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.

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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