MNA) (19); comorbid conditions (e.g., diabetes, cancer); medication exposure previous surgery, use of mechanical ventilation, central venous catheter or urethral catheter; solute contents of a peripheral intravenous infusion; number of days of peripheral catheter placement. Data of the solute content of peripheral intravenous infusions were collected within 30 days before the BSI episode with regard to electrolytes-only solutions; 5% glucose and electrolytes solutions; 7.5% glucose and electrolytes solutions; 7.5% glucose, amino acids, and electrolytes (i.e., PPN) solutions.
Risk factors associated with *B. cereus* PVCBSI were analyzed between the patients and controls for clinically important variables, Univariate analyses used the chi-square test or Fisher’s exact test for categorical variables, or the Student *t* test or Mann–Whitney *U* test for continuous variables, when appropriate. A multivariable-adjusted conditional logistic regression model was constructed by adjusting for possible risk factors for PVCBSI. The odds ratios (OR) with 95% confidence interval (95% CI) were estimated. Statistical analyses were conducted using SPSS Statistics, version 21 software (IBM, Armonk, NY, USA) or STATA, version 13 software (StataCorp LP, College Station, TX, USA). The institutional review board of the International University of Health and Welfare (Tokyo, Japan) gave ethical approval (No.07-64).

In total, 38,495 patients were admitted to the hospital during the study period. Thirty-seven patients had confirmed cases of *B. cereus* PVCBSI. Thus, 180 patients remained as the control patients.

Table I shows clinical characteristics of the case and control patients. Among the case patients, the mean age was 70 years (SD, 13.9 years) and median age, 74 years (IQR,
60–80 years. This group comprised 26 men (70%) and 11 women (30%). The median number of days to the onset of PVCBSI was 44 days (range, 3–207 days).

Among the controls, the mean age was 64.3 years (SD, 19.5 years) and the median age, 68 years (IQR, 55.8–79 years). The group comprised 87 men (48%) and 93 women (52%).

The case patients were older than the controls ($P = 0.04$), and had a greater proportion of men ($P = 0.02$). The case patients also had a greater proportion of cerebrovascular diseases (35.1%, $P = 0.001$).

Table II shows potential risk factors for $B$. cereus PVCBSI between the case patients and controls. In univariate analyses, significant risk factors included age, male sex, steroid therapy, and use of 7.5% glucose, amino acids, and electrolytes solution for PPN.

In multivariate analysis using a conditional logistic regression model, the factors significantly associated with $B$. cereus PVCBSI were steroid therapy [adjusted OR, 5.7...
(95% CI, 1.3-24.4)] and use of PPN solution with 7.5% glucose, amino acids, and electrolytes [adjusted OR, 88.7 (95% CI, 17.4-451.9)].

We found that significant risk factors for *B. cereus* PVCBSI were use of PPN solution and steroid therapy. For the first time, PPN solution was identified in our study as a risk factor.

The most probable mechanism for the increased risk of developing *B. cereus* PVCBSI in patients on PPN solutions is that *B. cereus* grows rapidly in a PPN solution and can thus contaminate it. A previous *in vitro* study proved *B. cereus* grows rapidly in PPN solutions with 3% amino acid, 7.5% glucose solution, and electrolytes (Aminofluid; Otsuka Pharmaceutical Factory, Tokyo, Japan) (20, 21).

Another possible mechanism that the use of PPN solutions is likely associated with higher risk for peripheral thrombophlebitis is because of greater vessel damage resulting from the chemical characteristics of the solutions (e.g., low pH [6.4] and high solution-to-serum osmolality ratio of approximately 3) (18, 22, 23). A third possible mechanism is that *B. cereus* is very capable of forming a biofilm in artificial tubes (12,
In 1996, PPN was introduced after a previous study demonstrated the efficacy of nutritional support by peripherally inserted venous catheters in 1993(25). A double bag product of PPN solutions have been developed and distributed throughout Japan (26). The timing of the product development may be associated with *B. cereus* BSI case reports (9, 10, 12-15, 17).

Possible infectious routes may include bacterial contaminations over the skins of patients or healthcare providers or in venous lines or three-way stopcocks. Especially in peripheral venous catheters, three-way stopcocks are frequently left open and alcohol-resistant and rapidly growing *B. cereus* could contaminate inside lumens of venous line hubs.

Steroid use was an independent risk factor. This result may implicate cellular immunodeficiency as a host risk factor for *B. cereus* PVCBSI.

Our study may have some limitations. First, this study was based on a single hospital
retrospective study. Second, the hospital stay was longer in the case patients than in the control patients. *Bacillus cereus* PVCBSI may have caused the longer hospital stay in the case patients or the longer stay may have increased the risk of contracting a PVCBSI.

