1 **Title:** Clinical relevance of *Clostridium* bacteremia: an 8-year retrospective study.

2 **Running title:** Clinical relevance of *Clostridium* bacteremia.

3 **Author names and affiliations:** Sarah Stabler^{1,2}, Marie Titécat^{3,4}, Claire Duployez^{2,3},
4 Frédéric Wallet^{2,3}, Caroline Loïez³, Perrine Bortolotti^{2,5}, Emmanuel Faure^{1,2}, Karine
5 Faure^{1,2}, Eric Kipnis^{2,5}, Rodrigue Dessein^{2,3}, Rémi Le Guern^{2,3}

6 ¹ CHU Lille, Service de Maladies Infectieuses, F-59000 Lille, France.

7 ² Univ. Lille, CNRS, Inserm, CHU Lille, Institut Pasteur de Lille, U1019 - UMR 9017 -
8 CIIL - Center for Infection and Immunity of Lille, F-59000 Lille, France.

9 ³ CHU Lille, Service de Bactériologie-Hygiène, F-59000 Lille, France.

10 ⁴ Univ. Lille, Inserm, CHU Lille, U1286 - INFINITE - Institute for Translational Research
11 in Inflammation, F-59000 Lille, France.

12 ⁵ CHU Lille, Service de Réanimation Chirurgicale, F-59000 Lille, France.

13 **Corresponding author:** Rémi Le Guern. Service de Bactériologie, Centre de Biologie
14 Pathologie Génétique. Boulevard du Professeur Jules Leclercq. 59037 Lille France.

15 Email address: remi.leguern@chru-lille.fr

Abstract:

Clostridium spp. are recovered from 25% of the blood culture positive with anaerobes. However, the clinical relevance of *Clostridium* bacteremia has been controverted in the literature, particularly for *C. perfringens*. We aimed to evaluate the clinical relevance of *Clostridium* bacteremia, either due to *C. perfringens* or other *Clostridium* species, and to identify the risk factors of mortality in these patients. A retrospective cohort study was conducted from January 2010 to April 2018. All the patients with at least one blood culture positive with any *Clostridium* species were included. Eighty-one patients with a least one blood culture positive with any *Clostridium* species were included. Seventy patients (86.4%) fulfilled the criteria for clinically relevant bacteremia. Bacteremia due to *C. perfringens* tended to be less clinically relevant than other *Clostridium* species but this was not statistically significant (76% vs 91.2%, $P=0.09$). In case of clinically relevant bacteremia, the 30-day mortality rate was 31.4%. In multivariate analysis, adequate empiric antimicrobial therapy was significantly associated with survival ($P=0.03$). In conclusion, bacteremia due to *C. perfringens* or other *Clostridium* species is usually clinically relevant. This finding was also supported by an improved survival at 30 days when adequate empiric antimicrobial therapy was administered.

Keywords:

Clostridium infection; Bacteremia; Pseudobacteremia; Anaerobe; Contamination; Clinical relevance; Clinical significance

Introduction

Anaerobes are recovered from 5% of clinically relevant bacteremia [1]. *Clostridium* spp. represent 23% of the obligate anaerobic bacteria isolated from blood cultures, the second most frequent anaerobe after *Bacteroides* [2]. However, the clinical relevance of *Clostridium* bacteremia has been controverted in the literature [3-5].

Positive blood cultures are not always clinically relevant as they can represent contamination by the skin microbiota or transient bacteremia. Transient bacteremia can occur after dental procedures [6], tooth brushing [7], or digestive procedures [8]. In a study from 1997, *C. perfringens* was considered clinically relevant only in 33% of the cases [3], whereas for other *Clostridium* species this rate was higher at 80%. In another study, inadequate treatment for *Clostridium* bacteremia did not affect patient survival, leading the authors to call into question the relevance of *Clostridium* bacteremia [4]. *C. perfringens* and some other *Clostridium* species possess several virulence factors [9]. Usually, virulent bacteria recovered in blood cultures are considered clinically relevant, but for anaerobes this has been a controversial area.

