Clinical and Epidemiological Features of *Clostridium perfringens* Bacteremia: A Review of 18 Cases over 8 Year-Period in a Tertiary Care Center in Metropolitan Tokyo Area in Japan

Hiroshi Fujita¹, Shigeko Nishimura¹, Saiko Kurosawa¹, Itsuo Akiya², Fukumi Nakamura-Uchiyama¹ and Kenji Ohnishi³

**Abstract**

**Objective** Clostridial sepsis has a very poor prognosis, owing to the life-threatening combination of shock and acute massive hemolysis. No papers have described the clinical features of clostridial sepsis cases in Japan. Therefore, we retrospectively examined the clinical features of patients with systemic inflammatory response syndrome (SIRS) from whose blood cultures *Clostridium perfringens* was isolated.

**Subjects and Materials** Blood samples were obtained from SIRS patients and cultured between January 1, 2001 and June 30, 2009. The samples were retrospectively reviewed, and 18 samples were positive for *C. perfringens*. The medical records of these 18 patients were reviewed for age, gender, underlying disease, past illnesses, results of physical and laboratory testing, and radiographic data.

**Results** All patients were diagnosed with SIRS. Fifteen patients (83.3%) were >65 years old—mean age, 75±2 years (range, 59-88 years). There were more men (13) than women (5). The blood cultures were obtained from patients in various wards: tertiary care center (8), emergency room (5), surgical ward (4), and medical ward (1). Hepatobiliary tract diseases such as gallbladder stones and hepatic carcinoma were the most frequent underlying diseases (8). Five patients died, resulting in an overall mortality rate at 30 days of 27%. In the non-survival group, patients presented with septic shock (4) and gas-forming infection (2), and with significantly lower fibrinogen levels than those in the survival group. Septic shock at initial presentation was significantly associated with 30-day mortality for *C. perfringens* infection.

**Discussion and Conclusion** There were no specific characteristics among clinical features of *C. perfringens* infection accompanied with SIRS. This may indicate that, in emergency rooms, diagnosing and initiating appropriate treatment for *C. perfringens* infection may be considerably difficult. It is important to be especially vigilant in identifying patients with *C. perfringens* infection underlying SIRS, and accompanied by shock.

**Key words:** hemolysis, sepsis, shock

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**Introduction**

*Clostridium perfringens* is a gram-positive bacillus. Patients who contract *C. perfringens* infections exhibit various clinical symptoms such as gastroenteritis, alimentary intoxication, gas gangrene, necrotizing enteritis, and septic shock with acute hemolysis. *C. perfringens* infection is considered to be the cause of many diseases in non-urban regions (1). In addition, increasing incidence of enteric transmission of *C. perfringens* has been reported in the city of Tokyo and the surrounding area (2).

In previous research for which blood samples were obtained from patients in tertiary-care departments, 0.5-2.0%...
of all isolates from blood cultures indicated a diagnosis of clostridial sepsis. *C. perfringens* was the most frequently identified organism, accounting for 20-50% of isolates (3).

Rechner et al (1) also reported the clinical features of clostridial bacteremia in a rural area. Again, *C. perfringens* was the most frequently encountered organism, accounting for 21.7% of isolates. Over the past 40 years, observational studies from large metropolitan hospitals have shown that the presence of clostridial species in blood cultures may be explained on the basis of multiple factors, including contamination; transient bacteremia, often from an unknown source; traumatic or surgically related bowel leakage or abscess; and, rarely, gas-forming tissue infections, such as emphysematous cholecystitis, crepitant cellulitis, fasciitis, or myonecrosis (1, 3).

A number of case reports on severe clostridial sepsis with hemolysis were previously described (4-6). However, no papers have reported the clinical features of clostridial sepsis cases in Japan. We speculated that *C. perfringens* infection may not be uncommon in Tokyo (2). Therefore, we retrospectively studied the clinical features of patients from whose blood cultures *C. perfringens* was isolated in Tokyo Metropolitan Bokutoh General Hospital.

