Non–*C. difficile Clostridioides* Bacteremia in Intensive Care Patients, France

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Assess the background of patients with *Clostridioides* bacteremia (CB) in the current study
- Distinguish clinical features of severe CB in the current study
- Assess the microbiology of CB in the current study
- Identify risk factors for mortality due to CB in the current study (VSPB)

CME Editor

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Usually responsible for soft tissue infections, *Clostridioides* species can also cause bacteremia, life-threatening infections often requiring intensive care unit (ICU) admission. We conducted a multicenter retrospective study to investigate *Clostridioides* bacteremia in ICUs to describe the clinical and biologic characteristics and outcomes in critically ill patients. We identified 135 patients with *Clostridioides* bacteremia, which occurred almost exclusively (96%) in patients with underlying conditions. Septic shock and digestive symptoms were the hallmarks of *Clostridioides* bacteremia in the ICU. We identified 16 different species of *Clostridioides*, among which *C. perfringens* accounted for 31% of cases. Despite the high sensitivity of *Clostridioides* to common antimicrobial drugs, mortality rates were high: 52% for ICU patients and 71% overall at 3 months. In multivariate analysis, the most important factor associated with increased risk for death was the presence of hemolysis. *Clostridioides* bacteremia often leads to multiple organ failures, which have high mortality rates.

Obligate anaerobic bacteremia is a rare event, accounting for ≈0.1%–10% of positive blood cultures; *Clostridioides* spp. bacteremia represents 8%–46% of the cases (*1*–*4*). *Clostridioides* (formerly *Clostridium*) species are ubiquitous, gram-positive, spore-forming (most species), and toxin-producing bacteria (*3*). The most well-known toxins, *C. perfringens* α and θ toxins, induce platelet aggregation, diffuse formation of thrombi, cell lysis, and gas gangrene (*5*). Anaerobic bacteria are not only found in the soil or rotting vegetation but also are commensal constituents of the human microbiome, especially in the gastrointestinal tract or genital organs of women (*3*,*6*). Humans are usually infected by direct entry of the bacteria through a wound (*C. tetani*, *C. perfringens*) or by contaminated food (*C. botulae*). However, contamination of a wound by spores is not sufficient to generate the infection because *Clostridioides* spp. need hypoxic and acidic conditions to proliferate. Conditions such as vascular trauma, atherosclerosis, or malignancies may induce tissue hypoxia. Moreover, the liberation of both α and θ toxin, which induce the formation of occlusive thrombi, may increase tissue hypoxia, sometimes leading to gas gangrene formation (*3*,*7*–*9*).

Thus, *Clostridioides* infections are especially known to cause myonecrosis with rapid extension and gas gangrene formation, which, if not treated rapidly, may be fatal. This outcome has largely been described in the context of war wounds, trauma, and surgery (*10*–*12*). Although *C. perfringens* is mostly involved in gas gangrene, other *Clostridioides* subspecies can also be responsible for such infections (*13*).

Clostridioides bacteria can also cause primary bacteremia, with or without gas gangrene (*2*,*6*). *Clostridioides* bacteremia are usually fulminant and life-threatening infections. Data focusing on *Clostridioides* bacteremia rely mainly on case reports (*14*–*16*), case series on selected populations (*17*,*18*), or larger epidemiologic series that contain microbiological data but few clinical descriptions (*2*,*19*,*20*). Although *Clostridioides* bacteremia often leads to sudden and massive organ failure requiring transfer to a hospital intensive care unit (ICU), no study has focused on *Clostridioides* bacteremia in the ICU. Therefore, we conducted a multicenter retrospective study of case-patients who were positive for all *Clostridioides* species except *C. difficile* to investigate *Clostridioides* bacteremia in the ICU; we described the clinical spectrum of critically ill patients, ICU admission conditions, microbiological characteristics, and outcomes. We aimed to identify risk factors associated with mortality.

Methods

Ethics

This study was approved by an Institutional Review Board (Comité d'Ethique de la Société de Réanimation de Langue Française no. CE-SRLF 18–38) in accordance with the French regulation on noninterventional studies, which waived the need for signed informed consent for patients included in this database. No data allowing identification of the patients included in the study were recorded. The study was conducted in accordance with the Declaration of Helsinki principles.

Study Population

We retrospectively recorded cases of *Clostridioides* bacteremia in the period July 2003–December 2018 in 15 ICUs in France. Patients were identified by review of ICU medical records and hospital microbiological databases; we selected only cases with ≥1 positive blood culture for all *Clostridioides* species except *C. difficile*. Blood samples had been collected with specific anaerobic blood culture bottles and incubated in automated systems, in accordance with routine practice (*21*). Anaerobes were identified using the API System (bioMérieux, https://www.biomerieux.com) until 2010; as of 2010, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry methods were used in most of the centers to identify anaerobic bacteria (*3*,*22*). Antimicrobial susceptibility test results of *Clostridioides* species, evaluated by diffusion methods according to guidelines of the Comité

de l'Antibiogramme de la Société Française de Microbiologie, were also collected for our study.

We reviewed ICU medical records of selected patients for age, sex, underlying diseases, clinical and biologic symptoms at ICU admission, the need for organ support, antimicrobial drug treatment, and outcome. We recorded Charlson index, simplified acute physiology score (SAPS2), and sequential organ failure assessment (SOFA) scores as previously defined (*23*–*25*). We defined septic shock according to the Sepsis-3 consensus definition (*26*) and hemolysis as low hemoglobin level associated with other hemolysis parameters, such as an increase of lactate dehydrogenase (LDH) or unconjugated bilirubin and reduced haptoglobin levels.