We aimed to evaluate the clinical relevance of *Clostridium* bacteremia, either due to *C. perfringens* or other *Clostridium* species, and to identify the risk factors of mortality in these patients.

Material and methods

This retrospective cohort study was conducted in Lille University Hospital, a 3200-bed hospital in France. From January 2010 to April 2018, all the consecutive patients with at least one blood culture positive with any *Clostridium* species were included.

Data collected included demographical and clinical characteristics, associated comorbidities, inflammatory markers, source of infection, antimicrobial therapy, and 30-day mortality following the first positive blood culture. The source of infection was based on a consensus of both clinical and microbiological data. Hypotension was defined as a systolic blood pressure of less than 90 mmHg. Hypothermia and hyperthermia were defined as a temperature of less than 35°C or more than 38°C, respectively. Adequate empiric therapy was defined as antimicrobial therapy with anti-anaerobic activity administered at most 24 hours after blood cultures were sampled.

Blood cultures were incubated on a BacT/ALERT® 3D automated blood culture system (bioMérieux, Marcy l'Etoile, France) from January 2010 to June 2015, then on a VIRTUO™ (bioMérieux, Marcy l'Etoile, France) from July 2015 to April 2018. Time-to-detection values were collected. Bacteria were identified by MALDI-TOF mass spectrometry (Bruker Daltonics, Wissembourg, France), or 16S rDNA sequencing. Antimicrobial susceptibility was evaluated by diffusion, according to the guidelines of the CA-SFM (Comité de l'Antibiogramme de la Société Française de Microbiologie; <http://www.sfm-microbiologie.org/>).

Clostridium bacteremia was considered clinically relevant if at least one of these characteristics was present: (i) more than one positive blood culture with *Clostridium*

spp., (ii) appropriate source of infection (intra-abdominal, skin and soft tissues, urinary tract infection) or neutropenic fever, (iii) sepsis (including two or more criteria of systemic inflammatory response syndrome, without another evident source of infection) [10].

Statistical analysis was performed with R software [11]. Qualitative variables were compared with Fisher's exact test or the Chi-2 test, and continuous variables with Student's t-test. For multivariate analysis, we used stepwise logistic regression to calculate odds ratios (OR) and 95% confidence intervals (CI). Survival distributions were compared using the log-rank test using the survminer R package.

This retrospective analysis on existing, routinely collected data, was declared to the French National Commission on Informatics and Liberty under the reference number DEC20-001.

Results

During the study period, 688 189 blood cultures were sampled: 337 579 aerobic, 309 299 anaerobic, and 41 311 pediatric bottles. Out of these, 68 749 were positive with any bacteria (9.99%), including 111 with any *Clostridium* species (0.16% of the positive blood cultures). Nineteen patients had more than one blood culture positive with the same *Clostridium* species. In total, 81 patients with bacteremia due to any *Clostridium* species were included: 25 corresponded to *Clostridium perfringens* and 56 to other *Clostridium* species (Table 1).

Demographic data and clinical presentation

The mean age of patients was 61.4 years old (standard deviation 17.4), and 54.3% were male (Table 2). No differences were observed between bacteremia due to *C. perfringens* or other *Clostridium* species concerning sex, age, and comorbidities. Frequent comorbidities were cancer (45.7%), recent digestive surgery (24.7%), chemotherapy (23.5%), diabetes (22.2%) and renal insufficiency (22.2%). A potential source of infection was identified for 76.5% of the patients. A potential source of infection was identified for 76.5% of the patients, with the most common being non-biliary abdominal infection (50.6%), skin and soft tissue infection (12.3%), and biliary tract infection (8.6%). Bacteremia due to *C. perfringens* was more often community-acquired than for other *Clostridium* species (64.3% vs 36.0%, $P=0.03$), and the mortality rate during the first week was higher for *C. perfringens* (28.0% vs 8.9%, $P=0.04$).