Third, the selection of our control patients did not take into consideration a seasonal trend with a higher risk in summer.

In conclusion, our study suggested that use of PPN solutions or steroids were independent risk factors for *B. cereus* PVCBSI. Appropriate use of PPN solutions should be promoted to prevent *B. cereus* PVCBSI, and nutritional outcomes should be assessed by using these solutions. Future prospective studies are needed to confirm these issues.

**Conflict of interest:** None declared.

**Acknowledgements:** We express our greatest appreciation for the excellent advice from Dr. Kazuo Endo who was the great infectious disease physician, but unfortunately passed away at a young age from an illness.
References


Table I. Clinical characteristics of the participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Case (n = 37)</th>
<th>Control (n = 180)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), mean (standard deviation)</td>
<td>70.1 (13.9)</td>
<td>64.3 (19.5)</td>
<td>0.04</td>
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<tr>
<td>Sex: male, no. (%)</td>
<td>26 (70.3)</td>
<td>87 (48.3)</td>
<td>0.02</td>
</tr>
<tr>
<td>Admission diagnosis, no. (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cerebrovascular disease</td>
<td>13 (35.1)</td>
<td>20 (11.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Solid tumour</td>
<td>9 (24.3)</td>
<td>36 (20.0)</td>
<td>0.66</td>
</tr>
<tr>
<td>Gastrointestinal disease</td>
<td>4 (10.8)</td>
<td>30 (16.7)</td>
<td>0.46</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>3 (8.1)</td>
<td>18 (10.0)</td>
<td>0.73</td>
</tr>
<tr>
<td>Haematological disease</td>
<td>2 (5.4)</td>
<td>7 (3.9)</td>
<td>0.65</td>
</tr>
<tr>
<td>Community-acquired infection</td>
<td>2 (5.4)</td>
<td>20 (11.1)</td>
<td>0.38</td>
</tr>
<tr>
<td>Orthopaedic disease</td>
<td>2 (5.4)</td>
<td>7 (3.9)</td>
<td>0.65</td>
</tr>
<tr>
<td>Obstetric/gynaecologic disease</td>
<td>0</td>
<td>12 (6.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Others</td>
<td>2 (5.4)</td>
<td>30 (16.7)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

IQR, interquartile range; NS, not significant.
Table II. Risk factors of *Bacillus cereus* bloodstream infections

<table>
<thead>
<tr>
<th>Factors</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
</tr>
<tr>
<td></td>
<td>(n = 37)</td>
<td>(n = 180)</td>
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<tr>
<td>Demographic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y), median (IQR)</td>
<td>74 (60-80)</td>
<td>68 (56-79)</td>
</tr>
<tr>
<td>Sex: male, no. (%)</td>
<td>26 (70.3)</td>
<td>87 (48.3)</td>
</tr>
<tr>
<td>Comorbid conditions, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>9 (24.3)</td>
<td>28 (15.6)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>10 (27.0)</td>
<td>27 (15.0)</td>
</tr>
<tr>
<td>Medication exposure in 30 days before the BSI, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticancer chemotherapy</td>
<td>4 (10.8)</td>
<td>30 (16.7)</td>
</tr>
<tr>
<td>Steroid</td>
<td>11 (29.7)</td>
<td>22 (12.2)</td>
</tr>
<tr>
<td>Previous surgery</td>
<td>8 (21.6)</td>
<td>31 (17.2)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>1 (2.7)</td>
<td>8 (4.4)</td>
</tr>
<tr>
<td>Central venous catheter</td>
<td>0</td>
<td>10 (5.6)</td>
</tr>
<tr>
<td>Urethral catheter</td>
<td>16 (43.2)</td>
<td>65 (36.1)</td>
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</tbody>
</table>

**Solute contents of peripheral intravenous infusion, no. (%)**

| (1) 5% glucose and electrolytes        | 32 (86.5) | 170 (94.4) | 0.4 (0.1-1.4) | 0.14 |
| (2) 7.5% glucose and electrolytes     | 5 (13.5)  | 18 (10.0)  | 1.4 (0.5-4.1) | 0.56 |
| (3) 7.5% glucose, 3% amino acids, and electrolytes (PPN) | 32 (86.5) | 26 (14.4)  | 37.9 (13.5-106.2) | <0.001 | 88.7 (17.4-451.9) |

BSI, bloodstream infection; CI, confidence interval; IQR, interquartile range; OR, odds ratio; PPN, peripheral parenteral nutrition; SD, standard deviation.