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Antimicrobial Original Research Paper

Enteropathogenetic nosocomial infections: predisposing clinical characteristics and risk of recurrent infections

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Nosocomial infections caused by *Clostridium difficile*, CP-Kp, ESBL-E or Candida spp. are usually associated with a high mortality rate. In this retrospective study, we evaluated the association between the patient characteristics and the risk of development of nosocomial BSI due to Candida or CP-Kp or ESBL-E. Moreover, we described the cumulative incidence of recurrent infections according to each group of nosocomial BSI. Enteral or parenteral nutrition and indwelling CVC at time of diagnosis were associated with an increased risk of candidemia or CP-Kp over ESBL-E and CDI. ESBL-E BSI was higher in patients undergoing hemodialysis, hematological stem cell transplant and neutropenic patients. The cumulative incidence for recurrent infections was higher for CP-Kp BSI and lower for candidemia. Our data highlight a different role of single patient comorbidities in the development of infections and the higher incidence of recurrent infections in CP-Kp BSI.

Keywords: BSI, ESBL, carbapenemase, candidaemia, *C. difficile*, enterobactaeriaceae, nosocomial Infections

Introduction

The gut is a large reservoir of multi drug resistant (MDR) bacteria that can reach high concentrations, especially in presence of gastrointestinal barrier damage (i.e. antibiotic therapies, immunosuppression, invasive devices) which may lead to translocation into the bloodstream by MDR organisms.[1] The causal role of dysbiosis is fully described for *Clostridium difficile* infections (CDI),[2] and dysbiosis may also favour gut colonization of MDR bacteria such as carbapenemase producing *Klebsiella pneumoniae* (CP-Kp), Enterobacteriaceae producing extended-spectrum beta-lactamase (ESBL-E) as well as the intestinal overgrowth of Candida spp.[3,4] The importance of microbiome in the pathogenesis of these nosocomial infections has important implications in therapeutic opportunities[4–6] and to highlight the common role of gastrointestinal dysbiosis in CDI and bloodstream infections (BSI) caused by Candida, CP-Kp and ESBL-E we suggested the term 'enteropathogenetic infectious syndromes'.[7,8]

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Moreover, nosocomial infections caused by CP-Kp, ESBL-E or Candida spp. are usually associated with a high mortality rate especially when appropriate antibiotic therapy is delayed, therefore the prompt identification of high risk patients based on clinical risk factors may help clinicians to choose the appropriate antibiotic therapy. The risk factors for the development of nosocomial enteropathogenic infections usually overlap (i.e. prolonged antibiotic therapies, previous hospitalization, invasive devices and comorbidities) and none of published studies have tried to evaluate the relevance of single clinical characteristics on the development of infections. The identification of specific clinical characteristics associated with a higher risk of CDI, Candidemia, CP-Kp or ESBL-E BSI, may be an additional tool for specific diagnostic, infection control and treatment strategies.

Therefore, our aim was to study the association between the patient characteristics and the risk of development of nosocomial BSI due to Candida or CP-Kp or ESBL-E. Moreover, we aimed to describe the cumulative incidence of recurrent infections according to each group of nosocomial BSI.

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Materials and methods

This was a single center retrospective study conducted at the City of Health and Sciences, Molinette Hospital, a 1200-bed Academic Hospital with primary and secondary referral, in Turin, Italy. Epidemiological data from the first two years of observation has been previously published.[8]

Enrolled patients had positive *stool test* for *C. difficile* toxins or positive blood cultures, either central or peripheral, for *Candida spp.*, ESBL-E or CP-Kp between January 2013 and June 2016. Among all positive stool tests for *C. difficile toxins* or all positive blood cultures for *Candida spp.*, ESBL-E or CP-Kp, we considered only the first positive isolate of infection for each patient during the time of observation for the analysis of risk factor for infection. Recurrent infections were defined as a new positive blood culture or stool sample positive for CDI, taken after a minimum of four days and within thirty days from the first episode of infection during the same hospital admission.

For each patient, demographic, clinical and microbiological data were collected from electronic medical records. Immunosuppressive corticosteroid therapy was defined as a use of $\geq$20 mg/die of prednisone for at least 10 days 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. Carbapenemases production was confirmed by phenotyping tests (modified Hodge test) and ESBL-E production was confirmed by standard test (NBC 46, 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 intravenous 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 $\geq$48 h. Moreover, in case of catheter related (CR)-BSI, CVC removal within 24 h, 48 h or 5 days was documented.