### Material and Methods

#### Clinical evaluation

Tokyo Metropolitan Bokutoh General Hospital has 729 acute-care hospital beds and is located in eastern Tokyo. We retrospectively reviewed the blood samples obtained from patients from January 1, 2001 through June 30, 2009. Among the total of 14,190 blood samples, 18 tested positive for *C. perfringens* (0.13%). The clinical evaluations of these 18 patients were analyzed. The charts of these SIRS (systemic inflammatory response syndrome) patients were reviewed for age, gender, underlying diseases, past history, the results of physical and laboratory testing, and radiographic data. Patients without findings on SIRS were excluded, and other clostridial spp. except for *C. perfringens* was not examined in this study.

The criteria for a diagnosis of SIRS were established in 1992 at the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference (7).

#### Microbiologic evaluation

Blood samples for culturing were obtained from patients by means of a standardized technique. In general, all blood samples were cultured anaerobically (10 mL) and aerobically (10 mL) by use of the BACTEC non-radiometric method (Becton Dickinson, Franklin Lakes, NJ). Cultures of blood samples that were positive for *C. perfringens* were subcultured on tryptic soy blood agar or chocolate agar, then on a thioglycollate medium that had been supplemented with hemin and vitamin K.

### Results

#### Clinical features

A total of 18 cultures were positive for *C. perfringens*. The number of isolates of *C. perfringens* obtained from the blood cultures slightly increased in later period. During the period from 2001 to 2004 (mean 1.4/year) 7 isolates obtained from patients were detected, whereas 11 isolates obtained from patients were detected during the period from 2005 to 2009 (mean 2.2/year). All patients were diagnosed as having SIRS. Fifteen patients (83.3%) were 65 years or older and the mean age was 75 years (range, 59-88 years). The number of isolates of *C. perfringens* obtained from the blood cultures increased with the patients’ age (50-59 years: 2 patients, 60-69 years: 3 patients, 70-79 years: 6 patients, 80-89 years: 7 patients). There were more male (13) than female (5) patients in our group. The patients came from several different wards: the tertiary care center (8 patients), emergency room (5 patients), surgical ward (4 patients), and medical ward (1 patient). A major symptom was a disturbance of consciousness (10 of 18 patients). Symptoms attributable to organs of the digestive system were often noted: epigastric pain (7 patients), vomiting and nausea (4 patients), appetite loss (1 patient), diarrhea (1 patient), swelling in the epigastrium (1 patient), melena (1 patient). Other symptoms were back pain (1 patient), hematuria (1 patient), left arm pain (1 patient), and dyspnea (1 patient).

Underlying conditions and diseases were mainly related to the hepatobiliary tract system (8 of 18 patients): gallbladder stones, 4 patients; hepatocellular carcinoma, 2 patients; liver cirrhosis, 1 patient; pancreatic cancer, 1 patient. Other underlying conditions and diseases, included urinary tract infection (1 patient); hypoglycemia (1 patient); cerebral bleeding (1 patient); cerebral infarction (1 patient); hip fracture (1 patient); colon cancer (1 patient); enteric necrosis (1 patient); hypertension (1 patient); epilepsy (1 patient); and polymyositis with pneumonia, undergoing treatment with steroids (1 patient). Two patients had previously been diagnosed with diabetes mellitus.

