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Epidemiology of *Clostridium* species bacteremia in Calgary, Canada, 2000–2006

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Summary *Objectives:* To define the incidence, risk factors for acquisition, and outcomes associated with clostridial bacteremia in a large Canadian health region.
Methods: Retrospective population-based surveillance for clostridial bacteremia was conducted among all residents of the Calgary Health Region (population 1.2 million) during 2000–2006.
Results: One hundred and thirty-eight residents had incident *Clostridium* species bacteremia (1.8 per 100,000/year); 45 (33%) were nosocomial, 55 (40%) were healthcare-associated community onset, and 38 (28%) were community acquired. Older age and a number of underlying conditions were risk factors for acquiring *Clostridium* species bacteremia most importantly hemodialysis [relative risk (RR) 212.3; 95% confidence interval (CI) 106.5–385.5], malignancy (RR 40.2; 95% CI 27.6–58.1), and Crohn's disease (RR 11.2; 95% CI 3.0–29.4). *Clostridium perfringens* was most commonly identified with 58 (42%) isolates followed by *Clostridium septicum* (19; 14%), *Clostridium ramosum* (13; 9%), *Clostridium clostridiiforme* (8; 6%), and *Clostridium difficile* (7; 5%). Reduced susceptibility to penicillin occurred in 14/135 (10%), to metronidazole in 2/135 (1%), and to clindamycin in 36/135 (27%) isolates. The median length of stay was 12.7 days and 39/130 (30%) patients died in hospital for mortality rate of 0.5 per 100,000/year.
Conclusions: Clostridium species bacteremia is associated with a significant burden of illness and hemodialysis and cancer patients are at highest risk.

Introduction

Clostridium species are important agents of anaerobic infections in humans.[1] While they may be associated with

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a wide range of clinical disease, the histocytotoxic infections including gas gangrene, fulminant intravascular hemolysis, botulism and tetanus are most notable.[2] The clostridial species are the second most common causes of anaerobic bacteremia, with *Clostridium perfringens* the most frequently isolated species.[1,3] A number of series have identified a high rate of malignancies, gastrointestinal disorders, and other chronic illnesses associated with these infections.[4–8] In addition, different *Clostridium* species bloodstream infections have been associated with certain clinical syndromes including *C. perfringens* with fulminant intravascular hemolysis,[9] *Clostridium septicum* and *Clostridium tertium* with leukemia and malignancies,[10] *Clostridium sordellii* with uterine and postpartum infections,[11] and *Clostridium novyi* with injection drug use.[12]

Several reviews on clostridial bacteremias have been previously reported.[3,5–8,13–20] However, these studies have focused primarily on either a single clostridial species or have been hospital-based investigations. The incidence and outcome of all clostridial bacteremias have not been previously defined in a non-selected population at large. Furthermore, although a number of factors have been associated with acquiring these infections, no previous study has been adequately designed to quantify the actual magnitude of risk. Our objective was to conduct population-based surveillance in a large Canadian health region during 2000–2006 in order to define the incidence, risk factors, and outcomes associated with *Clostridium* species bacteremia.

Patients and methods

Study population

The Calgary Health Region (CHR) administers virtually all medical and surgical care to the residents of the cities of Calgary and Airdrie and a large surrounding area (population 1.2 million) in the Province of Alberta, Canada.[21] Only patients requiring acute liver, heart, or lung transplantation surgery are routinely referred elsewhere. All persons who resided in the CHR and who developed incident (first isolate per species per year) *Clostridium* species bacteremia during January 1, 2000 and December 31, 2006 were included in the study. The Conjoint Health Research Ethics Board at the University of Calgary and CHR approved this study and waived the requirement for individual written informed consent.

Study protocol

An active, population-based surveillance cohort design was utilized. Surveillance for *Clostridium* species bacteremia was conducted by Calgary Laboratory Services, a regional laboratory system that receives approximately 99% of all blood samples submitted for culture from hospitals, nursing homes, and clinics in the CHR. Further clinical and outcome detail were obtained on all patients admitted to any of the 4 major acute care hospitals (representing $\geq$95% CHR admissions) using data available from the regional corporate data warehouse.

Definitions

Clostridium species bacteremia was defined by their isolation from one or more sets of aseptically obtained blood culture bottles. All blood cultures during the study period were performed using the BacT/ALERT system (bioMérieux Canada) and incubated for 4 days. An anaerobic bottle was collected routinely in all sets collected. Anaerobic Gram-positive isolates were speciated using standard methods.[22] Organisms that could not be speciated by standard methods were identified by bi-directional 16S RNA sequencing.[23] Antimicrobial susceptibility testing was performed using microbroth dilution methodology.[24]

Residency status was established using the 2003 boundaries of the CHR.[21] Incident cases were defined by the new first isolation of *Clostridium* species; repeated isolation of the same species within 365 days after the first was deemed to represent the same incident infection. Nosocomial bacteremias were those with first culture positive $\geq$48 h after hospital admission or within 48 h of discharge. Community onset infections were those where first positive culture was obtained $<$48 h of admission or $>$48 h after discharge from hospital. A healthcare-associated community onset *Clostridium species* bacteremia also had at least one of: (1) discharge from the emergency room, adult Home Parenteral Therapy Program (HPTP) clinic, or other specialized hospital-based clinic within the prior 2–30 days before bacteremia[25]; (2) admitted to CHR acute care hospital for 2 or more days within the prior 90 days before bacteremia; (3) sample submitted from a resident of a nursing home or long-term care facility; or (4) hemodialysis patient. Data on HPTP clinics assessment and dialysis were not available for children. In these and the rare other community onset cases where data were unavailable they were assumed to be absent. Community acquired infections were those community onset bacteremias that were not healthcare-associated.

Statistical analysis

Analysis was performed using Stata version 9.0 (Stata Corp, College Station, TX). Non-normally distributed variables were reported as medians with inter-quartile ranges (IQR) and compared using the rank sum test for pairs or median test for multiple groups. Differences in proportions among categorical data were assessed using Fisher's exact test for pair-wise comparisons and the Chi-square test for multiple groups. The incidence of bacteremic *Clostridium* species infection was calculated by dividing the number of incident cases by the regional population.[21] Population-based risk factors for developing *Clostridium* species bacteremia were quantified by dividing the incidence of these infections among those with a given factor by those without the factor. Regional demographic data were used to determine the population at risk for assessment of age and gender. For other potential risk factors, the population at risk was ascertained or estimated using local patient registry data,[26] regional or Canadian survey data,[21,27] or published North American epidemiology studies.[28] Risks were expressed as incidence rate ratios (RR) and reported with 95% confidence intervals. For all statistical comparisons