Statistical Analysis

We described categorical variables as counts and percentages and quantitative variables as median and interquartile range. We estimated mortality rate at 28 days and 90 days after the date of bacteremia, as a binary variable, and examined factors associated with overall survival as a time-to-event endpoint. We defined overall survival as the time between the date of *Clostridioides* bacteremia and the date of death or last follow-up, whichever occurred first. We performed survival analysis using a Cox regression model, estimating hazard ratios (HR) and 95% CIs. We checked the proportional hazards (PH) assumption and the log-linearity assumptions for the models; if the PH assumption was not valid, we used time-dependent coefficient for time-varying effect over time; we used a step function, with time-intervals defined based on the Schoenfeld's residuals. Factors which were associated to OS with a $p<0.1$ in univariate analysis were candidates for a multivariate adjusted model. We selected the adjusted model using a backward stepwise procedure, based on the Akaike criterion. All tests were 2-sided; $p<0.05$ was considered significant. We performed analyses by using the R statistical platform version 3.6.1 (https://www.r-project.org).

Results

Clinical and Biologic Manifestations

In total, 135 patients with *Clostridioides* bacteremia were identified in 15 ICUs in France during the study period (Table 1); 60% (n = 81) of the patients were men. Median age at diagnosis was 64 years. Most (96%) patients had ≥1 underlying medical condition; among patients >65 years of age, diabetes mellitus, neoplasms, and chronic obstruction pulmonary disease (COPD) were the most frequent. Thirty-four (26%) patients had an underlying solid tumor from digestive (n = 14, 41%), gynecological (n = 7, 21%), and pancreatic or biliary (n = 4, 12%) origins. Three patients (9%) had urinary tract tumors, 2 (6%) neuroendocrine tumors, 1 (3%) an Ewing tumor, 1 (3%)

Table 1. Global characteristics of patients with *Clotristridium* bacteremia, France*

Characteristic	Baseline population, n = 135	Survived, n -= 65	Died in ICU, n = 70
Age			
Age at diagnosis, median (IQR)	64 (51–75)	62 (50–70)	66 (54–79)
Age at diagnostic >65 y	67 (50)	27 (42)	40 (57)
Sex			
M	81 (60)	43 (66)	38 (54)
F	54 (40)	22 (33)	32 (46)
All underlying conditions	130 (96)	62 (95)	68 (97)
Diabetes mellitus	34 (26)	19 (31)	15 (22)
Neoplasm	34 (26)	17 (27)	17 (25)
Chronic obstructive pulmonary disease	33 (25)	15 (24)	18 (26)
Alcoholism	26 (20)	11 (18)	15 (22)
Heart failure	26 (20)	9 (15)	17 (25)
Hematological malignancy	19 (15)	7 (11)	12 (18)
Liver cirrhosis	13 (10)	4 (6)	9 (13)
Chronic renal failure	10 (8)	8 (13)	2 (3)
Arteriopathy	9 (7)	3 (5)	6 (9)
Autoimmune diseases	7 (5)	4 (6)	3 (4)
HIV	1 (1)	0	1 (1)
Other predisposing conditions			
Surgery or trauma in the previous 15 d	13 (10)	10 (16)	3 (4)
Digestive surgery	10 (77)	7 (70)	3 (100)
Trauma	3 (23)	3 (30)	0
Immunosuppressive agents			
Patients receiving Immunosuppressive agents	38 (28)	18 (28)	20 (29)
Steroids	20 (53)	9 (50)	11 (55)
Chemotherapy	20 (53)	9 (50)	11 (55)
Immunosuppressive drugs	10 (26)	6 (33)	4 (20)

*Data are no. (%) unless otherwise indicated.

oral cancer, and 1 (3%) testicular cancer. In all, 94% of tumors were active at the time of the bacteremia. Nineteen (15%) patients had also received diagnoses of hematological malignancies (7 lymphoma, 4 acute lymphoblastic leukemia, 4 myelodysplastic syndrome, 3 acute myeloid leukemia, and 1 myeloproliferative disorder); 3 of those patients had undergone bone marrow transplantation. Thirty-eight patients (28%) had been treated with immunosuppressive agents. In addition, 13 (10%) patients had experienced recent surgery or trauma, and these situations were associated with a better outcome in univariate analysis (Appendix Figure 1, http://wwwnc.cdc.gov/EID/article/27/7/20-3471-App1.pdf). However, this difference was not significant in multivariate analysis (HR 0.41, 95% CI 0.13–1.32; p = 0.13) (Figure 1).

Clostridioides bacteremia manifested with septic shock at ICU admission in 115 patients (85%), and 26 (19%) patients experienced a cardiac arrest in the ICU (Table 2). Indeed, *Clostridioides* bacteremia causes severe illness, as assessed by high SAPS2 and SOFA scores, high lactate levels, and substantial need for organ supports during an ICU stay. Of note, digestive symptoms were the main symptoms associated with *Clostridioides* bacteremia (62% of patients), whereas myonecrosis represented only 16% of ICU admissions. Acute hemolysis, a distinctive biologic signature of *Clostridioides* bacteremia, was present in 22 (17%) cases (Appendix Table 1). Median hemoglobin level was significantly lower in the hemolysis group (4.9, IQR 3.6–7.0) compared with the rate in patients without hemolysis (10.9, IQR 9.3–12.6; p<0.001). Multiple organ failure, experienced as hepatic cytolysis, acute kidney injury and thrombocytopenia (Table 2), was also common. Of note, aspartate aminotransferase levels were higher than alanine aminotransferase levels, which is commonly found in case of hemolysis. Twenty-seven patients (28%) had $<4 \times 10^9$ leukocytes/L; 23 (85%) of those had an underlying solid tumor or a hematological malignancy.

