Original Article

Epidemiology and risk factors for mortality in bloodstream infection by CP-Kp, ESBL-E, Candida and CDI: A single center retrospective study

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A R T I C L E   I N F O

A B S T R A C T

Background: The incidence of *C. difficile* infection (CDI) and of bloodstream infection (BSI) caused by *Candida* spp., ESBL-E-producing Enterobacteriaceae (ESBL-E) and carbapenemase-producing *K. pneumoniae* (CP-Kp) is associated with high mortality.
Methods: We conducted a single centre retrospective study on patients admitted to Molinette Hospital, Turin, Italy, from January 2013 to April 2015 with CDI or BSI caused by Candida, ESBL-E or CP-Kp. For each patient demographic, clinical and microbiological data were collected. Aims of this study were to describe epidemiology and to evaluate risk factors for in-hospital mortality in this group of patients.
Results: Seven hundred-eighty six cases were analyzed: 398 CDI, 137 candidemia, 125 ESBL-E BSI and 126 CP-Kp BSI. CDI, candidemia and ESBL-E BSI were more frequently reported in internal medicine wards (IMW), whilst CP-Kp were more described in intensive care unit (ICU). Sixty-six percent of patients had a previous hospitalization and the majority of patients had several medical comorbidities. In-hospital death occurred in 23.4%. Independent risk factors for mortality were antibiotic therapy before hospital admission, cardiovascular diseases, neutropenia, urinary catheter, total parenteral nutrition, SIRS and higher creatinine levels at diagnosis. Previous abdominal surgery, inflammatory bowel disease, higher serum albumin levels at the admission and fever at diagnosis were significantly associated with survival.
Conclusion: Our data showed that CDI, ESBL-E BSI and candidemia are more frequent in frail patients, admitted to IMW, with chronic comorbidities and broad exposure to antibiotic therapies, with the exception for CP-Kp BSI, still more common in the ICU.

1. Introduction

The alterations of gut microbiome composition can occur for several factors, including dietary modifications, social behavior, environmental changes (i.e., hospitalization) and alteration in host immunity [1–4]. The causal role of dysbiosis is fully described for *C. difficile* infections (CDI), in which the altered microbiome creates a conducive environment for *C. difficile* growth. *C. difficile* pathogenesis through disruption of epithelial barrier function and alterations of inflammatory responses likely contributes to the dysbiotic state [5]. Dysbiosis may also favor colonization of multidrug resistant organisms such as carbapenemase producing *K. pneumoniae* (CP-Kp) or Enterobacteriaceae producing extended-spectrum beta-lactamase (ESBL-E) or an excessive intestinal

growth of *Candida* spp., favoring bloodstream infections (BSI) [6–11].

The incidence of candidemia has increased over the past two decades [12], as well as CDI which has recently become the most common health-care associated infection in community hospitals in the southeastern United States [13]. Over the last decade, multidrug resistant Gram-negative bacteria, including ESBL-E and CP-Kp, have been implicated in severe hospital acquired infections (HAIs) and their occurrence has increased steadily [14]. To highlight the increasing importance of these pathogens in the epidemiology scenario we proposed a new acronym "CCC" (CDI, CR-Kp and Candidemia) [15]. Furthermore, the importance of microbiome in the pathogenesis of these infections has important implications in therapeutic opportunities, and to highlight the common role of gastrointestinal dysbiosis in CDI and BSI

caused by Candida, CP-Kp and ESBL-E we suggested the term "enteropathogenetic infectious syndromes" [16].

Aims of this study were to describe the epidemiology and to evaluate and compare risk factors for and in-hospital mortality in patients with CDI, candidemia and BSI by CP-Kp or ESBL-E.

2. Materials and methods

This is a single center retrospective study conducted between January 2013–April 2015 at the City of Health and Sciences, Molinette Hospital, a 1200-bed Academic Hospital with primary and secondary referral, in Turin, Italy.

All patients with positive stool test for *C. difficile* toxins or with positive blood cultures, defined as at least one positive blood culture either central or peripheral, for *Candida* spp., ESBL-E-producing Enterobacteriaceae or CP-Kp were enrolled in the study. For each patient, demographic, clinical and microbiological data were collected. Charlson score and age-adjusted Charlson score were used as comorbidity index [17–18]. Immunosuppressive corticosteroid therapy was defined as a prolonged use of ≥ 20 mg/die of prednisone or equivalent. Neutropenia was defined as an absolute neutrophil count $< 0.5 \times 10^9$/L.

The Walkaway automation system (Siemens, Sacramento, California) was used for isolates identification and antimicrobial susceptibility testing with EUCAST breakpoints. Carbapenemase production was confirmed by phenotyping tests (modified Hodge test) and ESBL-E production was confirmed by standard test (Beckman Coulter, Brea, California, USA). Candida species identification was based on MALDI-TOF MS and VITEK MS (bioMérieux, Marcy l'Etoile, France). *C. difficile* toxin detection was performed by Tox A/B quick chek (TechLab).

In patients with BSI, appropriate empiric antibiotic or antifungal treatment was defined as the administration of one or more antimicrobial agents with an in vitro activity against the pathogen within 24 h from the blood culture collection, administered for ≥ 48 h. In case of CDI, appropriate empiric antibiotic treatment was defined as the administration of vancomycin, metronidazole or fidaxomicin per os or metronidazole IV within 24 h from the stool collection, administered for ≥ 48 h. Moreover, in case of catheter related (CVC)-BSI, CVC removal within 24 h, 48 h or 5 days was documented. In-hospital mortality was evaluated.