Fifty-six patients received adequate empiric antimicrobial therapy. Thirty-five (62.5%) of these patients received beta-lactams associated with beta-lactamase

inhibitors (piperacillin-Tazobactam 53.6%, ticarcillin-clavulanic acid 5.3%, amoxicillin-clavulanic acid 3.6%), 12 (21.4%) metronidazole, 9 (16.1%) carbapenems (imipenem 10.7%, meropenem 5.3%), and one (1.8%) vancomycin. One patient received both piperacillin-tazobactam and metronidazole.

Seventy patients (86.4%) fulfilled defined criteria for clinically relevant bacteremia. Bacteremia due to *C. perfringens* tended to be less frequently clinically relevant than other *Clostridium* species, but this was not statistically significant (76% vs 91.2%, $P=0.09$). Patients with clinically relevant bacteremia presented a higher CRP than patients with non-clinically relevant bacteremia (171 vs 74, $P<0.001$) (Supplementary Table 1). Adequate antimicrobial therapy was also more frequently prescribed in case of clinically relevant bacteremia (81.5% vs 30%, $P=0.002$). The 30-day mortality rate was higher in case of clinically relevant bacteremia (31.4% vs 18.2%, $P=0.49$), but this difference was not statistically significant.

Microbiological data

Time-to-positivity of the first blood culture was shorter for patients with *C. perfringens* bacteremia compared to other *Clostridium* species (16.9 hours vs 31.8 hours, $P=0.002$) (Table 3). Blood cultures positive with *C. perfringens* were more frequently associated with *Enterobacteriales* growth in the same blood culture (24% vs 2%, $P=0.003$). Blood cultures positive with other *Clostridium* species were more frequently associated with other anaerobes growth in the blood cultures sampled in the 7 days before or after inclusion (48.2% vs 20, $P=0.03$).

Risk factors of mortality in case of clinically relevant bacteremia

132 The 30-day mortality rate in case of clinically relevant bacteremia was 31.4%,
133 with a median time between blood culture positivity and death of 7 days (Table 4).
134 Hypothermia at initial presentation was associated with death ($P=0.02$). Variables
135 associated with survival in univariate analysis were adequate empiric antimicrobial
136 therapy ($P=0.005$) (Figure 1) and associated surgical treatment ($P=0.001$). In
137 multivariate analysis, adequate empiric antimicrobial therapy was significantly
138 associated with survival (OR = 0.17; CI95%: 0.03 – 0.81) (Table 5).

Discussion

We provide evidence that bacteremia due to *C. perfringens* or other *Clostridium* species is clinically relevant in the majority of patients in this study. Moreover, adequate empiric antimicrobial therapy was associated with improved survival at 30 days, which supports the criteria used to define clinical relevance.

Clinical relevance of bacteremia due to *Clostridium* spp. is variable in the literature, with rates ranging from 56 to 89% for *Clostridium* spp. [10, 12-14], and from 33 to 73% when *C. perfringens* is studied specifically [3, 15]. In a previous study, *C. perfringens* bacteremia sometimes presented no evident relation to the underlying illness and could be observed in meningitis due to *Neisseria meningitidis*, or in pulmonary tuberculosis [16]. In those cases, blood culture contamination may be considered. Nevertheless, our study shows a high frequency of clinically relevant bacteremia, both for *C. perfringens* (76.0%) and other *Clostridium* species (91.2%), supporting a causative role in infection.

The definition of clinically relevant bacteremia varies amongst studies but typically includes growth in multiple blood cultures. For some authors, bacteremia is considered clinically relevant when at least one of the following criteria is met: white blood cell count lower or higher than normal, hyperthermia (temperature >38°C), or any clinical evidence consistent with infection [17-20]. In our study, we used rather broad criteria for clinical relevance of *Clostridium* bacteremia that were proposed by Benjamin et al.: either more than one positive blood culture with *Clostridium*, presence of a source of infection potentially associated with *Clostridium* infection, or sepsis without another evident

source of infection [10]. To validate the suitability of these criteria, we analyzed the risk factors of mortality in case of clinically relevant bacteremia.

