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Clostridium bacteremia: emphasis on the poor prognosis in cirrhotic patients

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Bacteremic episodes caused by anaerobes are unusual and the clinical importance of *Clostridium* bacteremia remains unclear. This retrospective case study examined the risk factors among a group of patients who developed *Clostridium* bacteremia. Medical records from 73 episodes of clostridial bacteremia in 73 patients treated in a medical center during an 11-year period were reviewed. Of all episodes, 96% were community-acquired. Twelve percent of patients had polymicrobial bacteremia, with *Escherichia coli* being the most common accompanying bacterium. Diabetes mellitus (26%) and liver cirrhosis (25%) were the most common underlying diseases. The most common etiological organisms were *Clostridium perfringens* (77%), *Clostridium bifermentans* (9%), and *Clostridium septicum* (4%). Only one patient with *C. septicum* bacteremia had a histocytotoxic infection, which was a fatal gas gangrene. Univariate analysis of data from patients with monomicrobial *Clostridium* bacteremia revealed that younger age (age < 65 years), underlying liver cirrhosis, and presence of septic shock at initial presentation were associated with fatality; but only the latter two variables were independently associated with fatality in multivariate logistic regression analysis. Appropriate antimicrobial therapy for monomicrobial *Clostridium* bacteremia did not significantly affect clinical outcomes, which might suggest that *Clostridium* species in the bloodstream can be regarded as merely contaminants or transient bacteremia. This suggestion was not supported by the finding that seven of 13 cirrhotic patients with monomicrobial *Clostridium* bacteremia died of sepsis, of whom six had not receive appropriate antimicrobial therapy. Therefore, the clinical importance of *Clostridium* bacteremia should be interpreted with caution because of its high risk of mortality in susceptible hosts, particularly cirrhotic patients, who do not receive appropriate therapy timely.

Key words: *Clostridium* bacteremia, liver cirrhosis

There are almost 90 recognized species in the genus *Clostridium*, but less than 20 species are associated with clinical illness in humans [1]. Cell wall structure indicates that *Clostridium* are gram-positive bacteria [1]. *Clostridium* species vary in oxygen tolerance, motility, nutritional requirements, and limiting or optimal temperatures for growth [1]. Some organisms such as *Clostridium histolyticum* and *Clostridium tertium* are relatively aerotolerant and may actually replicate, though not sporulate, with aerobic incubation [1]. Other species, such as *Clostridium novyi* and *Clostridium haemolyticum*, are strict anaerobes and will not replicate when oxygen concentration exceeds 0.05% [1].

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Clostridium species are often found in the human gastrointestinal tract and female genital tract, and they are known to cause invasive cellulitis, myonecrosis, fulminant intravascular hemolysis, food poisoning, pseudo-membranous colitis, botulism, and tetanus through exotoxins targeted on the nervous system [2]. Differentiating species of *Clostridium* in cases of clinical infection is important, as some species indicate underlying bowel pathology (*Clostridium septicum*) [3], require antitoxin administration (*Clostridium tetani*), or indic-ate increased resistance to certain antimicrobials (*Clostridium ramosum*, *Clostridium innocuum*, and *Clostridium clostridioforme*) [4]. There is abundant evidence showing the morbid significance of clostridial bacteremia. As most patients with clostridial bacteremia have few clinical signs of sepsis, it has been suggested that the presence of *Clostridium* species alone in the blood is often of little medical importance [8]. This

study sought to determine the clinical characteristics of patients with *Clostridium* bacteremia and their risk factors for mortality.

Material and Methods

Medical records of patients with episodes of *Clostridium* bacteremia treated at National Cheng Kung University Hospital from February 1989 to March 1999. Data on demographic characteristics, underlying medical diseases, clinical manifestations, laboratory findings at the onset of bacteremia, relevant microbiologic information, antimicrobial therapy, and clinical outcome were recorded.