The need for informed consent was waived due to the retrospective nature of the study, which was approved by the Medical Direction of the Hospital (PROT.N. 0076007). Data were collected according to the Italian laws on privacy.

3. Statistical analysis

Each patient was assigned a unique code number prior to statistical analysis. Statistics were studied by SAS program. Descriptive statistics were used to compare selected categories of pathogen over time and to analyze risk factors for in-hospital mortality. Data are expressed as means and standard deviation (SD) for continuous variables and with frequencies and percentages for categorical variables. Chi square test was used for categorical variables; Fisher's exact test was used in case of low frequency of the considered variable. All tests were two-tailed and $P < 0.05$ was considered significant.

4. Results

Seven hundred eighty-six patients were enrolled in the study: 398 CDI, 137 Candida BSI, 125 ESBL-E BSI and 126 CP-Kp BSI. The main demographic characteristics are reported in Table 1. The majority of patients were male (437; 56%), with a median age of 69 years (SD ± 16); median age was lower in patients with CP-Kp BSI (62 ± 16 years).

The median age-adjusted Charlson comorbidity score was 6 (SD ± 3). By an internal medicine perspective, leading comorbidities were cardiovascular diseases (44.7%), especially among CP-Kp BSI (57.9%; P = 0.0114) while neurologic (36.5%), chronic pulmonary diseases (33.6%) and solid tumor (29.2%) were especially documented among patients with candidemia (P = 0.08; P = 0.0149 and P = 0.0023, respectively). Among cases of candidemia, there was a higher number of patients with total parenteral nutrition (78.1%; P < 0.0001) or with a diagnosis of acute pancreatitis (5.1%; P = 0.0107). Hematologic malignancies and neutropenia were more frequently reported in ESBL-E BSI (24%; P < 0.0001 and 17.6%; P ≤ 0.0001, respectively).

Forty-three percent (338) of patients were treated with antibiotics before hospital admission, and 82.1% of patients received antibiotic therapy during hospital stay with the highest percentage among CP-Kp BSI (93.7%; P = 0.0002). Infections were usually diagnosed after a mean of 12 days (IQR = 4; 22) from hospital admission; CP-Kp BSI usually arise after a mean of 23 days (IQR = 11; 39; P < 0.0001) and the affected patients also had a longer hospital stay (42 days, IQR = 23; 78; P < 0.0001).

Regarding local epidemiology, *C. albicans* was the leading cause (58.4%), followed by *C. parapsilosis* (16.1%) and *C. glabrata* (14.6%). Among ESBL-E BSI, *E. coli* was isolated in 76% of patients (95/125) and *K. pneumoniae* in 20% (25/125). CDI, candidemia and ESBL-E BSI were more frequent in medical wards (78.9%, 64.2% and 68.8%, respectively; P < 0.0001), while CP-Kp BSI were more frequent in ICU (54%; P < 0.001) than in medical (31%) or surgical (15.1%) wards.

Overall in-hospital mortality was 23.4% and was higher in CP-Kp BSI group (43.7% vs. 16.1%, 31.4% and 17.6% for CDI, Candida BSI and ESBL-E BSI, respectively; P < 0.0001).

4.1. Risk factors for in-hospital mortality: univariate analysis

At univariate analysis the overall in-hospital mortality was significantly associated with cardiovascular diseases (P = 0.0002), chronic pulmonary diseases (P = 0.0114), neutropenia (P = 0.0207), dialysis (P = 0.0193), invasive mechanical ventilation (P < 0.0001), total parenteral nutrition (P < 0.0001), enteral nutrition (P = 0.0004), CVC (P < 0.0001) and urinary catheter (P < 0.0001). Furthermore, in-hospital mortality was significantly associated with antibiotic intravenous treatment the six months before admission (P = 0.0114) or during the hospitalization (P = 0.001). Mortality was also associated with admission at ICU ward (P < 0.0001), fever at the time of diagnosis (P = 0.0433) and CP-Kp BSI (P < 0.0001) (Table 2).

In-hospital mortality was lower in patients with inflammatory bowel diseases (IBD) (P = 0.0162), previous abdominal surgery (P = 0.0049), with appropriate empiric antibiotic treatment (P < 0.0001) and when CVC was removed within 5 days (P = 0.0321).

4.2. Risk factors for in-hospital mortality: multivariate analysis

Multivariate analysis is presented in Table 3. Independent risk factors for mortality were chronic pulmonary diseases (OR: 1.58; 95% CI: 1.02–2.44), neutropenia (OR: 3.48; 95% CI: 1.57–7.73), antibiotic therapy before hospital admission (OR: 1.52; 95% CI: 1.01–2.28), urinary catheterization (OR: 2.23; 95% CI: 1.41–3.53), total parenteral nutrition (OR: 2.08; 95% CI: 1.29–3.36), SIRS (OR: 4.81; 95% CI: 2.87–8.05) and higher serum creatinine levels (OR: 1.22; 95% CI: 1.05–1.41) at the time of diagnosis.

In-hospital mortality was lower in patients with previous abdominal surgery (OR: 0.47; 95% CI: 0.25–0.87), IBD (OR: 0.16; 95% CI: 0.03–0.86), higher serum albumin levels at the admission (OR: 0.58; 95% CI: 0.42–0.80) and fever at time of diagnosis (OR: 0.46; 95% CI: 0.26–0.81).