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 (Protocol number 0071567). Data were collected according to the Italian laws on privacy.

Statistical analysis

Demographic and clinical characteristic at the time of blood cultures were summarized using absolute and percentage frequencies (qualitative variables) or using mean and standard deviation or percentile (quantitative variables). In order to assess differences in risk factors of the four types of infection, a multinomial logistic model was estimated considering as reference group patients with CDI.

The cumulative incidence of recurrent infections was estimated considering as competing event the duration of hospital stay or discharge.

Results

During the study period, 961 nosocomial infections due to enteropathogens were recorded and considered for the analysis. The most frequent infection was CDI (474; 49.3%), followed by E-ESBL BSI (171; 17.8%), candidemia (165; 17.2%) and CP-Kp BSI (151; 15.7%). E-ESBL BSI were mostly due to *E. coli* (127; 74%) whilst candidemia was more frequently caused by *C. albicans* (54%). CP-Kp BSI were all caused by *K. pneumoniae*.

The risk of development of candidemia or CP-Kp was higher in patients with enteral and parenteral nutrition [(Candida OR: 2.09 95%CI [1.01–4.34]; CP-Kp OR: 3.45 95% CI [1.77–6.71]); for parental nutrition (Candida OR: 10.58 95%CI [6.65,16.83]; CP-Kp OR: 1.74 95% CI [1.02–2.99]), indwelling CVC at time of diagnosis (Candida OR: 2.19 95%CI [1.32,3.64]; CP-Kp OR: 4.68 95% CI [2.38,9.19])) and mechanical ventilation [(Candida OR: 6.58 95%CI [2.56–16.9]; CP-Kp OR: 10.94 95% CI [4.65–25.71]) (Figure 1; Table 1). Moreover, the risk of candidemia and CP-Kp increased with the duration of hospitalization (OR: 1.13; 95% CI [1.05–1.21]) and patients with previous pancreatitis had a higher risk for candidemia (OR: 7.47; 95% CI [1.82–30.61]). The risk of E-ESBL BSI was higher in patients undergoing hemodialysis (OR: 2.25 95%CI [10.9–4.64]), hematological stem cell transplant and neutropenic patients (OR: 2.63 95%CI [1.36–5.08]) (Table 1 and Figure 1).

The Kaplan-Meier curve of the cumulative incidence of any recurrent infection is represented in Figure 2. A recurrent infection was mostly due to enteric pathogens, for which we have considered CDI, ESBL-E, CP-Kp (38; 65.5%) and *Candida* spp. (9; 15.5%). The recurrent infection rate was higher for patient with primary BSI caused by CP-Kp (8.4% and 10.9% at day 14 and 28, respectively) and lower in patients with previous candidemia (0.07% and 6.7% at 14 and 28 days, respectively) (Figure 2).

Discussion

Over the last decade, candidemia, CDI and MDR Gram-negative bacteria, including ESBL-E and

