Clinical characteristics and outcomes of clostridial bacteraemia in cancer patients

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Abstract

Clostridial bacteraemia is usually associated with substantial morbidity and mortality in cancer patients. However, clinical characteristics and risk factors for early mortality in this population are poorly described. We retrospectively studied cancer patients with clostridial bacteraemia treated between January 1996 and December 2011. We compared clinical manifestations between patients with solid tumour and haematological malignancy and assessed risk factors for 7-day mortality. In all, 164 cancer patients developed clostridial bacteraemia during the study period—85 (52%) with solid tumour and 79 (48%) with haematological malignancy. Common isolates were *Clostridium perfringens* (27%), *Clostridium septicum* (19%) and *Clostridium tertium* (14%). Solid tumour malignancy patients were more likely to have a focal gastrointestinal source for bacteraemia and were more likely to undergo subsequent surgery. Haematological malignancy patients were more often neutropenic and more often had no focal source of bacteraemia. Seven-day mortality was 20% (33/164) and did not vary based on malignancy type. The adjusted odds ratio of dying within 7 days of clostridial bacteraemia among patients with hypotension (40/164) was 7.2 (95% CI, 2.9–18.1) and in patients with acute haemolysis (7/164) was 10.5 (95% CI, 1.3–85.2). Clostridial species also impacted mortality; no patient with *C. tertium* bacteraemia died within 7 days. In conclusion, clinical manifestations of clostridial bacteraemia differed between patients with solid tumour and haematological malignancy, but 7-day mortality was similar. Patients with hypotension and haemolysis at time of bacteraemia were at increased risk for early death.

Keywords: Cancer, Clostridia, *Clostridium septicum*, *Clostridium tertium*, neutropenia
Original Submission: 30 July 2013; **Revised Submission:** 8 November 2013; **Accepted:** 16 November 2013
Editor: M. Paul
Article published online: 25 November 2013
Clin Microbiol Infect 2014; **20:** 752–757
10.1111/1469-0691.12462

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Presented in abstract form at the 49th annual meeting of the Infectious Diseases Society of America, Boston, MA, 22 October 2011.

Introduction

Clostridial bacteraemia is associated with fulminant clinical illness and high mortality attributed to bacterial toxin production [1,2]. However, recent studies have demonstrated that clostridial bacteraemia infrequently causes a histotoxic syndrome, but is often a marker of significant gastrointestinal disease and underlying immunocompromise [3,4]. Despite the infrequency with which clostridial bacteraemia is associated with fulminant toxin-mediated illness, associated mortality ranges from 20% to 48% in adults and may be higher in adults with malignancy [3–6].

Initial observations linking clostridial bacteraemia and malignancy date back at least 50 years [1,2]. More recently, observational studies have supported this association [7–13]; a recent population-based study demonstrated that risk for clostridial bacteraemia is significantly higher in patients with cancer [5]. Among cancer patients, clostridial bacteraemia is typically seen in two distinct groups: patients with solid tumour malignancy and patients with haematological malignancy (usually acute leukaemia) [1,2,4,14].

Few studies have systematically assessed the clinical characteristics of clostridial bacteraemia in cancer patients [1,2,14].

The most recent of these, now over 20 years old, reports high overall associated mortality (42%); *Clostridia* were frequently isolated in the context of polymicrobial bacteraemia, which was associated with further increased risk of death [14].

Because management of solid tumour and haematological malignancies has changed in the last 20 years, we undertook this study to characterize clinical manifestations of clostridial bacteraemia in a recent cohort of cancer patients. Study goals were to delineate differences in clinical characteristics and outcomes of patients with solid tumour malignancy and haematological malignancy with clostridial bacteraemia and further to determine the risk factors and mortality associated with clostridial bacteraemia in cancer patients.

Methods

Patients

All adults with malignancy who developed clostridial bacteraemia at Dana-Farber Cancer Institute/Brigham and Women's Hospital (DFCI/BWH) between 1 January 1996 and 31 December 2011 were included in this analysis. BWH is a 793-bed tertiary care medical centre with approximately 45 000 admissions per year. DFCI, an affiliated facility dedicated to cancer care, has over 320 000 outpatient visits per year. Inpatient care for DFCI patients occurs at BWH. The Office for Human Research Studies at DFCI/BWH approved this study.

