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

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16 **Abstract:**

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

33 **Keywords:**

34 *Clostridium* infection; Bacteremia; Pseudobacteremia; Anaerobe; Contamination;
35 Clinical relevance; Clinical significance

36 **Introduction**

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

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

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

54

55 **Material and methods**

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

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

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

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

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

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

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

88 **Results**

89 During the study period, 688 189 blood cultures were sampled: 337 579 aerobic,
90 309 299 anaerobic, and 41 311 pediatric bottles. Out of these, 68 749 were positive with
91 any bacteria (9.99%), including 111 with any *Clostridium* species (0.16% of the positive
92 blood cultures). Nineteen patients had more than one blood culture positive with the
93 same *Clostridium* species. In total, 81 patients with bacteremia due to any *Clostridium*
94 species were included: 25 corresponded to *Clostridium perfringens* and 56 to other
95 *Clostridium* species (Table 1).

96 **Demographic data and clinical presentation**

97 The mean age of patients was 61.4 years old (standard deviation 17.4), and
98 54.3% were male (Table 2). No differences were observed between bacteremia due to
99 *C. perfringens* or other *Clostridium* species concerning sex, age, and comorbidities.
100 Frequent comorbidities were cancer (45.7%), recent digestive surgery (24.7%),
101 chemotherapy (23.5%), diabetes (22.2%) and renal insufficiency (22.2%). A potential
102 source of infection was identified for 76.5% of the patients. A potential source of
103 infection was identified for 76.5% of the patients, with the most common being non-
104 biliary abdominal infection (50.6%), skin and soft tissue infection (12.3%), and biliary
105 tract infection (8.6%). Bacteremia due to *C. perfringens* was more often community-
106 acquired than for other *Clostridium* species (64.3% vs 36.0%, $P=0.03$), and the mortality
107 rate during the first week was higher for *C. perfringens* (28.0% vs 8.9%, $P=0.04$).

108 Fifty-six patients received adequate empiric antimicrobial therapy. Thirty-five
109 (62.5%) of these patients received beta-lactams associated with beta-lactamase

110 inhibitors (piperacillin-Tazobactam 53.6%, ticarcillin-clavulanic acid 5.3%, amoxicillin-
111 clavulanic acid 3.6%), 12 (21.4%) metronidazole, 9 (16.1%) carbapenems (imipenem
112 10.7%, meropenem 5.3%), and one (1.8%) vancomycin. One patient received both
113 piperacillin-tazobactam and metronidazole.

114 Seventy patients (86.4%) fulfilled defined criteria for clinically relevant bacteremia.
115 Bacteremia due to *C. perfringens* tended to be less frequently clinically relevant than
116 other *Clostridium* species, but this was not statistically significant (76% vs 91.2%,
117 $P=0.09$). Patients with clinically relevant bacteremia presented a higher CRP than
118 patients with non-clinically relevant bacteremia (171 vs 74, $P<0.001$) (Supplementary
119 Table 1). Adequate antimicrobial therapy was also more frequently prescribed in case of
120 clinically relevant bacteremia (81.5% vs 30%, $P=0.002$). The 30-day mortality rate was
121 higher in case of clinically relevant bacteremia (31.4% vs 18.2%, $P=0.49$), but this
122 difference was not statistically significant.

123 **Microbiological data**

124 Time-to-positivity of the first blood culture was shorter for patients with *C.*
125 *perfringens* bacteremia compared to other *Clostridium* species (16.9 hours vs 31.8
126 hours, $P=0.002$) (Table 3). Blood cultures positive with *C. perfringens* were more
127 frequently associated with *Enterobacteriales* growth in the same blood culture (24% vs
128 2%, $P=0.003$). Blood cultures positive with other *Clostridium* species were more
129 frequently associated with other anaerobes growth in the blood cultures sampled in the
130 7 days before or after inclusion (48.2% vs 20, $P=0.03$).

131 **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).

139 **Discussion**

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

144 Clinical relevance of bacteremia due to *Clostridium* spp. is variable in the
145 literature, with rates ranging from 56 to 89% for *Clostridium* spp. [10, 12-14], and from
146 33 to 73% when *C. perfringens* is studied specifically [3, 15]. In a previous study, *C.*
147 *perfringens* bacteremia sometimes presented no evident relation to the underlying
148 illness and could be observed in meningitis due to *Neisseria meningitidis*, or in
149 pulmonary tuberculosis [16]. In those cases, blood culture contamination may be
150 considered. Nevertheless, our study shows a high frequency of clinically relevant
151 bacteremia, both for *C. perfringens* (76.0%) and other *Clostridium* species (91.2%),
152 supporting a causative role in infection.

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

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

163 The 30-day mortality rate was 31.4% in our cohort, for clinically relevant
164 bacteremia. Half of these patients (n=11/22) died during the first week. In the literature,
165 the 30-day mortality due to *Clostridium* spp. bacteremia generally ranges from 27% to
166 30% [10, 13, 21], but can attain 43% in cancer patients [22]. In a study including 73
167 patients with clinically relevant bacteremia, mortality was higher for *Clostridium* spp. than
168 for other anaerobes [23]. Risk factors for mortality related to *Clostridium* spp. bacteremia
169 have been identified, such as septic shock at initial presentation [15, 24], or nosocomial
170 infection [15]. In our study, hypothermia seemed to be an interesting warning sign to
171 consider. However, given the small number of patients with hypothermia (n=7), further
172 studies are needed to assess this association. Hypothermia was previously associated
173 with increased mortality in septic patients [25], but not specifically with bacteremia due
174 to *Clostridium* species.