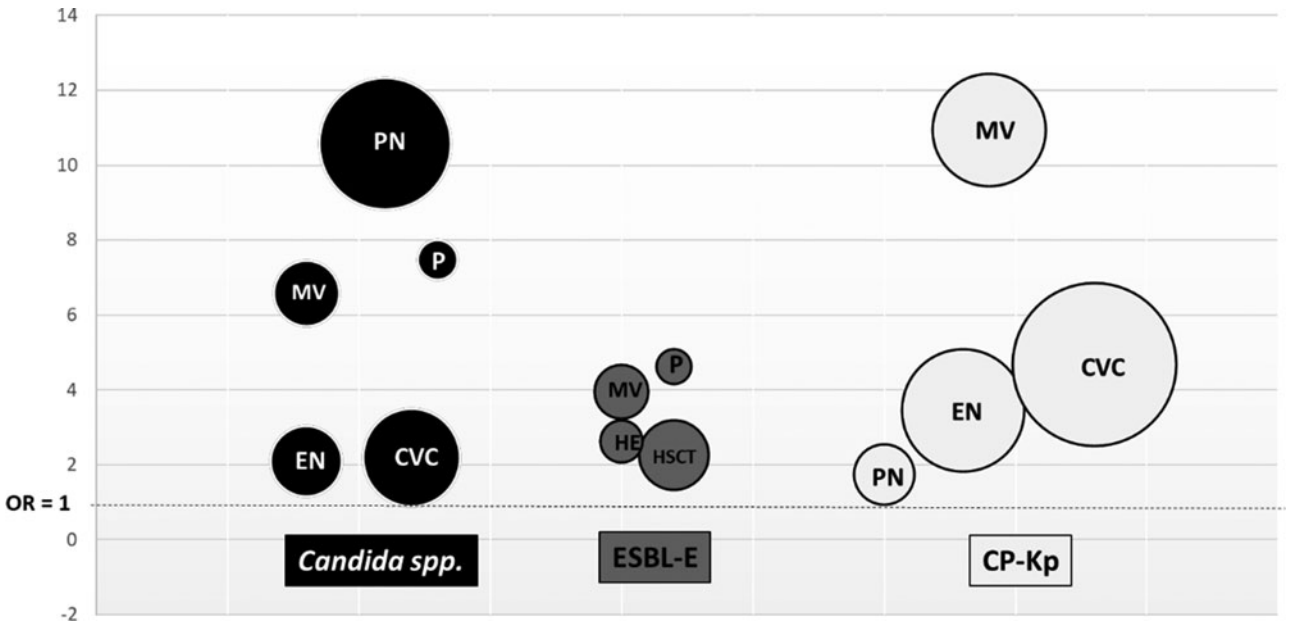

Figure 1 Clinical factors associated with higher risk for enteropathogenetic nosocomial infections.
CP-Kp: carbapenemase producing *K. pneumoniae*; ESBL-E: Enterobacteriaceae producing extended-spectrum beta-lactamase; HE: hemodialysis; HSCT: Hematopoietic stem cell transplantation; PN: parenteral nutrition; MV: mechanical ventilation; EN: enteral nutrition; CVC: central venous catheter; P: pancreatitis

CP-Kp, have been implicated in severe hospital acquired infections and their occurrence has increased steadily. Several studies have described the common risk factors associated with the development of CP-Kp BSI, candidemia or ESBL-E, as central venous line, ICU stay, multisite colonization, invasive procedures or previous antibiotic therapies.[7–22] However, the risk factors usually overlap and none of the published studies tried to differentiate the relevance of clinical characteristics on the development of different infections.[9–22] Stratifying the risk factors in patients at high risk for nosocomial infections may be a useful stewardship tool to promptly target empirical antimicrobial therapies and reducing inappropriate treatment as well as to optimize diagnostic and infection control procedures.[23,24]

Aims of this study were to assess if different clinical characteristics can be associated with a higher risk of development of nosocomial infections by CP-Kp rather than ESBL-E or candidemia, as compared to CDI. Furthermore, we aimed to describe the risk of recurrent infections after first episode of BSI.

Our results identified the enteral and parenteral nutrition, mechanical ventilation and central venous line as main risk factors for candidemia and CP-Kp, suggesting that the critically ill or frail patients are more susceptible to these infections compared to candidemia or CDI or ESBL-E.

In contrast, the risk for ESBL-E BSI was higher in hematological setting, confirming reports from oncology centers in North America, Europe and Asia where ESBL-E prevalence rates of 17%–37% among bloodstream isolates from patients with hematologic malignancies.[25–28] Furthermore, our data showed that ESBL-E epidemiology is important in HSCT recipients, with a risk for ESBL-E 2.63 time higher than other settings.

We further evaluated the incidence of recurrent infections during the hospital stay. Recurrent infection incidence was low, but it was higher in patients with previous CP-Kp BSI, and lower in patients with candidemia. Moreover, in the majority of cases, recurrent infection was due to enteric pathogens or candida, supporting the hypothesis that recurrent infections may reflect the presence of a persistent insult to intestinal microbiota during the hospital stay, favoured by antibiotic treatments and colonization.[7,8,29–32]

In fact, treatment of CP-Kp BSI is usually made of combination antibiotic therapy for 10–14 days, making difficult to reduce antibiotic pressure on gut microbiome. The prolonged antibiotic exposure may maintain dysbiosis, resulting in altered microbiota milieu and intestinal barrier damage that lead to translocation of enteric pathogens from the lumen to the bloodstream.[8,19,24]

On the contrary, antibiotic therapy is usually stopped in patients with candidemia, and antifungal therapy is promptly started. This targeted antifungal therapy may help to restore the physiological gut microbiome condition and consequently reduce the incidence of recurrent infections.