Patients were identified by searching the DFCI/BWH microbiology database for all blood cultures that grew clostridial species using WHONET software (http://www.who.int/drugresistance/whonetsoftware/en/). Clostridial bacteraemia was defined as growth of any clostridial species in one or more blood culture bottles. Blood cultures were drawn for assessment of clinical signs or symptoms of infection. Antibiotic susceptibility of anaerobic isolates was not routinely tested.

Medical records were reviewed for covariates of interest at bacteraemia onset including age, gender, malignancy, infection symptoms (nausea, vomiting, diarrhoea and abdominal pain), hypotension requiring use of vasopressors, source of bacteraemia if identified, surgical management of infection, absolute neutrophil count, acute haemolysis, antimicrobials being given before bacteraemia and in response to bacteraemia, clostridial species isolated, presence and species of additional isolates for polymicrobial infections and 7-day mortality. Neutropenia was defined as absolute neutrophil count <500 cells/mm^3. Polymicrobial bacteraemia was defined as growth of more than one bacterial species (including if two different clostridial species grew) in one or more blood culture bottles drawn on the same day as the *Clostridia* spp. grew. Acute haemolysis was defined as a decline in haemoglobin of >2 g/dL over 24 h or less in patients without evidence of bleeding and in conjunction with gross haemolysis seen in blood specimens and/or new indirect hyperbilirubinaemia of 8 mg/dL or higher.

Clostridia

All blood culture samples were incubated and monitored using the bioMérieux BacT/ALERT system (bioMérieux Inc., Durham, NC, USA). Anaerobic gram-positive bacteria that grew from blood cultures were identified using the RapID ANA II panel (Thermo Scientific, Atlanta, GA, USA).

Statistical analysis

Baseline and infection-related characteristics were initially compared using two-sided Fisher's exact test or Wilcoxon rank sum test where appropriate. Possible predictors of 7-day mortality identified on initial analysis were evaluated in a univariate logistic regression analysis. Only covariates closely associated with 7-day mortality ($p \leq 0.05$) were included in a multivariate logistic regression model. Statistical analyses were performed using SAS version 9.2 (SAS institute, Cary, NC, USA).

Results

Cohort characteristics and microbiology

During the 16-year study period 164 patients with malignancy developed clostridial bacteraemia including 85 (52%) with solid tumour and 79 (48%) with haematological malignancy. Overall characteristics of the cohort are shown in Table 1. There were similar numbers of men and women. A substantial number of patients were neutropenic (42%) and nearly a quarter had hypotension requiring support with vasopressors when bacteraemia developed (24%). Seven-day mortality was 20% (33/164). Six patients (4%) presented with clostridial bacteraemia leading to diagnosis of unrecognized cancer, including four with solid tumour and two with haematological malignancy. The rest (158/164, 96%) developed bacteraemia after cancer treatment was started.

Clostridium perfringens accounted for 44 of 164 episodes of clostridial bacteraemia (27%) and was the most common isolate, followed by *Clostridium septicum*, which caused 31 episodes (19%) and *Clostridium tertium*, which caused 23 episodes (14%). Many less common clostridial species caused a substantial proportion of episodes of bacteraemia, as presented in Table 1. The number of episodes of clostridial bacteraemia per year in DFCI/BWH patients varied over time. The median number of episodes was 2.9 per 1000 oncology

TABLE 1. Baseline and infection related characteristics compared by type of malignancy