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

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

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

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

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

214 **Conclusion**

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

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299

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 ± SD	65.4 ± 13.2	59.7 ± 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 ± SD	136 ± 94.8	167 ± 111	0.22
Leukocytes, Mean ± SD	16776 ± 12210	11807 ± 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 ± 4.27	16.1 ± 11.3	0.26
Mortality			
Early (<= Day 7)	7 (28.0%)	5 (8.9%)	0.04
Late (<= 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 ± SD)	16.9 ± 17.8	31.8 ± 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

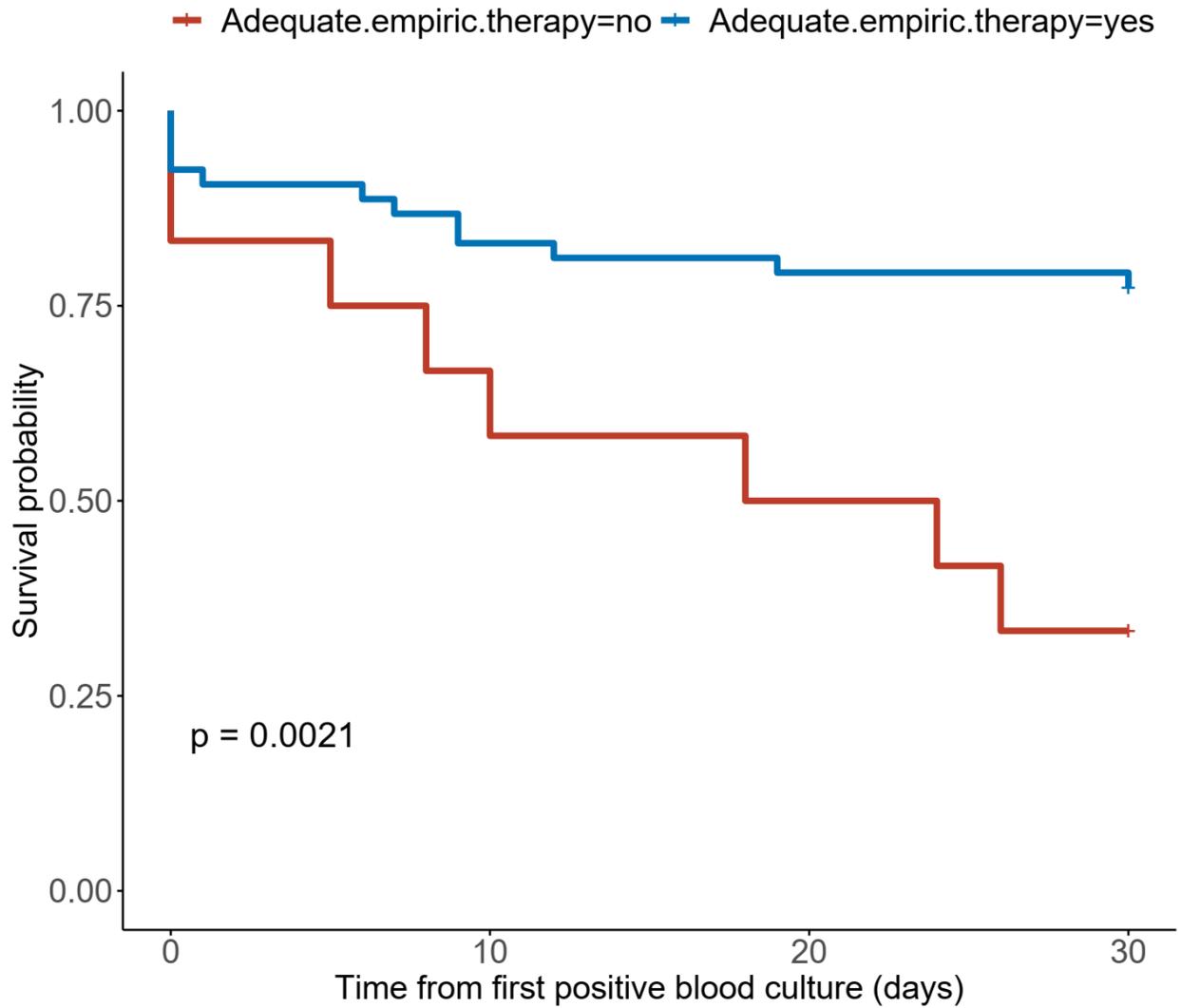
Table 4. Risk factors of mortality for clinically relevant bacteremia.

	Survived (n = 48)	Died (n = 22)	<i>P</i>
Demographics			
Male gender	27 (56.2%)	12 (54.5%)	1.00
Age, Mean ± SD	60.3 ± 17.2	63.9 ± 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 ± SD	175 ± 112	162 ± 97.5	0.65
Leukocytes, Mean ± SD	12906 ± 10078	15701 ± 13081	0.38
Source of infection			
Biliary tract infection	6 (13.0%)	1 (6.25%)	0.67
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

306 **Table 5. Multivariate logistic regression analysis of risk factors associated with**
 307 **30-day mortality for clinically relevant bacteremia.**
 308

	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

309



310

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