Species was identified using the rapid ID 32A system (bioMerieux, France), an identification system for anaerobes using standardized and miniaturized enzymatic tests with a specially adapted database. Fever was considered to be present if the patient has an axillary temperature of ≥ 38.3°C. Leukocytosis was defined as a white blood cell count of ≥ 12 000 /mm^3, thrombocytopenia as a platelet count below 100 000 /mm^3, impaired renal function as a serum creatinine level above 1.5 mg/dL and abnormal liver function as an aspartate aminotransferase level above 40 U/L (normal range, 5-40 U/L), or an alanine aminotransferase level above 55 U/L (normal range, 5-55 U/L). The severity of hepatic decompensation in cirrhotic patients was assessed by using the Pugh's score, based on serum bilirubin and albumin level, presence of ascites and encephalopathy, and prothrombin time [5]. The infection was classified as pneumonia, urinary tract infection, meningitis, incisional wound infection, other soft tissue infection, or intra-abdominal infection using the definitions of the United States Centers for Disease Control and Prevention [6]. Primary bacteremia was defined as a bacteremic episode without any identifiable infection site. Cases with bacteremia caused exclusively by *Clostridium* species were considered as monomicrobial bacteremia whereas those with bacteremia by concurrent organisms other than *Clostridium* species as polymicrobial bacteremia.

As the standard susceptibility tests of clostridial isolates were not performed, the appropriateness of antimicrobial therapy was assessed on the basis of the susceptibility data presented by Finegold *et al* [7]. Treatment with antimicrobial agents *in vitro* active against more than 85% of *Clostridium* species was categorized as appropriate therapy. These agents included ampicillin, piperacillin, ampicillin/sulbactam, amoxicillin/clavulanate, ticarcillin/clavulanate, piperaillin/tazobactam, chloramphenicol, metronidazole, and imipenem.

The chi-square test or two-tailed Fisher's exact test was used to compare the categorical variables, and a p value less than 0.05 was considered to be statistically significant. Variables with a p value less than 0.05 were entered into logistic regression analysis to determine whether they were independent risk factors.

Results

Seventy-three episodes of *Clostridium* bacteremia in 73 patients were included in the analysis. The male-to-female ratio was 1.3:1. The mean age was 60 years, ranging from 40 to 85 years. Forty-two (58%) patients were more than 65 years of age. All but six patients had underlying diseases, including diabetes mellitus (19 cases, 26%), liver cirrhosis (18 cases, 25%), malignancy (7 cases of solid tumors and 4 cases of leukemia), uremia (7 cases), chronic pulmonary disease (7 cases), cholelithiasis (6 cases), and prior cerebrovascular accident (6 cases). Twenty-four patients had more than one underlying disease. The vast majority (70 episodes, 96%) of all episodes were community-acquired and only three episodes occurred after hospitalization for 72 h.

Only 18 (25%) cases had fever at presentation, 11 had abdominal pain and three had chills. Leukocytosis was found in 38 (51%) cases, thrombocytopenia in 22 (30%), impaired renal function in 32 (44%), abnormal liver function in 40 (55%), septic shock in 40 (55%), and consciousness disturbance in 33 (45%). None had intravascular hemolysis at presentation or during hospitalization.

Clostridium perfringens, the most frequently isolated species, was found in 58 (77%) cases. *Clostridium bifermentans* was isolated from seven cases, *Clostridium septicum* from three, *Clostridium ramosum* from two, *Clostridium limosum*, *Clostridium thermobutyricum*, and *Clostridium paraputrificium* from one, respectively. One case had concurrent *C. perfringens* and *C. bifermentans* bacteremia. Of the three patients with *C. septicum* bacteremia, two had colon cancer and bladder cancer, respectively, and both received appropriate antimicrobial therapy and survived. The other patient with *C. septicum* bacteremia was a diabetic woman who developed gas gangrene in her left thigh and retroperitoneum, and died of fulminant sepsis within 2 days.