In the blood cultures, three cases were detected in the aerobic bottles in the survival (1) and non-survival groups (2). Bacterial growth was noted in all of the anaerobic blood cultures. For 7 patients for whom two sets of aerobic and anaerobic bottles were taken, bacterial growth was detected...
Table 1. Comparison between Survival and Non-survival Groups

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Survival group</th>
<th>Non-survival group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 18</td>
<td>n = 13</td>
<td>n = 5</td>
</tr>
<tr>
<td></td>
<td>Mean (SE)</td>
<td>Mean (SE)</td>
<td>Mean (SE)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>75 (2)</td>
<td>76 (3)</td>
<td>72 (4)</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>13/5</td>
<td>10/3</td>
<td>3/2</td>
</tr>
<tr>
<td>Fever (temp., °C)</td>
<td>37.6 (0.5)</td>
<td>37.3 (0.5)</td>
<td>38.4 (0.8)</td>
</tr>
<tr>
<td>Shock</td>
<td>6</td>
<td>2**</td>
<td>4 (septic shock)</td>
</tr>
<tr>
<td>Hemolysis</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>WBCs (cells/μL)</td>
<td>15833 (2150)</td>
<td>17323 (2562)</td>
<td>12140 (3827)</td>
</tr>
<tr>
<td>%PT</td>
<td>68 (7)</td>
<td>72 (9)</td>
<td>62 (13)</td>
</tr>
<tr>
<td>APTT (sec)</td>
<td>51 (8)</td>
<td>46 (9)</td>
<td>62 (19)</td>
</tr>
<tr>
<td>Fibrinogen (mg/dL)</td>
<td>328 (36)</td>
<td>375 (40)</td>
<td>235 (56)*</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>11.6 (2.1)</td>
<td>11.5 (2.7)</td>
<td>11.9 (4)</td>
</tr>
<tr>
<td>Gas formation (on radiology)</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Blood cultures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 set</td>
<td>10</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>2 set</td>
<td>8</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Number of positive blood cultures</td>
<td>21/52 bottles (40%)</td>
<td>14/38 bottles (38%)</td>
<td>7/14 bottles (50%)</td>
</tr>
<tr>
<td>Aerobic culture</td>
<td>3(16%)</td>
<td>17(%)</td>
<td>2(40%)</td>
</tr>
<tr>
<td>Anaerobic culture</td>
<td>18(100%)</td>
<td>13(93%)</td>
<td>5(100%)</td>
</tr>
<tr>
<td>Antibiotic therapy***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin group</td>
<td>9</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Cephem group</td>
<td>6</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Carbapenem group</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>No use</td>
<td>1</td>
<td>0</td>
<td>1#</td>
</tr>
</tbody>
</table>

*p < 0.05 survival group vs. non-survival group
WBC: white blood corpuscle, APTT: activated partial thromboplastin time, CRP: C reactive protein.
**: Hypotension in one patient recovered with hydration, and hypotension in another patient with melena recovered with blood transfusion.
***: The number of patients receiving antibiotics after examination of blood culture.
#: This patient died within 5 hours without using antibiotics.

Figure 1. Shock at initial presentation is a risk factor for 30-day mortality.

in only one anaerobic bottle of each patient.

As for therapy, one patient did not receive antibiotics due to death within 5 hours, as shown in Table 1. In the remaining 17 patients, antibiotic therapy was started following the examination of blood cultures.

Five patients died; giving an overall mortality rate of 27%. Of these 5 patients, 2 suffered septic shock with massive hemolysis. Two others also died of septic shock, but without hemolysis. One patient died of the pancreatic can-

cer, rather than the effects of SIRS.

Comparison between survival and non-survival groups

As shown in Table 1, we compared the clinical features, laboratory data and radiographic data of the survival and non-survival groups. In the non-survival groups, patients exhibited septic shock with hemolysis (2 patients), gas-forming infections (2 patients), and significantly lower fibrinogen levels than those of the survival group. There was no difference of the number of positive blood cultures and penicillin use between the survival and non-survival groups.