Documentation of Infectious Species

In total, 16 different *Clostridioides* species were identified by blood cultures, including *C. perfringens* in one third of the patients (Table 3; Figure 2). In univariate analysis, documented *C. perfringens* infection was not associated with a worse outcome than other *Clostridioides* species (HR 0.78, CI 95% 0.49–1.23; p = 0.285) (Appendix Figure 2). Blood cultures were mainly performed by peripheral venipuncture (58%), followed by central venous catheter puncture (23%) and arterial catheter puncture (17%). One blood culture revealed *Clostridioides* bacteremia in 87% of cases. Of note, 49 cases of *Clostridioides* bacteremia were polymicrobial bacteremia, yielding the presence of ≥1 type of bacteria in blood cultures, balanced between gram-negative, gram-positive, and other anaerobic bacteria. Nine patients had both gram-negative and gram-positive bacteria cultures. Hematogenous spread with gas-forming abscess was one particular complication,

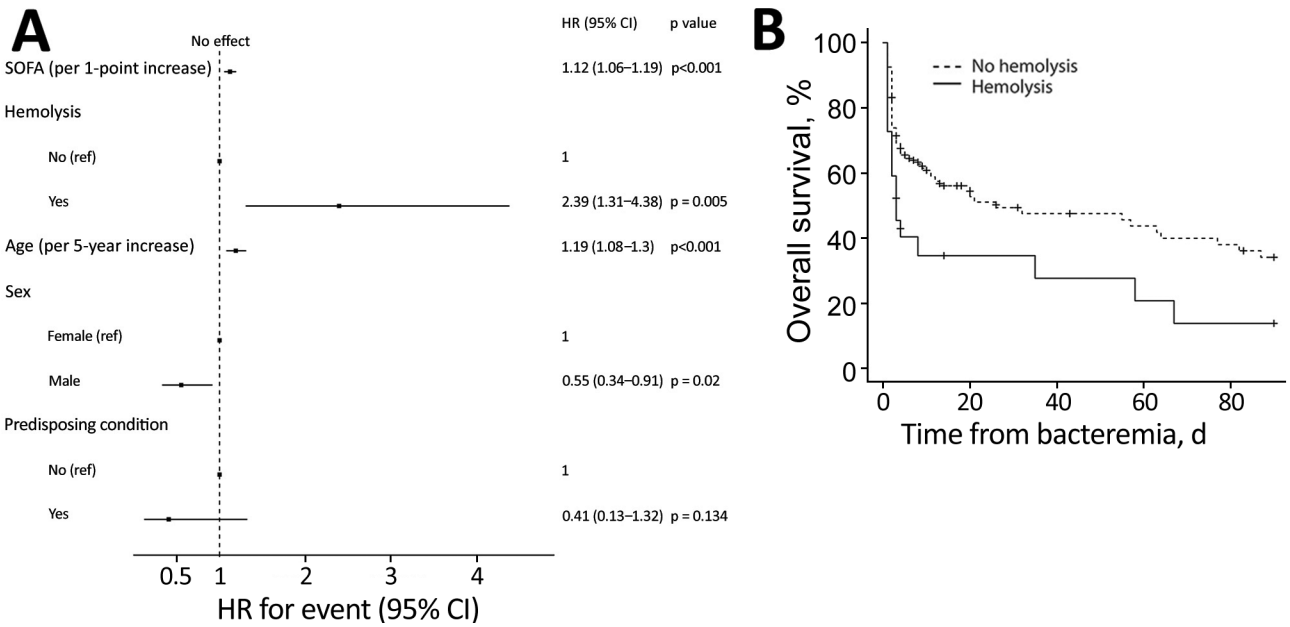

Figure 1. Survival analysis with Cox regression model for patients with *Closteridiodes* bacteremia, France. A) Forest plot of multivariate factors associated with overall survival. Predisposing conditions were trauma or surgery. B) Kaplan-Meier curve of mortality depending on hemolysis. HR, hazard ratio; ref, referent; SOFA, sequential organ failure assessment.

Table 2. Clinical and biologic characteristics of patients with *Closteridiodes* bacteremia, France*