Monomicrobial bacteremia was noted in 60 (82%) cases. In 13 (18%) cases, aerobic or other anaerobic organisms were isolated from the bloodstream concurrently, and the most common accompanying species was *Escherichai coli* (5 cases). The concurrent infections at the onset of *Clostridium* bacteremia were pneumonia (14 cases), soft tissue infection (10 cases),

Table 1. Risk factors for mortality in patients with *Clostridium bacteremia*

Clinical characteristic	Total no. of bacteremia (n = 73) No. of fatal cases/ Total no. of cases (%)	*p* value	Monomicrobial bacteremia (n = 60) No. of fatal cases/ Total no. of cases (%)	*p*
Age (yr)		0.09		0.04
≥ 65	10/44 (23)		7/37 (19)	
< 65	12/29 (41)		10/23 (43)	
Gender		0.6		0.9
Male	12/43 (28)		10/36 (28)	
Female	10/30 (33)		7/24 (29)	
Septic shock		< 0.0001		< 0.001
Yes	22/40 (55)		17/31 (55)	
No	0/33 (0)		0/29 (0)	
Fever		0.7		0.5
≥ 38.3 °C	6/18 (33)		3/14 (21)	
< 38.3 °C	16/55 (29)		14/46 (30)	
Leukocytosis		0.3		0.2
Yes	13/37 (35)		11/31 (35)	
No	9/36 (25)		6/29 (21)	
Liver cirrhosis		0.003		0.002
Yes	10/17 (59)		8/13 (54)	
No	12/56 (21)		9/47 (19)	
Diabetes mellitus		0.2		0.8
Yes	3/17 (18)		3/14 (21)	
No	19/56 (34)		14/56 (25)	
Number of positive blood cultures		0.1		0.06
One set	15/58 (26)		11/48 (23)	
Two sets	7/15 (47)		6/12 (50)	
Antibiotic therapy		0.3		0.3
Inappropriate	14/39 (36)		11/33 (33)	
Appropriate	8/34 (24)		6/27 (22)	
Concurrent bacteremia		0.5		
Monomicrobial	17/60 (28)			
Polymicrobial	5/13 (38)			
Species[a]				0.07
C. perfringens			11/47 (23)	
Non-*perfringens Clostridium* species			6/12 (46)	

[a]A patient with bacteremia caused by concurrent *C. perfringens* and *C. bifermentans* was excluded from the analysis.

intra-abdominal abscess (7 cases), urinary tract infection (5 cases), acute cholangitis (4 cases), infective endocarditis (1 case), and periodontitis (1 case). Two patients had combined infection, including one with intra-abdominal abscess and pneumonia and the other with urinary tract and soft tissue infection. However, none had an isolation of *Clostridium* species from clinical specimens other than blood. Primary bacteremia was found in 33 (45%) patients.

Twenty-two (30%) patients died within 14 days, and 21 of them died of clostridial sepsis directly. As shown in Table 1, in patients with *Clostridium* bacteremia, septic shock at presentation and underlying liver cirrhosis were significantly associated with fatality. However, age, gender, the presence of diabetes mellitus, polymicrobial or monomicrobial bacteremia, the number of positive blood culture, the species of *Clostridium*, and the appropriateness of antibiotics were not significantly associated with fatality.

To avoid the confounding influence of accompanying microorganisms in cases of polymicrobial bacteremia on the analysis, we investigated the risk factors for mortality only in the 60 cases of *Clostridium* monomicrobial bacteremia, for which the crude mortality rate at 14 days was 28% (17/60). Univariate analysis found that younger age (age < 65 years, $p = 0.04$), underlying liver cirrhosis ($p = 0.002$), and septic shock at presentation ($p < 0.0001$) were significantly associated with fatality (Table 1). Patients with more than one positive blood culture or non-*perfringens Clostridium* bacteremia tended to have a higher fatality rate than those with one set of positive

Table 2. Clinical characteristics and outcome of 13 patients with liver cirrhosis and monomicrobial clostridial bacteremia