Table 1. Effect of demographical and clinical characteristics on the development of infections

	Crude effect						Adjusted effect					
	Candida		ESBL-E		CP-Kp		Candida		ESBL-E		CP-Kp	
	OR [95%CI]	*p*	OR [95%CI]	OR [95%CI]	*p*	OR [95%CI]	OR [95%CI]	*p*	OR [95%CI]	*p*	OR [95%CI]	*p*
Age (every 10 years)	1.04 [0.91,1.18]	0.59	0.86 [0.76,0.96]	0.010	0.74 [0.66,0.83]	<0.001	1.18 [0.99,1.40]	0.061	0.97 [0.84,1.12]	0.68	0.91 [0.77,1.08]	0.275
Gender (male)	0.77 [0.54,1.10]	0.15	0.54 [0.38,0.78]	0.001	0.53 [0.36,0.77]	0.001	0.89 [0.57,1.38]	0.601	0.62 [0.42,0.91]	0.014	0.63 [0.39,1.01]	0.053
Mechanical ventilation	8.37 [3.79,18.50]	<0.01	5.33 [2.31,12.31]	<0.001	41.21 [19.79,85.82]	<0.001	6.58 [2.56,16.95]	<0.001	3.95 [1.49,10.44]	0.006	10.94 [4.65,25.71]	<0.001
Previous infection	0.92 [0.44,1.92]	0.829	0.89 [0.43,1.85]	0.751	2.31 [1.28,4.15]	0.005	0.46 [0.19,1.13]	0.089	0.79 [0.36,1.76]	0.568	1.11 [0.50,2.43]	0.803
Enteral nutrition	14.82 [9.58,22.91]	<0.001	1.3 [0.86,1.97]	0.216	9.11 [6.02,13.76]	<0.001	2.09 [1.01,4.34]	0.048	1.18 [0.57,2.47]	0.651	3.45 [1.77,6.71]	<0.001
Parenteral nutrition	5.04 [3.34,7.61]	<0.001	1.98 [1.39,2.82]	<0.001	14.92 [8.21,27.12]	<0.001	10.58 [6.65,16.83]	<0.001	0.62 [0.35,1.10]	0.105	1.74 [1.02,2.99]	0.043
Indwelling CVC	0.96 [0.42,2.17]	0.913	2.63 [1.42,4.85]	0.002	6.09 [3.50,10.58]	<0.001	2.19 [1.32,3.64]	0.002	1.38 [0.89,2.13]	0.149	4.68 [2.38,9.19]	<0.001
Hemodialysis	1.21 [1.14,1.29]	<0.001	1.07 [0.99,1.15]	0.072	1.27 [1.19,1.35]	<0.001	0.57 [0.21,1.53]	0.264	2.25 [1.09,4.64]	0.027	1.69 [0.80,3.55]	0.167
Length of hospital stay prior to detection*	0.87 [0.60,1.24]	0.436	0.88 [0.62,1.25]	0.475	0.75 [0.51,1.09]	0.130	1.13 [1.05,1.21]	0.001	1.02 [0.94,1.10]	0.63	1.13 [1.05,1.21]	0.001
Antibiotic exposure (prior 6M)	0.80 [0.52,1.23]	0.314	1.20 [0.81,1.77]	0.365	1.00 [0.66,1.53]	0.988	0.94 [0.60,1.46]	0.774	0.87 [0.59,1.27]	0.466	0.93 [0.58,1.49]	0.764
Diabetes	0.67 [0.44,1.03]	0.069	0.82 [0.55,1.22]	0.328	0.93 [0.62,1.41]	0.745	0.87 [0.52,1.45]	0.593	1.25 [0.82,1.90]	0.295	1.14 [0.67,1.93]	0.637
Chronic kidney disease	6.78 [2.06,22.32]	0.002	3.54 [0.94,13.34]	0.062	4.02 [1.07,15.18]	0.040	0.74 [0.43,1.27]	0.273	0.83 [0.52,1.33]	0.447	1.18 [0.67,2.06]	0.565
Pancreatitis	0.78 [0.31,1.95]	0.588	1.83 [0.92,3.67]	0.087	1.61 [0.76,3.41]	0.21	7.47 [1.82,30.61]	0.005	4.62 [1.15,18.67]	0.031	4.47 [0.92,21.83]	0.064
SOT	0.78 [0.35,1.75]	0.548	2.75 [1.57,4.82]	<0.001	1.57 [0.81,3.05]	0.186	1.16 [0.35,3.81]	0.806	1.56 [0.69,3.55]	0.284	0.7 [0.26,1.91]	0.485
HSCT	2.08 [1.38,3.14]	<0.001	1.87 [1.24,2.82]	0.003	0.98 [0.58,1.60]	0.927	0.89 [0.34,2.32]	0.819	2.63 [1.36,5.08]	0.004	1.97 [0.88,4.40]	0.099
Malignancy	1.43 [0.92,2.24]	0.115	1.22 [0.78,1.93]	0.384	1.61 [1.02,2.52]	0.040	2.11 [1.23,3.62]	0.006	2.18 [1.38,3.46]	0.001	1.57 [0.85,2.89]	0.149
Abdominal surgery	1.04 [0.91,1.18]	0.596	0.86 [0.76,0.96]	0.010	0.74 [0.66,0.83]	<0.001	0.77 [0.42,1.38]	0.376	0.82 [0.48,1.40]	0.459	1.21 [0.66,2.21]	0.538