Characteristic	All patients, n = 135		Survived, n = 65		Died in ICU, n = 70	
	No.	Result	No.	Result	No.	Result
Temperature	75	37 (36–39)	30	38.5 (37.3–39)	45	37 (35.6–38.7)
Clinical manifestations associated with bacteremia at ICU admission						
Septic shock	115	85%	49	75%	66	94%
Digestive symptoms	84	62%	42	65%	42	60%
Acute respiratory failure	41	30%	15	23%	26	37%
Coma	38	28%	6	9%	32	46%
Cardiac arrest	26	19%	2	3%	24	34%
Myonecrosis	21	16%	11	17%	10	14%
Prognostic scores at ICU admission						
Charlson score	135	5 (3–6)	65	5 (2–7)	70	4.5 (3–6)
SAPS2 score	106	63 (44–88)	47	45 (33–57)	59	82 (63–97)
SOFA score	105	10 (7–14)	47	8 (5–10)	58	12 (9–15)
Organ support in ICU						
Vasopressors, n = 132	108	82%	42	66%	66	97%
Mechanical ventilation, n = 133	105	79%	41	63%	64	94%
Renal-replacement therapy, n = 131	44	34%	17	26%	27	41%
Biologic parameters at ICU admission						
Leukocytes, $\times 10^9$/L	97	9.5 (2.8–17.8)	49	9.5 (6.1–20.2)	48	9.3 (1.6–16.0)
Platelets, $\times 10^9$/L	93	141 (76–214)	45	143 (73–217)	48	138 (84–206)
Hemoglobin, g/dL	92	10.3 (7.8–12.2)	45	10.2 (8.8–12.2)	47	10.3 (7.0–11.9)
Hemolysis, n = 130	22	17%	6	9%	16	24%
Acute renal failure, n = 107						
KDIGO classification 1	14	13%	10	20%	4	7%
KDIGO classification 2	34	32%	19	38%	15	26%
KDIGO classification 3	59	55%	21	42%	38	67%
Other						
Aspartate aminotransferase, U/L	80	92 (41–269)	38	71 (41–172)	42	134 (44–346)
Alanine aminotransferase, U/L	81	54 (25–142)	39	47 (21–125)	42	69 (27–152)
Bilirubin, µmol/L	69	22 (10–45)	34	27 (10.3–52.3)	35	19.5 (10.5–35.7)
Lactatemia, mmol/L	93	5.3 (2.3–8.8)	40	3.2 (1.5–5.2)	53	8 (4.9–12)
pH	93	7.29 (7.13–7.4)	40	7.38 (7.32–7.43)	53	7.18 (7.05–7.31)

*Results are given as percentages or median (interquartile range). ICU, intensive care unit; KDIGO, Kidney Disease: Improving Global Outcomes (https://kdigo.org); SAPS2, simplified acute physiology score (SAPS2); SOFA, sequential organ failure assessment.

found in 9 patients and leading to death in 5 in the ICU (Figure 3, panels A–C). As suggested by clinical symptoms, cases of bacteremia were mostly from the gastrointestinal tract (74%), followed by myonecrosis (16%) (Figure 3, panels D–E). In total, 110 (91%) of the patients were treated with antimicrobial drugs in the ICU, and 64 (47%) patients underwent surgery that was mostly gastrointestinal surgery (67% of surgery interventions).

Most strains of *Clostridioides* were sensitive to β-lactam drugs. *Clostridioides* species were sensitive to clindamycin in 69% of the cases. Two species (*C. tertium* and *C. septicum*) were resistant to metronidazole. We did not find any association between specific antimicrobial agents used to treat *Clostridioides* bacteremia and mortality (HR 1.01, 95% CI 0.57–1.77; p = 0.977) (Appendix Table 2).

Outcomes and Mortality Risk Factors

Although *Clostridioides* spp. were for the most part efficiently treated by common antimicrobial drugs, *Clostridioides* bacteremia remained very aggressive and life-threatening; the overall mortality rate at 6 months was 71%. Of 135 patients, 84 died; 70 (52%) of all patients died in the ICU. The 28-day mortality rate was 55% (95% CI 45%–64%), and the 90-day mortality rate was 71% (95% CI 60%–79%). The rapid need for hospitalization after the occurrence of the first symptoms (median days 0, IQR 0–1) highlighted the aggressiveness of *Clostridioides* bacteremia; direct ICU transfer was necessary in most cases (median time between hospitalization and ICU transfer 0 days, IQR 0–2). Median length of stay in ICU was 2 days for patients who did not survive (IQR 1.25–5.75) and 11 days for survivors (IQR 5–23).

In multivariate analysis for overall survival, factors associated with increased risk for death were increasing age (in 5-year increments) (HR 1.19, 95% CI 1.08–1.31; p<0.001), increasing SOFA score (per point) (HR 1.12, 95% CI 1.06–1.19; p<0.001), and presence of hemolysis (HR 2.39, 95% CI 1.31–4.38; p = 0.005). On the other hand, male sex was associated with a reduced risk for death (HR 0.56, 95% CI 0.34–0.91; p = 0.02) (Figure 2).

Discussion

In our study, we found that *Clostridioides* bacteremia is an aggressive and rapidly life-threatening infec-

tion, occurring mainly in patients with underlying conditions. Septic shock with digestive symptoms is the usual manifestation. Despite rapid transfer to the ICU, large use of organ support, and active antimicrobial treatment, *Clostridioides* bacteremia remains highly lethal; 52% of ICU patients died. Massive intravascular hemolysis, associated with fatal complications, should alert clinicians to the possibility of sepsis.

Data on *Clostridioides* bacteremia consist mainly of case reports (*14*–*16*,*27*) or case series that include a small number of patients (*17*,*28*–*30*). Larger publications focusing on anaerobic bacteremia do not provide details on patients' characteristics and outcomes (*2*,*19*). Furthermore, we could find no previous publications on *Clostridioides* bacteremia in ICU patients, even though anaerobic bacteremia is frequent in this population (*2*,*31*). Our study provides a thorough description of the clinical and biologic characteristics as well as the outcomes of this serious condition.