The 30-day mortality rate was 31.4% in our cohort, for clinically relevant bacteremia. Half of these patients (n=11/22) died during the first week. In the literature, the 30-day mortality due to *Clostridium* spp. bacteremia generally ranges from 27% to 30% [10, 13, 21], but can attain 43% in cancer patients [22]. In a study including 73 patients with clinically relevant bacteremia, mortality was higher for *Clostridium* spp. than for other anaerobes [23]. Risk factors for mortality related to *Clostridium* spp. bacteremia have been identified, such as septic shock at initial presentation [15, 24], or nosocomial infection [15]. In our study, hypothermia seemed to be an interesting warning sign to consider. However, given the small number of patients with hypothermia (n=7), further studies are needed to assess this association. Hypothermia was previously associated with increased mortality in septic patients [25], but not specifically with bacteremia due to *Clostridium* species.

Our study highlights the importance of early adequate anti-anaerobe therapy to improve patient's survival. Salonen *et al.* showed that failure to add appropriate antimicrobial was associated with higher mortality (55% vs 17%) in case of bacteremia due to any anaerobe (mostly *Bacteroides*) [12]. Another study including 117 cases of anaerobic bacteremia also found that inadequate antimicrobial therapy was associated with mortality [17]. However, in a large study including 93 patients with *C. perfringens* bacteremia, adequate antibiotic use was not significantly associated with survival [15]. To the best of our knowledge, only one previous study suggested a significant association between early appropriate antimicrobial therapy and survival in patients with

clinically relevant bacteremia due to *Clostridium* spp [26]. The 2-weeks mortality rate was 28% in patients who received appropriate therapy and 78% in patients who received no antimicrobial therapy [26]. Recently, a study focusing on a rapid-diagnostics platform from positive blood cultures showed that the delay before starting adequate antimicrobial therapy was high for bacteremia due to anaerobes, contributing to higher mortality in this subgroup [27]. Indeed, 59% of the organisms not detected by the platform were anaerobes (mostly *Bacteroides* and *Clostridium*), because they were not included in the panel. In the future, the development of rapid diagnostic platforms including anaerobes could lead to a quicker initiation of adequate antimicrobial therapy.

Another factor associated with patient's survival in univariate analysis was adjunctive surgery. Prompt control of the source infection has been shown to reduce the mortality of patients with bacteremia due to any anaerobe [28]. Surgery should be considered to treat the focus of infection in case of *Clostridium* bacteremia. However, some bias exists due to the retrospective nature of the study, as patients dying in the first 24 hours may not have the time to benefit from surgery.

Concerning the microbiological data, differences between *C. perfringens* and other *Clostridium* species were shown. Time-to-positivity of blood cultures was shorter for *C. perfringens*, a bacteria known for its fast generation time [29]. *C. perfringens* and other *Clostridium* species were frequently associated with different bacteria, either in the same blood culture (polymicrobial) or during the seven days before or after inclusion. For *C. perfringens*, 24% of the blood cultures were polymicrobial with *Enterobacteriales*. As blood cultures with *Enterobacteriales* are usually positive in the first 24 hours, it is possible that only *C. perfringens* has the time to grow in such a short delay, which may

explain the preferential association observed in our study. Polymicrobial bacteremia with *Clostridium* spp. and *Enterobacteriales* was also described recently [22], but the role of *C. perfringens* was not specifically studied. For *Clostridium* species other than *C. perfringens*, other anaerobes were recovered from the blood cultures sampled within 7 days before or after inclusion in 48.2% of the cases. These results suggest that keeping a broad anti-anaerobic coverage is important in case of bacteremia due to *Clostridium* spp., as other anaerobes may participate in the infection process.