CVC: central venous catheter.
*Each 7 days.

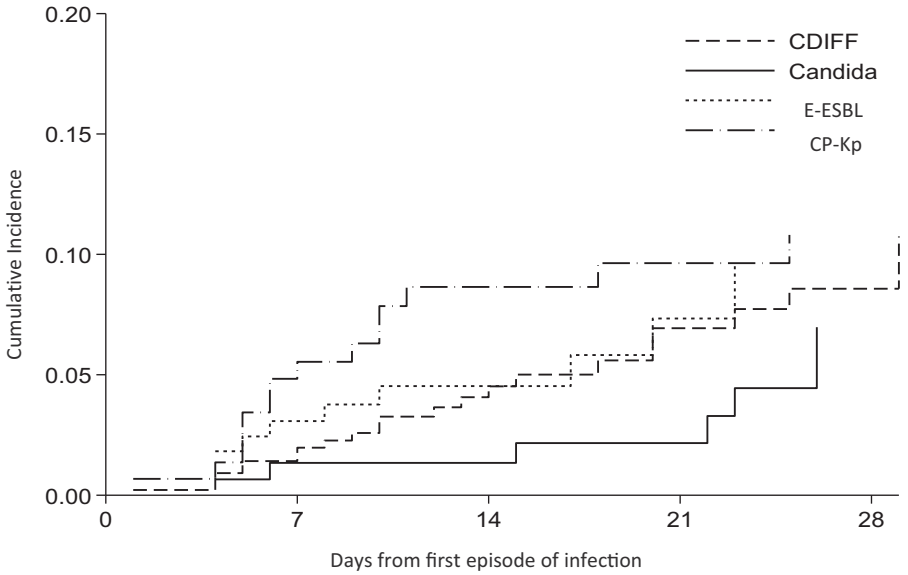

Figure 2 Cumulative incidence of recurrent infections in enteropathogenetic nosocomial infections.

Our study has several limitations: first, it was a retrospective study and we did not include a group without infections as control group; second, this was a monocentric study, thus the local epidemiology may have influenced the results, third, we did not analyze the impact of inappropriate therapies on the development of recurrent infections as well as the source control effectiveness which may have contributed to the relapse.

In conclusion, our data highlight significant differences between patients' characteristics and the risk of development of CP-Kp, ESBL-E, CDI and Candida infections. Strong efforts still need to be pursued to prompt identify and treat at risk patients with appropriate empiric regimens, de-escalation and appropriate duration of treatment.[33–35] These interventions should be reinforced by effective antimicrobial stewardship programs, either directed toward antibacterial and antifungal treatment, specifically aimed to reduce further selective pressure on gut microbiome.[35–38] Hence, an increased focus on the role of gut dysbiosis may allow to introduce innovative therapeutic strategies to prevent, to treat these diseases and to avoid reinfections, especially in a setting in which new effective therapies against infections due to MDR pathogens are urgently needed.

Disclosure statement

None to declare

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Conflict of interest

The authors report no conflict of interest

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