Table 3. Characteristics of non–*C. difficile* bacteria in cases of *Clostridioides* bacter emia, France

Characteristic	No. (%) patients		
	All patients, n = 135	Survived, n = 65	Died in ICU, n = 70
Clostridium species			
Perfringens	42 (31)	16 (25)	26 (37)
Ramosum	18 (13)	10 (15)	8 (11)
Any *Clostridioides* sp.	16 (12)	6 (9)	10 (14)
Tertium	14 (10)	9 (14)	5 (7)
Clostridiforme	12 (9)	8 (12)	4 (6)
Septicum	10 (7)	2 (3)	8 (11)
Innocuum	6 (4)	5 (8)	1 (1)
Butyricum	4 (3)	2 (3)	2 (3)
Paraputrificum	3 (2)	2 (3)	1 (1)
Baratii	2 (1)	1 (2)	1 (1)
Orbiscindens	2 (1)	1 (2)	1 (1)
Sporogenes	2 (1)	1 (2)	1 (1)
Cadaveris	1 (1)	0 (0)	1 (1)
Novyi	1 (1)	1 (2)	0 (0)
Sordellii	1 (1)	0 (0)	1 (1)
Symbosium	1 (1)	1 (2)	0 (0)
No. positive blood cultures for *Clostridioides* spp.			
1	117 (87)	52 (80)	65 (93)
2	13 (10)	9 (14)	4 (6)
3	5 (4)	4 (6)	1 (1)
Other microbes associated with *Clostridioides* bacteremia, n = 49		27	22
Gram-negative bacteria	33 (67)	20 (74)	13 (59)
Gram-positive bacteria	24 (49)	12 (44)	12 (55)
Candida fungemia	1 (2)	1 (4)	0 (0)
Effectiveness of tested antimicrobial drugs against *Clostridioides* species			
Penicillin, n = 84	83 (99)	37 (100)	46 (98)
Clindamycin, n = 67	46 (69)	22 (67)	24 (71)
Vancomycin, n = 67	67 (100)	33 (100)	34 (100)
Metronidazole, n = 84	82 (98)	36 (97)	46 (98)
Patients receiving drugs	110 (91)	64 (98)	46 (82)
Beta-lactams	102 (94)	60 (94)	42 (95)
Amoxicillin/clavulanic acid	9 (9)	6 (10)	3 (7)
Piperacillin/tazobactam	46 (45)	25 (42)	21 (50)
Cephalosporins	22 (22)	15 (25)	7 (17)
Carbapenems	26 (25)	15 (25)	11 (26)
Aminoglycoside	58 (54)	34 (53)	24 (55)
Anti–gram positive bacteria	46 (43)	29 (45)	17 (39)
Metronidazole	39 (36)	26 (41)	13 (30)
Others	10 (9)	5 (8)	5 (11)
Missing data	2	0	2
Origin of bacteremia			
Digestive origin	87 (74)	43 (70)	44 (79)
Bowel pathology	33 (28)	14 (23)	19 (34)
Mesenteric ischemia	25 (21)	7 (11)	18 (32)
Peritonitis	19 (16)	16 (26)	3 (5)
Pancreatic or biliary origin	10 (9)	6 (10)	4 (7)
Myonecrosis	19 (16)	11 (18)	8 (14)
Abscess	8 (7)	5 (8)	3 (5)
Pneumonia	3 (3)	2 (3)	1 (2)
Missing data	18	4	14

Our results are consistent with earlier reports; most *Clostridioides* bacteremia cases occur in patients >65 years of age, and prevalence is higher in men (*17*,*29*,*31*). Diseases such as diabetes, chronic kidney disease, heart failure, and COPD, which maintain a baseline degree of organ ischemia and cause chronic organ failure, can lead to *Clostridioides* proliferation and consequently to bacteremia (*1*,*19*,*29*,*31*). Cancer patients or patients with hematological malignancies are also at high risk (*18*,*32*). Chemotherapy-induced cytopenia may result in neutropenic enterocolitis (*33*); this impairment of the natural digestive barrier favors the development of *Clostridioides* bacteremia. Digestive symptoms that have been described as hallmarks of this condition (*1*,*17*,*29*) were frequently associated with *Clostridioides* bacteremia in the ICU. Of note, although *Clostridioides* bacteremia is mostly from digestive origins, myonecrosis was identified as the origin of the bacteremia in 16% of the cases in our study, which is consistent with previous reports (*17*,*18*,*29*,*31*).

Among *Clostridioides* species, *C. perfringens* was more often identified as the source of bacteremia, as previously published (*1*,*19*,*34*). Fifteen other *Clostridioides* species have been identified; distribution is similar to the one described by Leal et al. (*19*). In this study, we chose to exclude *C. difficile* infections because this pathogen is mainly responsible for healthcare-associated digestive infections. *C. difficile* can still present as extradigestive infections; however, few cases of bacteremia have been reported (*35*,*36*).

Data on incidence of anaerobic and *Clostridioides* bacteremia are conflicting. Some authors report an increasing incidence of anaerobic bacteremia since the 1990s, whereas other report decreasing trends (*2*,*6*,*20*,*37*). The incidence of anaerobic bacteremia depend on patients' age and underlying conditions (especially cancer or cardiovascular illness), and antibiotic selection pressure driven by antimicrobial drug use and environmental conditions. In addition, as suggested by Morris et al. (*38*), blood cultures for anaerobic bacteria may be influenced by patients' background and clinical symptoms. Indeed, in a recent study evaluating anaerobic bacteremia, 39.7% of the positive blood cultures were considered to be bloodstream infections; the remaining 60.3% were attributed to contaminants (*39*). The evolution of microbiologic techniques, including growing use of automated techniques and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry, might have also influenced the increasing isolation of anaerobic bacteremia. Although we cannot rule out that some infections may have been overestimated, the severity of clinical presentations in our cohort suggests that these cases resulted from true bloodstream infections.