Conclusion

Bacteremia due to *C. perfringens* or other *Clostridium* species is usually clinically relevant. The clinical relevance of these bacteremia was supported by an improved survival at 30 days when adequate empiric antimicrobial therapy was administrated.

Funding Statement

Univ. Lille, CHU Lille.

Word count: 2037 words

221 **References:**

- 222 [1] E.J. Goldstein. Anaerobic bacteremia. Clin Infect Dis 23 Suppl 1 (1996) S97-101.
- 223 [2] F.R. Cockerill, 3rd, J.G. Hughes, E.A. Vetter, R.A. Mueller, A.L. Weaver, D.M.
- 224 Ilstrup, et al. Analysis of 281,797 consecutive blood cultures performed over an eight-
- 225 year period: trends in microorganisms isolated and the value of anaerobic culture of
- 226 blood. Clin Infect Dis 24 (1997) 403-18.
- 227 [3] M.P. Weinstein, M.L. Towns, S.M. Quartey, S. Mirrett, L.G. Reimer, G.
- 228 Parmigiani, et al. The clinical significance of positive blood cultures in the 1990s: a
- 229 prospective comprehensive evaluation of the microbiology, epidemiology, and outcome
- 230 of bacteremia and fungemia in adults. Clin Infect Dis 24 (1997) 584-602.
- 231 [4] R.I. Haddy, D.D. Nadkarni, B.L. Mann, D.R. Little, T.D. Domers, R.D. Clover, et
- 232 al. Clostridial bacteremia in the community hospital. Scand J Infect Dis 32 (2000) 27-30.
- 233 [5] C.C. Lee, W.J. Lin, H.I. Shih, C.J. Wu, P.L. Chen, H.C. Lee, et al. Clinical
- 234 significance of potential contaminants in blood cultures among patients in a medical
- 235 center. J Microbiol Immunol Infect 40 (2007) 438-44.
- 236 [6] I. Tomas, M. Alvarez, J. Limeres, C. Potel, J. Medina, P. Diz. Prevalence,
- 237 duration and aetiology of bacteraemia following dental extractions. Oral Dis 13 (2007)
- 238 56-62.
- 239 [7] P.B. Lockhart, M.T. Brennan, H.C. Sasser, P.C. Fox, B.J. Paster, F.K. Bahrani-
- 240 Mougeot. Bacteremia associated with toothbrushing and dental extraction. Circulation
- 241 117 (2008) 3118-25.
- 242 [8] N. Thosani, R.S. Zubarik, R. Kochar, S. Kothari, N. Sardana, T. Nguyen, et al.
- 243 Prospective evaluation of bacteremia rates and infectious complications among patients
- 244 undergoing single-operator choledochoscopy during ERCP. Endoscopy 48 (2016) 424-
- 245 31.
- 246 [9] M.R. Popoff, P. Bouvet. Clostridial toxins. Future Microbiol 4 (2009) 1021-64.
- 247 [10] B. Benjamin, M. Kan, D. Schwartz, Y. Siegman-Igra. The possible significance of
- 248 *Clostridium* spp. in blood cultures. Clin Microbiol Infect 12 (2006) 1006-12.
- 249 [11] R Core Team. R: A language and environment for statistical computing. 2013.
- 250 [12] J.H. Salonen, E. Eerola, O. Meurman. Clinical significance and outcome of
- 251 anaerobic bacteremia. Clin Infect Dis 26 (1998) 1413-7.
- 252 [13] P.C. Woo, S.K. Lau, K.M. Chan, A.M. Fung, B.S. Tang, K.Y. Yuen. *Clostridium*
- 253 bacteraemia characterised by 16S ribosomal RNA gene sequencing. J Clin Pathol 58
- 254 (2005) 301-7.
- 255 [14] P.M. Rechner, W.A. Agger, K. Mruz, T.H. Cogbill. Clinical features of clostridial
- 256 bacteremia: a review from a rural area. Clin Infect Dis 33 (2001) 349-53.
- 257 [15] C.C. Yang, P.C. Hsu, H.J. Chang, C.W. Cheng, M.H. Lee. Clinical significance
- 258 and outcomes of *Clostridium perfringens* bacteremia--a 10-year experience at a tertiary
- 259 care hospital. Int J Infect Dis 17 (2013) e955-60.
- 260 [16] S.L. Gorbach, H. Thadepalli. Isolation of *Clostridium* in human infections:
- 261 evaluation of 114 cases. J Infect Dis 131 Suppl (1975) S81-5.
- 262 [17] R. Robert, A. Deraignac, G. Le Moal, S. Ragot, G. Grollier. Prognostic factors and
- 263 impact of antibiotherapy in 117 cases of anaerobic bacteraemia. Eur J Clin Microbiol
- 264 Infect Dis 27 (2008) 671-8.