Characteristic	Solid tumour malignancy *n* = 85	Haematological malignancy *n* = 79	Total *n* = 164	p value
Male gender	34 (40)	47 (59)	81 (49)	0.02
Median age, years (range)	57 (18–86)	56 (25–87)	57 (18–87)	0.61
Neutropenic[a]	8 (9)	61 (77)	69 (42)	<0.0001
Diarrhoea	11 (13)	31 (39)	42 (26)	0.0001
Nausea and vomiting	37 (44)	19 (24)	56 (34)	0.01
Abdominal pain	54 (64)	23 (29)	77 (47)	<0.0001
Hypotension[b]	19 (22)	21 (27)	40 (24)	0.59
Haemolysis	2 (2)	5 (6)	7 (4)	0.26
Source of bacteraemia				
No focal source	13 (15)	44 (56)	57 (35)	<0.0001
Focal gastrointestinal source[c]	61 (72)	29 (37)	90 (55)	
Other source[d]	11 (13)	6 (8)	17 (10)	
Skin and soft tissue involvement	2 (2)	4 (5)	6 (4)	0.43
Clostridium species				
C. perfringens	25 (29)	19 (24)	44 (27)	<0.0001
C. septicum	14 (16)	17 (22)	31 (19)	
C. tertium	0 (0)	23 (29)	23 (14)	
C. ramosum	9 (11)	3 (4)	12 (7)	
C. clostridioforme	7 (8)	3 (4)	10 (6)	
C. innocuum	4 (5)	4 (5)	8 (5)	
C. paraputrificum	6 (7)	1 (1)	7 (4)	
C. cadaveris	2 (2)	1 (1)	3 (2)	
C. subterminale	3 (4)	1 (1)	4 (2)	
C. hastiforme	3 (4)	0 (0)	3 (2)	
Others[e]	12 (14)	7 (9)	19 (12)	
Polymicrobial bacteraemia	35 (41)	26 (33)	61 (37)	0.33
Surgical intervention	21 (25)	7 (9)	28 (17)	0.007
Antibiotics before bacteraemia[f]	10 (12)	43 (54)	53 (32)	<0.0001
7-day mortality	19 (22)	14 (18)	33 (20)	0.56

[a]Defined as an absolute neutrophil count <500 cells/mm^3 at the time of bacteraemia.
[b]Requiring the use of supportive vasopressors.
[c]Includes: enteric perforation, peritoneal or liver abscess, solid tumour-enteric fistula, colitis or typhlitis, biliary obstruction, or incarcerated hernia.
[d]Includes: urinary obstruction, urinary tract infection, bladder perforation, graft-versus-host disease, genital herpes simplex virus, anal erosions, gluteus medius haematoma, severe skin burn.
[e]*C. acetobutylicum* (2), *C. bifermentans* (3), *C. butyricum* (1), *C. novyi* (1), *C. sartagoforme* (1), *C. sporogenes* (1), *C. sordelli* (1), unspecified clostridial species (9).
[f]Defined as patients on systemic antibiotics for other indications up to 24 h before the development of bacteraemia.

hospital admissions per year between 1998 and 2011 (range 1.8–5.0).

Polymicrobial bacteraemia occurred frequently (61/164, 37%). Most patients with polymicrobial bacteraemia had one co-pathogen identified (41/61, 67%) but a third had two or more co-pathogens identified (20/61, 33%). Common co-pathogens were coagulase-negative staphylococci (17 episodes), *Bacteroides* spp. (14 episodes), *Enterococcus* spp. (nine episodes), *Klebsiella* spp. (eight episodes) and *Escherichia coli* (seven episodes). Among 103 episodes of monomicrobial bacteraemia, *Clostridia* spp. was isolated in multiple blood culture bottles over 48 h in 42 episodes and from one bottle in 61 episodes.

Clinical characteristics by type of malignancy

There were several differences in baseline, clinical and microbiological characteristics of patients with solid tumour versus haematological malignancy (Table 1). More patients with haematological malignancy were male and more were neutropenic at bacteraemia onset. Patients with solid tumour malignancy more often had a focal gastrointestinal source of bacteraemia and more often underwent surgical intervention after clostridial bacteraemia developed. Patients with haematological malignancy were more likely to be on antibiotics (typically for empiric treatment of fever and neutropenia) when clostridial bacteraemia developed.

Clostridial species causing bacteraemia also differed between the two groups. Specifically, *C. perfringens* was the most common cause of bacteraemia among patients with solid tumour malignancy (25/85, 29%) and a frequent cause of bacteraemia among haematological malignancy patients (19/79, 24%). In contrast, *C. tertium* was the most common cause of bacteraemia in haematological malignancy patients (23/79, 29%) and caused no infections in patients with solid tumours. *Clostridium septicum* was also more common in haematological malignancy patients (17/79, 22%) than in solid tumour patients (14/85, 16%).

There were no differences in age, hypotension requiring vasopressors, haemolysis (only seen in 4% of the cohort), polymicrobial bacteraemia, or 7-day mortality based on malignancy type.