Of note, *Clostridioides* bacteremia can present either as a single microbial bacteremia or as a polymicrobial bacteremia (*2*,*28*,*30*,*31*). *Enterobacteriaceae* were the most commonly associated bacteria, followed by *Staphylococcus* species. Cultures for multiple microbes were positive for *Clostridioides* spp. in 18 patients. Comparable results were also found by Fujita et al. (*17*). *Clostridioides* species are largely susceptible to common antimicrobial drugs, except for clindamycin; susceptibility for clindamycin has been reported as reduced by 73%–96% (*1*,*3*,*5*,*19*,*31*). High susceptibility to penicillin should alert clinicians to rapidly initiate treatment in identified cases of *Clostridioides* bacteremia.

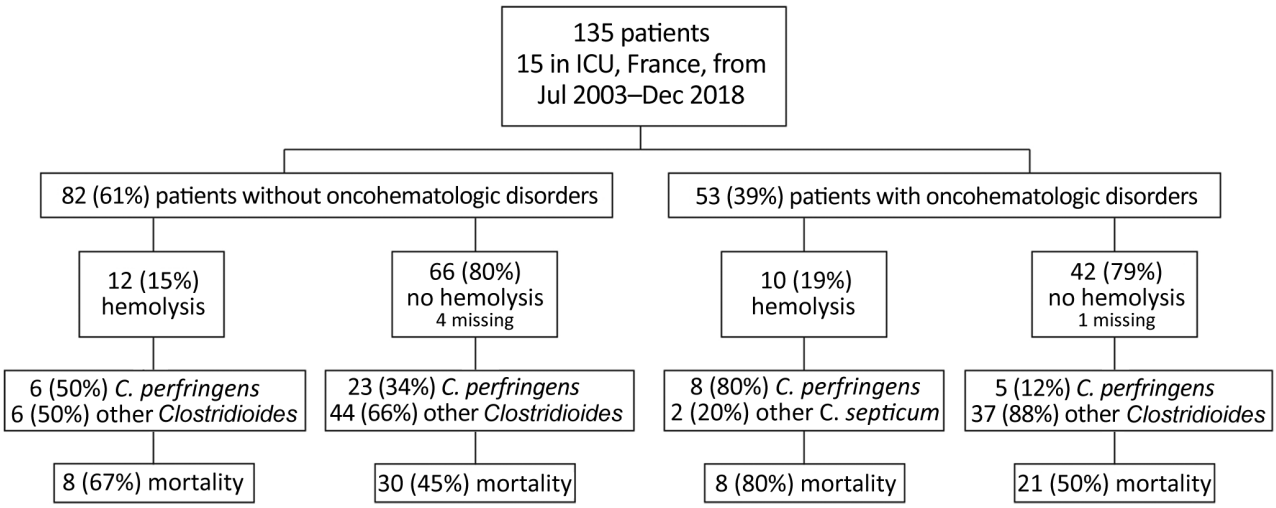

Figure 2. Flowchart of the repartition of *Clostridioides* bacteremia in patients in France according to the presence or absence of hemolysis. Hemolysis was associated with a high mortality rate.