- [18] S. De Keukeleire, I. Wybo, A. Naessens, F. Echahidi, M. Van der Beken, K. Vandoorslaer, et al. Anaerobic bacteraemia: a 10-year retrospective epidemiological survey. *Anaerobe* 39 (2016) 54-9.
- [19] L. Blairon, Y. De Gheldre, B. Delaere, A. Sonet, A. Bosly, Y. Glupczynski. A 62-month retrospective epidemiological survey of anaerobic bacteraemia in a university hospital. *Clin Microbiol Infect* 12 (2006) 527-32.
- [20] T. Umemura, Y. Hamada, Y. Yamagishi, H. Suematsu, H. Mikamo. Clinical characteristics associated with mortality of patients with anaerobic bacteremia. *Anaerobe* 39 (2016) 45-50.
- [21] J. Leal, D.B. Gregson, T. Ross, D.L. Church, K.B. Laupland. Epidemiology of *Clostridium* species bacteremia in Calgary, Canada, 2000-2006. *J Infect* 57 (2008) 198-203.
- [22] Y. Yamamoto, N. Itoh, T. Sugiyama, H. Kurai. Clinical features of *Clostridium* bacteremia in cancer patients: A case series review. *J Infect Chemother* (2019).
- [23] J.R. Wilson, A.P. Limalye. Risk factors for mortality in patients with anaerobic bacteremia. *Eur J Clin Microbiol Infect Dis* 23 (2004) 310-6.
- [24] H. Fujita, S. Nishimura, S. Kurosawa, I. Akiya, F. Nakamura-Uchiyama, K. Ohnishi. 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. *Intern Med* 49 (2010) 2433-7.
- [25] Z. Rumbus, R. Matics, P. Hegyi, C. Zsiboras, I. Szabo, A. Illes, et al. Fever Is Associated with Reduced, Hypothermia with Increased Mortality in Septic Patients: A Meta-Analysis of Clinical Trials. *PLoS One* 12 (2017) e0170152.
- [26] G.P. Bodey, S. Rodriguez, V. Fainstein, L.S. Elting. Clostridial bacteremia in cancer patients. A 12-year experience. *Cancer* 67 (1991) 1928-42.
- [27] P. Ny, A. Ozaki, J. Pallares, P. Nieberg, A. Wong-Beringer. Antimicrobial Stewardship Opportunities in Patients with Bacteremia Not Identified by BioFire FilmArray. *J Clin Microbiol* 57 (2019).
- [28] A. Vena, P. Munoz, L. Alcala, A. Fernandez-Cruz, C. Sanchez, M. Valerio, et al. Are incidence and epidemiology of anaerobic bacteremia really changing? *Eur J Clin Microbiol Infect Dis* 34 (2015) 1621-9.
- [29] R.G. Labbe, T.H. Huang. Generation Times and Modeling of Enterotoxin-Positive and Enterotoxin-Negative Strains of *Clostridium perfringens* in Laboratory Media and Ground Beef. *J Food Prot* 58 (1995) 1303-6.