Risk factors for 7-day mortality

Clinical factors associated with 7-day mortality were examined (Table 2). Patients with hypotension requiring vasopressors at bacteraemia onset were more likely to die within 7 days than those without hypotension (21/40 vs 12/124, p <0.0001). Similarly, patients with acute haemolysis when clostridial

TABLE 2. Baseline and infection-related characteristics compared by 7-day mortality

Characteristic	Died ≤7 days *n* = 33	Survived >7 days *n* = 131	Total *n* = 164	p value
Male gender	14 (42)	67 (51)	81 (49)	0.44
Median age, years (range)	62 (20–83)	56 (18–87)	57 (18–87)	0.29
Haematological malignancy	14 (42)	65 (50)	79 (48)	0.56
Acute leukaemia or myelodysplasia	11 (33)	46 (35)	57 (35)	
Chronic leukaemia	1 (3)	6 (5)	7 (4)	
Lymphoma and myeloma	2 (6)	13 (10)	15 (9)	
Solid tumour malignancy	19 (58)	66 (50)	85 (52)	
Colorectal cancer	5 (15)	13 (10)	18 (11)	
Gynaecological cancer[a]	3 (9)	16 (12)	19 (12)	
Other gastrointestinal cancer[b]	4 (12)	13 (10)	17 (10)	
Sarcoma	3 (9)	10 (8)	13 (8)	
Male genitourinary cancer[c]	0 (0)	7 (5)	7 (4)	
Other cancer type[d]	4 (12)	7 (5)	11 (7)	
Neutropenic	13 (39)	56 (43)	69 (42)	0.84
Diarrhoea	9 (27)	33 (25)	42 (26)	0.83
Nausea and vomiting	17 (52)	39 (30)	56 (34)	0.02
Abdominal pain	20 (56)	57 (44)	77 (47)	0.08
Hypotension	21 (64)	19 (15)	40 (24)	<0.0001
Haemolysis	5 (15)	2 (2)	7 (4)	0.004
Source of bacteraemia				
No focal source	8 (24)	49 (37)	57 (35)	0.07
Focal gastrointestinal source	24 (73)	66 (50)	90 (55)	
Other source[e]	1 (2)	16 (12)	17 (10)	
Skin and soft tissue involvement	2 (6)	4 (3)	6 (4)	0.35
Clostridium species				
C. perfringens	9 (27)	35 (27)	44 (27)	0.10
C. septicum	8 (24)	23 (16)	31 (19)	
C. tertium	0 (0)	23 (18)	23 (14)	
C. ramosum	4 (12)	8 (6)	12 (7)	
C. clostridioforme	3 (9)	7 (5)	10 (6)	
C. innocuum	3 (9)	5 (4)	8 (5)	
C. paraputrificum	2 (6)	5 (4)	7 (4)	
C. cadaveris	1 (3)	2 (2)	3 (2)	
C. subterminale	0 (0)	4 (3)	4 (3)	
C. hastiforme	0 (0)	3 (2)	3 (2)	
Others[f]	3 (9)	16 (12)	19 (12)	
Polymicrobial bacteraemia	17 (48)	44 (34)	61 (37)	0.07
Surgical intervention	4 (12)	24 (18)	28 (17)	0.60
Antibiotics before bacteraemia[g]	10 (30)	43 (33)	53 (32)	0.84
Penicillin or clindamycin within 48 h[h]	11 (33)	34 (26)	45 (27)	0.39
Active antibiotic within 48 h[i]	31 (94)	108 (82)	139 (85)	0.17

[a]Includes ovarian, cervical and endometrial cancer.
[b]Includes pancreatic cancer, cholangiocarcinoma.
[c]Includes testicular and prostate cancer.
[d]Includes laryngeal cancer (1), breast cancer (3), lung cancer (2), bladder cancer (1), renal cell carcinoma (2), Merkel cell carcinoma (1), melanoma (1).
[e]Includes: urinary obstruction, urinary tract infection, bladder perforation, graft-versus-host disease, genital herpes simplex virus, anal erosions, gluteus medius haematoma, severe skin burn.
[f]*C. acetobutylicum* (2), *C. bifermentans* (3), *C. butyricum* (1), *C. novyi* (1), *C. sartagoforme* (1), *C. sporogenes* (1), *C. sordelli* (1), unspecified clostridial species (9).
[g]Defined as patients on systemic antibiotics for other indications up to 24 h before the development of bacteraemia.
[h]Treatment given within 48 h of bacteraemia onset; penicillins included penicillin G, mezlocillin, ampicillin, or piperacillin.
[i]Treatment one or more of the following agents within 48 h of bacteraemia onset: penicillin G, mezlocillin, ampicillin, piperacillin, clindamycin, metronidazole, vancomycin and carbapenems.

bacteraemia was diagnosed were more likely to die within 7 days than those without haemolysis (5/7 vs 28/157, p 0.004). Symptoms at onset of bacteraemia were also associated with 7-day mortality. Specifically 7-day mortality was higher among patients with nausea and vomiting than those without these symptoms (17/56 vs 16/108, p 0.02) and there was a trend towards increased mortality among those who presented with abdominal pain compared with those who did not.