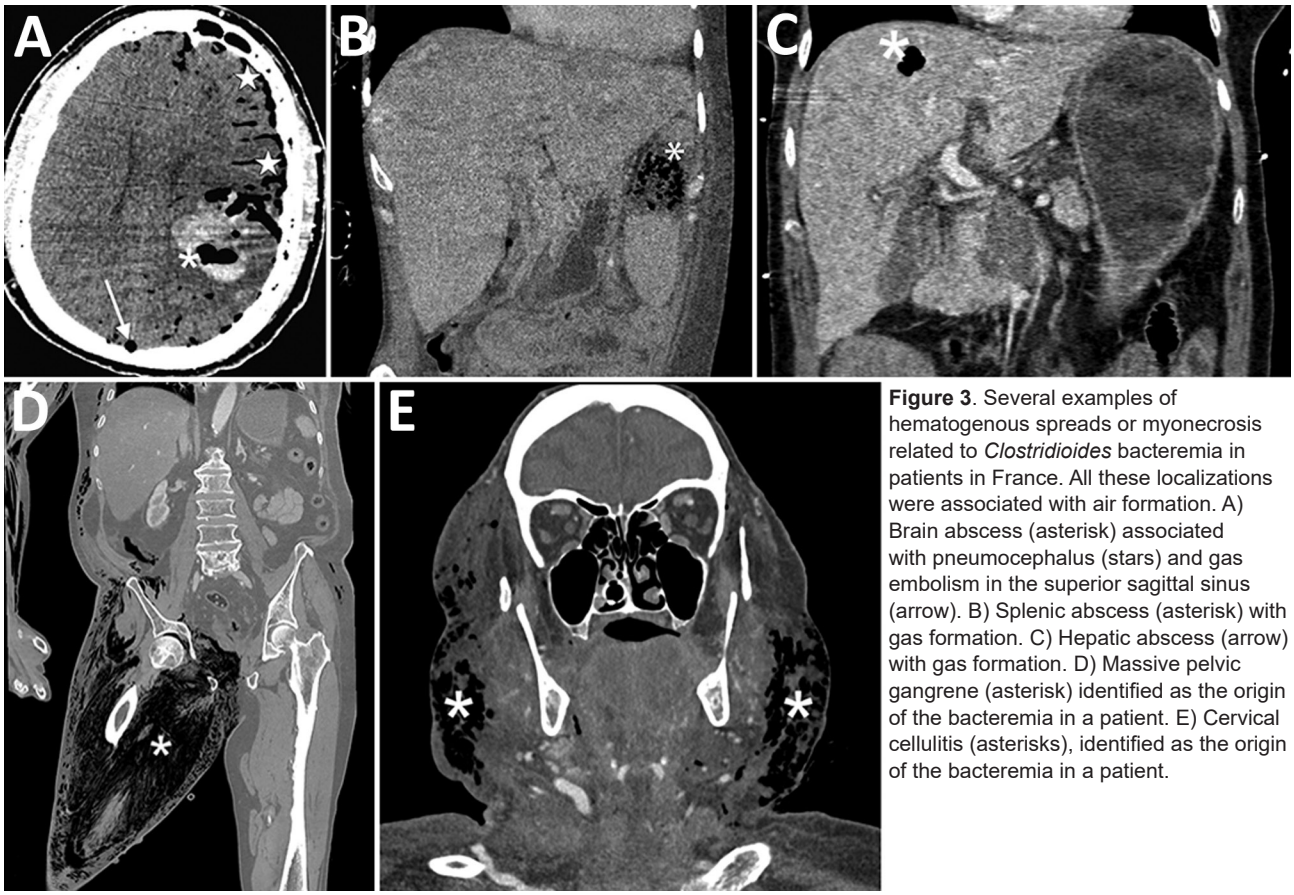

Figure 3. Several examples of hematogenous spreads or myonecrosis related to *Clostridioides* bacteremia in patients in France. All these localizations were associated with air formation. A) Brain abscess (asterisk) associated with pneumocephalus (stars) and gas embolism in the superior sagittal sinus (arrow). B) Splenic abscess (asterisk) with gas formation. C) Hepatic abscess (arrow) with gas formation. D) Massive pelvic gangrene (asterisk) identified as the origin of the bacteremia in a patient. E) Cervical cellulitis (asterisks), identified as the origin of the bacteremia in a patient.

Because 94% of the patients in our study received adequate antimicrobial drugs within 24 hours of ICU admission, we were not able to find any statistical association between early initiation of drugs and death. However, in a recent study published by Stabler et al. (*34*), adequate empiric antimicrobial therapy was associated with a better outcome. This result was also highlighted previously by Zahar et al. (*18*).

Mortality rates for *Clostridioides* bacteremia reported in the literature were 15%–48% (*17–19,28–31*), which is lower than the mortality rates reported in our study. Indeed, Yang (31) and Fujita (17) revealed that patients who developed shock and required transfer to the ICU had worse outcomes than other patients. In those studies, shock was statistically associated with increased deaths. The prognosis for *Clostridioides* bacteremia patients is also related to underlying conditions that predispose to *Clostridioides* bacteremia and possibilities of therapeutic interventions in addition to prompt and appropriate antimicrobial drugs. As demonstrated by Rechner et al. (*1*), patients who required medical intervention to treat *Clostridioides* bacteremia had lower survival rates than patients who were managed by surgery. Conversely, the presence of massive intravascular hemolysis is a marker of extreme severity, despite appropriate management (*16,40*). Hemolysis is induced by *Clostridioides* toxin A (*29*), which hydrolyzes phospholipids in erythrocyte membranes, causing spherocytosis and subsequent intravascular hemolysis. Present in 17% of patients in our cohort, hemolysis is associated with a dramatic increase in mortality rate and remains a strong prognostic factor identified in our study. Finally, *Clostridioides* bacteremia in the ICU is associated with a higher mortality rate than that for classic septic shock in the ICU (*41,42*), which makes *Clostridioides* bacteremia a particularly difficult infection to deal with in the ICU.

The first limitation of our study is its retrospective nature and the inherently associated bias, such as missing data and unidentified confounding factors that may have been overlooked in the data collection. However, because of the rarity of *Clostridioides* bacteremia, prospective studies would hardly be feasible. Second, there are no standardized ICU admission policies for these patients, and patient recruitment patterns may have influenced the findings. Given the rapidity of the onset of symptoms and the severity

of illness, rapid ICU management was the rule in the participating centers. However, we could not exclude that some patients, because of their advanced age or underlying conditions, were considered too sick for admission to the ICU and may have been denied intensive care.

In conclusion, *Clostridioides* bacteremia is an aggressive infection that often leads to failure of multiple organs, requiring prompt intensive care management. Particular attention should be paid to patients who have underlying conditions and are experiencing hemolysis. Early administration of antimicrobial agents active against *Clostridioides* bacteremia is essential, considering that most *Clostridioides* species are sensitive to β-lactams drugs. Even with prompt and appropriate management, however, *Clostridioides* bacteremia is associated with a high mortality rate in the ICU.

About the Author

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Non–*C. difficile Clostridioides* Bacteremia in Intensive Care Patients, France

Appendix

Appendix Table 1. Biologic parameters of 22 intensive-care patients with bacteremia experiencing hemolysis*