Shock at initial presentation was associated with 30-day mortality, as determined by a univariate logistic regression analysis (p<0.05) (Fig. 1). However, diabetes mellitus (p=0.5), hepatobiliary tract diseases (p=0.5), advanced age (>65 years old, p=1.65), gender (p=1.8), pyrexia (temperature >38°C, p=0.5), anemia (Hb <10 g/dL, p=0.9), leukocytosis (>10,000 cells/μL, p=0.15), hemolysis (n=2, p=0.065), fibrinogen level <300 mg/dL (p=0.9) and penicillin use (p=0.85) were not significantly associated with a 30-day mortality. In the univariate logistic regression analysis, only septic shock at presentation was significantly associated with 30-day mortality (p<0.05).
Discussion

Cancer and immunosuppressive conditions (4, 5, 8) are reported to be the main underlying diseases in individuals infected with *C. perfringens* (4-6). In the present study, the most frequent underlying conditions were diseases of the hepatobiliary tract system. Four patients had cancer (hepatocellular carcinoma, 2 patients; pancreatic cancer, 1 patient; colon cancer, 1 patient). There were 3 patients whom we suspected to be immunosuppressed; 2 had diabetes mellitus, and 1 had polymyositis and was receiving steroid therapy. Chen et al reported that diabetes mellitus and liver cirrhosis were the most common underlying diseases in Tainan (9). In our study, diabetes mellitus and liver cirrhosis were not common, but diseases of the hepatobiliary tract system were common. Moreover, the mean age was 60 years in Tainan, but mean age was 75 years in Tokyo. The difference of underlying diseases and age between the report of Chen et al and our study may be due to the differences in race or location.

Most of the patients had been admitted to ER or tertiary care units, but not to general wards. In Tokyo, the number of elderly patients is increasing. Moreover, the frequency of detection for *C. perfringens* from fecal specimens in rural areas is similar to that in the Tokyo area (2). Therefore, when SIRS is diagnosed in Tokyo residents, the possibility of sepsis due to *C. perfringens* infection should be considered.

Clinical features of SIRS included a disturbance of consciousness (10 of 18 patients). Complications of the central nervous system from *C. perfringens* infection are known to include meningitis and encephalitis (10, 11). However, without specific clinical findings, we concluded that the elderly patients became drowsy due to septic shock and the effects of meningitis, encephalitis, or psychosis.

Comparison between the survival and non-survival groups showed that the conditions associated with SIRS and the laboratory findings did not differ, except for the plasma fibrinogen level. Plasma fibrinogen levels were lower in the non-survival group than in the survival group. We considered that patients in the non-survival group with coagulopathy might be more common as compared with the survival group (12).

Plasma fibrinogen level is known to be a risk factor for shock (14, 15). In the present study, we suggested that septic shock was associated with fatality. In previous case reports, *C. perfringens* sepsis was almost always fatal, especially in combination with hemolysis (4-6). Of 4 fatal cases of septic shock, 2 were associated with massive hemolysis. The other 2 were associated with severe underlying conditions: massive enteric necrosis and polymyositis with pneumonia. Chen et al. reported that both underlying liver cirrhosis and the presence of septic shock were independently associated with fatality due to clostridial bacteremia (9). In our study, only 1 patient out of 18 had cirrhosis of the liver; there was no significant effect on 30-day mortality. Hemolysis by *C. perfringens* infection is due to its toxins. Using 4 strains of *C. perfringens* isolated from patients with hemolysis (1), septic shock without hemolysis (1), and survivors (2), 10^6 bacteria were seeded for each tube containing whole blood isolated from a volunteer, and hemolysis was noted at 24 hours for all strains in our preliminary *in vitro* experiments (data not shown). Hemolysis may be caused by various host conditions, not bacterial conditions.

Therefore, we should be vigilant in identifying patients with *C. perfringens* infection and shock, regardless of whether they have diabetes mellitus or cirrhosis of the liver.

Conclusion

Patients who had SIRS and whose blood cultures were positive for *C. perfringens* had a mortality rate of 27% at 30 days. There were no specific characteristics among clinical features of *C. perfringens* infection accompanied with SIRS. This may indicate that, in emergency rooms, diagnosing and initiating appropriate treatment for *C. perfringens* infection may be considerably difficult; it is necessary to be especially vigilant in identifying patients with *C. perfringens* infection underlying SIRS, and accompanied by shock.

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