Case no.	Age/Gender	Septic shock	*Clostridium* species	Underlying diseases other than liver cirrhosis	Concurrent infection	Antimicrobial therapy	Pugh's score	Outcome at 14 days[a]
1	76/M	Yes	*C. perfringens*	Prior cerebrovascular accident	No	Inappropriate: cefotaxime	B	Survived
2	65/M	No	*C. perfringens*	Diabetes mellitus	No	Appropriate: piperacillin	C	Survived
3	69/M	No	*C. perfringens*	–	No	Inappropriate: cephradine	C	Survived
4	36/M	No	*C. perfringens*	Uremia	Nosocomial pneumonia[b]	Inappropriate: oxacillin	A	Survived
5	74/F	Yes	*C. perfringens*	–	Urinary tract infection	Inappropriate: cefotaxime	B	Survived
6	60/M	Yes	*C. bifermentans*	–	No	Inappropriate: no treatment	C	Died (1 day)
7	51/M	Yes	*C. sordelli*	–	No	Inappropriate: cefuroxime	C	Died (10 days)
8	63/M	Yes	*C. bifermentans*	–	No	Inappropriate: cefmenoxime	C	Died (5 days)
9	58/M	Yes	*C. bifermentans*	–	No	Inappropriate: cefotaxime	C	Died (5 days)
10	80/F	Yes	*C. perfringens*	–	No	Inappropriate: cefotaxime	B	Died (11 days)
11	57/M	Yes	*C. perfringens*	–	No	Inappropriate: cefotaxime	C	Died (2 days)
12	39/M	Yes	*C. perfringens*	–	No	Appropriate: cefoxitin	C	Died (6 days)
13	60/M	Yes	*C. perfringens*	–	No	Appropriate: metronidazole	B	Died (8 days)

[a]All patients died of clostridial sepsis, except for one (case 12) who died of upper gastrointestinal bleeding-induced hypovolemic shock. Number of days within parentheses indicates the time period from the onset of sepsis to death.

[b]All cases were community-acquired, except case 4.

blood culture or *C. perfringens* bacteremia, although the difference was not statistically significant.

In the logistic regression analysis, only septic shock at presentation ($p = 0.001$) and presence of liver cirrhosis ($p = 0.03$) were independently associated with fatality in patients with monomicrobial *Clostridium* bacteremia. Although there were two cases of concurrent infection at the onset of *Clostridium* bacteremia, it was likely that at least 12 of 13 cases with underlying cirrhosis had primary *Clostridium* bacteremia. About one half of 13 cirrhotic patients with monomicrobial *Clostridium* bacteremia died within 2 weeks of the onset of sepsis (1-11 days), and all four patients with non-*perfringens Clostridium* bacteremia died of sepsis (Table 2).

Discussion

More than two decades ago, Gorbach and Thadepalli considered the microbiologic finding of *Clostridium* bacteremia as a relatively unimportant clinical problem which is often unrelated to the patients' clinical status [8]. Ten years later, Nelson *et al* described *Clostridium* bacteremia without classic clinical manifestations in patients with advanced malignancy and chronic illness [9]. There is a lack of data regarding optimal therapy for *Clostridium* bacteremia in patients who may appear relatively well or alternatively, critically ill.

Most of the patients had significant chronic systemic illnesses, especially diabetes mellitus (26%) and liver cirrhosis (25%). In contrast to the findings in the study of Myers *et al*, in which a half of 56 patients with *Clostridium* bacteremia had evident gastrointestinal or hematologic malignancy [10], only 11 (15%) of the patients in this study had a diagnosis of solid organ cancer or leukemia before the septicemic episodes. The presence of *C. septicum* bacteremia or nontraumatic myonecrosis is always linked to malignancy, particularly colon cancer and leukemia, cyclic neutropenia, or diabetes mellitus [3,11-13]. In the study, two of three patients with *C. septicum* bacteremia had documented malignancy and one died of fulminant *Clostridium* sepsis had never undergone testing for cancer.