The clostridial species causing the bacteraemia was also associated with 7-day mortality (Table 2). Specifically, no patients with *C. tertium* bacteraemia died within 7 days compared with those who were bacteraemic with other *Clostridia* (0/23 vs 33/141, p 0.005). The proportion of patients with *C. septicum* and *C. ramosum* bacteraemia was higher among those who died within 7 days than those who did not (24% vs 16%; 12% vs 6%, respectively). There was a trend towards increased 7-day mortality in patients with polymicrobial versus monomicrobial bacteraemia.

Logistic regression modelling was performed to assess risk factors for 7-day mortality (Table 3). Clostridial species were not included in the regression because no patients with *C. tertium* bacteraemia died within 7 days, but *C. septicum* (which appeared to be associated with increased mortality) was included. In univariate analysis nausea and vomiting, hypotension, acute haemolysis and focal gastrointestinal source of bacteraemia were associated with increased 7-day mortality. In multivariate analysis only hypotension and acute haemolysis were independently associated with 7-day mortality. The odds ratio of dying within 7 days of clostridial bacteraemia for patients with hypotension was 7.23 (95% CI 2.90–18.06) and for patients with acute haemolysis was 10.53 (95% CI 1.30–85.17).

TABLE 3. Logistic regression of 7-day mortality

Characteristic	Univariate odds ratio (95% CI)	p value	Multivariate odds ratio (95% CI)	p value
Nausea and vomiting	2.51 (1.15–5.46)	0.02	2.14 (0.85–5.38)	0.10
Abdominal pain	2.00 (0.92–4.35)	0.08	–	–
Hypotension	10.32 (4.37–24.37)	<0.0001	7.23 (2.90–18.06)	<0.0001
Haemolysis	11.52 (2.13–62.41)	0.005	10.53 (1.30–85.17)	<0.0001
Focal gastrointestinal source of bacteraemia	2.63 (1.14–6.08)	0.02	2.01 (0.70–5.78)	0.19
Clostridium septicum	1.50 (0.60–3.75)	0.38	–	–
Polymicrobial bacteraemia	2.10 (0.97–4.55)	0.06	–	–

Antimicrobial treatment

Within 48 h of clostridial bacteraemia 45 of 164 patients (27%) were treated with a penicillin (penicillin G, mezlocillin, ampicillin or piperacillin) or clindamycin and 139 (85%) were treated with at least one antimicrobial agent with *in vitro* activity against most *Clostridia* including penicillins, clindamycin, metronidazole, vancomycin or carbapenems [3,4,15–17]. Among the 25 patients who were not treated with an active antibiotic within 48 h, eight were treated with one or more antibiotics that are not typically active *in vitro* against *Clostridia* (ceftazidime, gentamicin, levofloxacin, ciprofloxacin) during the first 48 h, six were not treated with antibiotics (two of whom chose comfort-focused medical care only), and the remainder started active antibiotics more than 48 h after bacteraemia had developed. There was no association between 7-day mortality and treatment with penicillin or clindamycin within 48 h nor was there an association between 7-day mortality and treatment with any antimicrobial agents with *in vitro* activity against *Clostridia* (Table 2).

The relationship between 7-day mortality and antibiotic treatment was also assessed for episodes of bacteraemia caused by the two most common isolates, *C. perfringens* and *C. septicum*. Together, these clostridial species caused 46% (75/164) of bacteraemias in the cohort. The majority (69/75, 92%) were treated with two or more antibiotics in the first 48 h, including at least one agent active *in vitro* against *Clostridia* (as above). As with the entire cohort, there was no association between 7-day mortality and treatment with penicillins or clindamycin within 48 h, nor was there an association between 7-day mortality and treatment with at least one of the active agents (as above) within 48 h of bacteraemia.