Table 1. *Clostridium* species identified in the blood cultures.

Group	<i>Clostridium</i> species	n (%)
<i>Clostridium perfringens</i>	<i>C. perfringens</i>	25 (30.9%)
Other <i>Clostridium</i> species	<i>C. tertium</i>	12 (14.8%)
	<i>C. clostridioforme</i>	9 (11.1%)
	<i>C. ramosum</i>	7 (8.6%)
	<i>C. innocuum</i>	6 (7.4%)
	<i>C. paraputrificum</i>	5 (6.2%)
	<i>C. sporogenes</i>	4 (4.9%)
	<i>Clostridium</i> sp.	4 (4.9%)
	<i>C. septicum</i>	2 (2.5%)
	<i>C. symbiosum</i>	2 (2.5%)
	<i>C. aldenense</i>	1 (1.2%)
	<i>C. butyricum</i>	1 (1.2%)
	<i>Hungatella hathewayi</i> *	1 (1.2%)
	<i>Clostridioides manganotii</i> *	1 (1.2%)
	<i>Paeniclostridium sordellii</i> *	1 (1.2%)

* *Clostridium* species that were recently reclassified in another genus

Table 2. Characteristics of the patients with *Clostridium* bacteremia.

	<i>C. perfringens</i> (n = 25)	Other <i>Clostridium</i> (n = 56)	<i>P</i>
Demographics			
Male gender	15 (60.0%)	29 (51.8%)	0.66
Age, Mean $\pm$ SD	65.4 $\pm$ 13.2	59.7 $\pm$ 18.9	0.13
Comorbidities			
Diabetes	7 (28.0%)	11 (19.6%)	0.59
Cancer	10 (40.0%)	27 (48.2%)	0.66
Renal insufficiency	5 (20.0%)	13 (23.2%)	0.97
Cirrhosis	1 (1.8%)	3 (12.0%)	0.09
Chemotherapy	6 (24.0%)	13 (23.2%)	1.00
Immunosuppressive drugs	1 (4.0%)	5 (8.9%)	0.66
Corticotherapy	4 (16.0%)	5 (8.9%)	0.45
Recent digestive surgery	6 (24.0%)	14 (25.0%)	1.00
Clinical presentation			
Fever	16 (76.2%)	41 (77.4%)	1.00
Hypothermia	1 (4.8%)	6 (11.3%)	0.67
Hypotension	9 (40.9%)	29 (55.8%)	0.36
Nosocomial	9 (36.0%)	36 (64.3%)	0.03
Inflammatory markers			
CRP, Mean $\pm$ SD	136 $\pm$ 94.8	167 $\pm$ 111	0.22
Leukocytes, Mean $\pm$ SD	16776 $\pm$ 12210	11807 $\pm$ 9375	0.08
Source of infection			0.39
Biliary tract infection	4 (23.5%)	3 (6.7%)	
Other abdominal infection	11 (64.7%)	30 (66.7%)	
Skin and soft tissue infection	2 (11.8%)	8 (17.8%)	
Neutropenic fever	0 (0.0%)	3 (6.7%)	
Urinary tract infection	0 (0.0%)	1 (2.2%)	
Unknown	8 (32%)	11 (19.6%)	
Antimicrobial therapy			
Adequate empiric antimicrobial therapy	17 (73.9%)	39 (75.0%)	1.00
Duration of antibiotic therapy	13.4 $\pm$ 4.27	16.1 $\pm$ 11.3	0.26
Mortality			
Early ($\leq$ Day 7)	7 (28.0%)	5 (8.9%)	0.04
Late ($\leq$ Day 30)	9 (36.0%)	15 (26.8%)	0.57
Clinically relevant bacteremia	19 (76.0%)	51 (91.2%)	0.09