Primary *Clostridium* bacteremia has not been reported in patients with liver cirrhosis. In a retrospective review of 228 episodes of bacteremia in Taiwanese patients with liver cirrhosis, only 3.2% of bacteremia episodes were caused by anaerobes, and no *Clostridium* bacteremia episode was identified [14]. One-fourth of patients in this study had liver cirrhosis. Moreover, among a total of 269 episodes of *Clostridium* bacteremia in six recent reports with the cases number

ranging from 27 to 86 cases in each report, only 12 (4.4%) patients had liver cirrhosis [2,8-10,15,16]. The reason for the increased case number of *Clostridium* bacteremia in our hospital is not clear but it is, at least, partially attributable to the improvements of modern anaerobic culture techniques and to the increasing number of patients with chronic illness. The portal of entry of *Clostridium* species in cirrhotic cases is usually obscure and the gastrointestinal tract is the most likely source. It has been proposed that the high concentration of clostridial organisms in the gastrointestinal tract, coupled with systemic illness, might allow transmucosal migration of these organisms, resulting in portal bacteremia [17]. In patients with hepatic cirrhosis, the reticulo-endothelial system may be unable to defend against these organisms properly, thereby allowing development of systemic bacteremia [9].

In this study, the overall mortality rate of 73 episodes of *Clostridium* bacteremia in our university-affiliated hospital was 30%, which is much lower than the 58% rate reported in a previous study of 136 episodes in a cancer center, the largest reported cases series of *Clostridium* bacteremia [18]. It is likely that differences in patient populations and general patient care in these two series could explain the differences in clinical outcome. This is the first study to determine the independent prognostic variables among patients with *Clostridium* bacteremia by using multivariate logistic regression analysis. This study has demonstrated that septic shock at initial presentation, representing the overwhelming septicemic process, was significantly linked to a fatal outcome. Underlying liver cirrhosis was also shown to be associated with a poor prognosis. The fatality rate for patients with monomicrobial bacteremia and liver cirrhosis was significantly higher than that of patients without liver cirrhosis (54% vs 19%). Of the 29 cases reported by Nelson *et al*, eight had underlying cirrhosis and portal hypertension and only three (38%) died [9].

In patients with monomicrobial bacteremia, those with two sets of positive blood culture and those with non-*perfringens Clostridium* bacteremia had a higher fatality rate. This finding is in concordance with the results of a study by Pietrafitta and Deckers, who reported an increased mortality rate in patients with more than one positive blood culture [2]. These results indicate that the finding of two sets of positive blood culture represent a higher bacterial load in bloodstream, and is associated with a poor clinical outcome. A higher mortality rate was also found in patients with non-*perfringens Clostridium* bacteremia in this study. Among the seven patients with bacteremia caused by *C. bifermentans*, the second most common *Clostridium* species, three (43%) died whereas among the 47 patients with monomicrobial *C. perfringens* bacteremia, only 23% of patients died. However, the clinical outcome of cancer patients with bacteremia caused by species other than *C. perfringens* was diverse. In a previous study, patients with *C. septicum* bacteremia had a worse prognosis than those with *C. innocuum* or *C. sporogenes* [18]. In this study, the number of cases with *C. septicum* bacteremia (3 cases) was too small for useful analysis.

This study shows that the appropriateness of antibiotic therapy does not significantly improve the clinical outcome in patients with monomicrobial *Clostridium* bacteremia. In fact, 25 patients with *Clostridium* bacteremia survived for at least 2 weeks after the onset of bacteremic episodes despite inappropriate antimicrobial therapy. A recent study used a similar analytic strategy in determining the appropriateness of antimicrobial therapy in patients with *Clostridium* bacteremia, and found that appropriateness of antimicrobial therapy has insignificant impact on survival [16]. Thus, the application of antimicrobial agents for such patients must be based on their clinical characteristics, instead of basing only on a positive blood culture. However, in high-risk individuals with *Clostridium* sepsis, such as in cirrhotic patients or patients with shock at initial presentation, prompt administration of appropriate antibiotics should be considered.

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