Discussion

In this large cohort of cancer patients with clostridial bacteraemia we found several important differences in clinical characteristics of patients with haematological and solid tumour malignancies. Solid tumour patients were more likely to have a focal gastrointestinal abnormality as the source of bacteraemia and more often underwent a surgical procedure to correct the abnormality. In contrast, patients with haematological malignancy were more often neutropenic and more likely to be on antibiotics at bacteraemia onset, usually for empiric treatment of fever and neutropenia. There was also a difference in clostridial species that caused bacteraemia in these groups. While *C. perfrigens*, *C. septicum* and *C. tertium* accounted for 75% of isolates in patients with haematological malignancies, there was a greater diversity of clostridial species seen among solid tumour malignancy patients.

Despite these differences, there was no difference in the 7-day mortality between patients with haematological and solid tumour malignancies. Seven-day mortality in the entire cohort, 20%, is lower than the greater than 50% mortality reported in cancer patients in other studies [6,14]. Similar to an older study of clostridial bacteraemia in cancer patients, hypotension was an independent risk factor for death within 7 days [14].

Though it seems likely that initiation of appropriate antibiotics in a timely fashion impacts early mortality from clostridial bacteraemia (at least one study has suggested this [6]), no particular antibiotic regimen in the first 48 h of bacteraemia conferred a 7-day survival benefit in the entire cohort or when assessed among *C. perfringens* and *C. septicum* specifically. However, this conclusion is limited by the small number of patients in this cohort who did not receive an active antibiotic during the first 48 h after bacteraemia had developed (15%). Most studies assessing the antibiotic susceptibility of *Clostridia* have shown that most species, except *C. tertium*, are susceptible to penicillin, metronidazole, carbapenems and vancomycin [3–5,15–17]. This large number of active antibiotics is probably the reason that the large majority of patient in this cohort were treated empirically with an active antibiotic within 48 h of bacteraemia. An additional issue complicating interpretation of antibiotic impact on 7-day mortality in this study is the frequency of polymicrobial bacteraemia with other enteric pathogens that require specific antimicrobial therapy and confer their own associated risk of death.

Clostridium septicum was the second most common cause of bacteraemia in this cohort after *C. perfringens*, as has been observed in other cohorts [5,14]. Several previous publications

have observed an association between this pathogen and severe clinical illness and death in cancer patients [8–10]. The virulence of *C. septicum* is typically attributed to α-toxin production, which can cause rapid tissue invasion and haemolysin production, which can infrequently cause intravascular haemolysis [8,9].

In contrast, *C. tertium* bacteraemia was seen exclusively in patients with haematological malignancy in this cohort and was the most common cause of clostridial bacteraemia in this patient group. No patients with *C. tertium* bacteraemia died within 7 days. Unlike other clostridial species, *C. tertium* is aerotolerant and does not produce toxins [7,11,13]. Clinically it has been associated with mild clinical illness in patients with chemotherapy-induced neutropenia and related intestinal mucosal injury, as was seen in this cohort [7,11–13]. All patients in this cohort with *C. tertium* bacteraemia had underlying acute leukaemia and all were on a third- or fourth-generation cephalosporin for empirical treatment of fever and neutropenia when bacteraemia developed. Other studies have suggested that broad-spectrum cephalosporins, ceftazidime in particular, may select for this organism, which can be resistant to some β-lactams, metronidazole and clindamycin [7,11].

Notably, older studies considered isolated clostridial bacteraemia in the absence of a focal infection to be a contaminant [4]. A potential limitation of this study is that some episodes of clostridial bacteraemia included could have been due to blood culture contamination. However, this is unlikely for several reasons. First, all blood cultures were drawn for symptoms of infection. Second over 40% of patients in this cohort were neutropenic. Clostridial bacteraemia with lack of focal site of infection in the context of fever and neutropenia suggests pathogenic translocation of bacteria from the gastrointestinal tract, not contamination, similar to enteric gram-negative bacteria in this setting.

In conclusion, in this large cohort of cancer patients with clostridial bacteraemia we found several important differences in the clinical characteristics of patients with haematological malignancy compared with those with solid tumour malignancy, but mortality was similar. Hypotension and haemolysis, both of which have historically been associated with poor outcomes, remain independent risk factors for early mortality in this population. *Clostridium tertium* was exclusively seen in patients with haematological malignancy and was associated with no mortality.

Transparency Declaration

All authors have no conflicts to report.

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