302 **Table 3. Microbiological data of the patients with *Clostridium* bacteremia.**

	<i>C. perfringens</i> (n = 25)	Other <i>Clostridium</i> (n = 56)	<i>P</i>
More than one positive blood culture with <i>Clostridium</i> spp.	2 (8.0%)	17 (30.4%)	0.056
Time to positivity of the first blood culture (hours, Mean $\pm$ SD)	16.9 $\pm$ 17.8	31.8 $\pm$ 22.4	0.002
Other bacteria in the same blood culture	10 (40.0%)	8 (14.3%)	0.022
<i>Enterobacteriales</i> in the same blood culture	6 (24.0%)	1 (1.8%)	0.003
Other anaerobes in the same blood culture	0 (0.0%)	5 (9.0%)	0.317
Other bacteria in blood cultures 7 days before or after inclusion	17 (68.0%)	36 (64.3%)	0.943
<i>Enterobacteriales</i> in the 7 days before or after inclusion	10 (40.0%)	13 (23.2%)	0.200
Other anaerobes in the 7 days before or after inclusion	5 (20.0%)	27 (48.2%)	0.031

303

Table 4. Risk factors of mortality for clinically relevant bacteremia.

	Survived (n = 48)	Died (n = 22)	<i>P</i>
Demographics			
Male gender	27 (56.2%)	12 (54.5%)	1.00
Age, Mean $\pm$ SD	60.3 $\pm$ 17.2	63.9 $\pm$ 20.3	0.47
Comorbidities			
Diabetes	9 (18.8%)	5 (22.7%)	0.75
Cancer	22 (45.8%)	11 (50.0%)	0.95
Renal insufficiency	11 (22.9%)	5 (22.7%)	1.00
Cirrhosis	2 (4.2%)	1 (4.6%)	1.00
Chemotherapy	9 (18.8%)	7 (31.8%)	0.37
Immunosuppressive drugs	5 (10.4%)	0 (0.00%)	0.17
Corticotherapy	5 (10.4%)	3 (13.6%)	0.70
Recent digestive surgery	15 (31.2%)	5 (22.7%)	0.65
Clinical presentation			
Fever	39 (84.8%)	12 (63.2%)	0.09
Hypothermia	2 (4.4%)	5 (26.3%)	0.02
Hypotension	23 (50%)	12 (63.2%)	0.49
Nosocomial	28 (58.3%)	12 (54.5%)	0.97
Inflammatory markers			
CRP, Mean $\pm$ SD	175 $\pm$ 112	162 $\pm$ 97.5	0.65
Leukocytes, Mean $\pm$ SD	12906 $\pm$ 10078	15701 $\pm$ 13081	0.38
Source of infection			0.67
Biliary tract infection	6 (13.0%)	1 (6.25%)	
Other abdominal infection	30 (65.2%)	11 (68.8%)	
Skin and soft tissue infection	6 (13.0%)	4 (25.0%)	
Neutropenic fever	3 (6.5%)	0 (0.0%)	
Urinary tract infection	1 (2.2%)	0 (0.0%)	
Adequate empiric antimicrobial therapy	41 (91.1%)	12 (60.0%)	0.005
Associated surgical treatment	31 (64.6%)	4 (18.2%)	0.001

Table 5. Multivariate logistic regression analysis of risk factors associated with 30-day mortality for clinically relevant bacteremia.

	Survived (n = 48)	Died (n = 22)	Odds Ratio	<i>P</i>
Clinical presentation				
Hypothermia	2 (4.4%)	5 (26.3%)	13.70 [2.07 - 131.79]	0.01
Adequate empiric antimicrobial therapy	41 (91.1%)	12 (60.0%)	0.17 [0.03 - 0.81]	0.03
Associated surgical treatment	31 (64.6%)	4 (18.2%)	0.23 [0.04 - 1.01]	0.06

Figure 1. Survival curves depending on adequate empiric antimicrobial therapy administration.