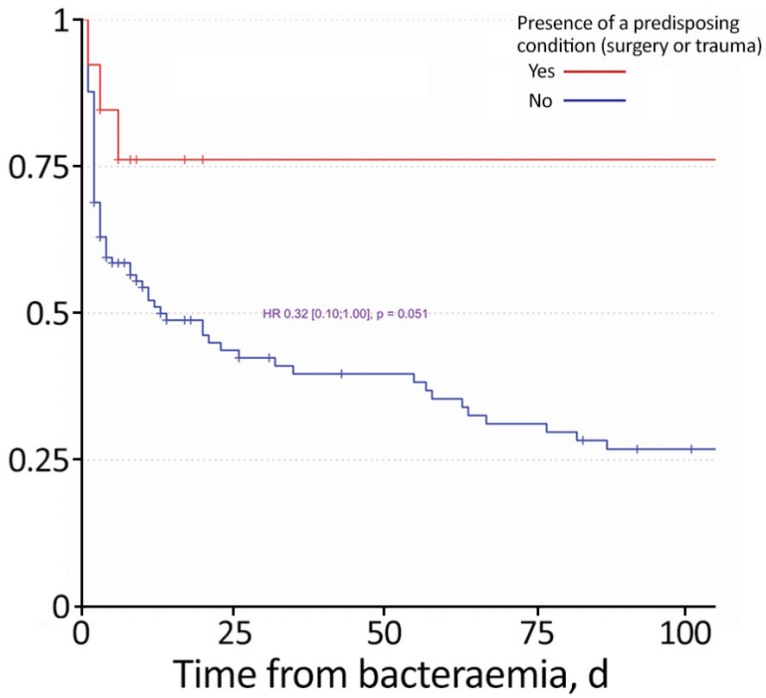
Patient no.	Hemolysis	Hemoglobin, g/dL	LDH, UI/L	ASAT, UI/L	ALAT, UI/L	Bilirubin, µmol/L	*Clostridioides* species
1	Yes	13.1	1,834	46	19	35.1	*C. perfringens*
4	Yes	5.3	HI	HI	HI	HI	*C. perfringens*
5	Yes	1.7	HI	HI	HI	HI	*C. perfringens*
6	Yes	1.2	HI	HI	HI	14	*C. perfringens*
13	Yes	2.8	510	–	–	63	*C. perfringens*
16	Yes	3.4	2,905	2,634	1,608	12.2	*C. septicum*
17	Yes	HI	HI	HI	HI	HI	*C. perfringens*
26	Yes	3.3	5,033	402	32	112	*C. perfringens*
27	Yes	7.1	–	137	26	9	*C. septicum*
28	Yes	3.8	–	38	47	8.6	*C. orbiscindens*
31	Yes	8.2	469	132	93	7.6	*C. perfringens*
32	Yes	4.0	446	46	16	14	*C. novyi*
34	Yes	8.5	3,788	878	1,094	37.4	*C. septicum*
35	Yes	HI	HI	HI	HI	HI	*C. perfringens*
53	Yes	8.8	4,501	1,644	588	10	*C. innocuum*
60	Yes	3.8	630	58	17	53	*C. perfringens*
74	Yes	4.9	3,830	50	30	72	*C. perfringens*
84	Yes	HI	HI	HI	HI	HI	*C. ramosum*
94	Yes	5.9	–	158	46	–	*C. perfringens*
96	Yes	6.9	–	1,696	476	11	*C. baratii*
115	Yes	6.0	–	–	–	25	*C. perfringens*
132	Yes	4.6	–	–	–	–	*C. perfringens*

*Biologic parameters were not measurable for 3 patients due to hemolysis interferences. ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; HI, hemolysis interference; LDH, lactate dehydrogenase.

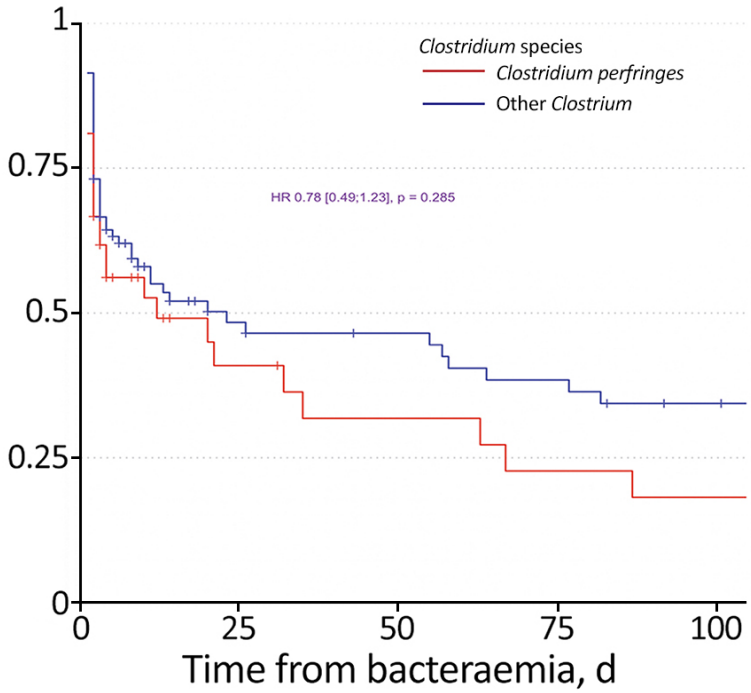
Appendix Table 2. Univariate analysis by antimicrobial agents of patients who died in study of non-*C. difficile Clostridiodies* bacteremia, France*

Category	HR (95% CI)	p value
Patients receiving antimicrobial drugs	1.01 (0.57–1.77)	0.977
Antimicrobial drugs		
Beta-lactams	0.88 (0.32–2.43)	0.799
Aminoglycoside	1.24 (0.73–2.08)	0.427
Anti–gram-positive bacteria	0.79 (0.47–1.34)	0.379
Metronidazole	0.81 (0.47–1.41)	0.461
Others	1.31 (0.56–3.06)	0.537

*HR, hazard ratio.



Appendix Figure 1. Kaplan-Meier curve depending on the presence of predisposing conditions. Patients with a recent history of surgery or trauma had a better, but not significant, prognostic compared to other patients. HR, hazard ratio.



Appendix Figure 2. Kaplan-Meier curve depending on *Clostridioides* species.