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

Epidemiology and Risk Factors for Mortality in Bloodstream infection by CP-Kp, ESBL-E, Candida and CDI: A Single Center Retrospective Study

Silvia Corcione*[1], Roberto Angilletta*[1], Stefania Raviolo[1], Claudia Filippini[2], Lucina Fossati[3], Giovanni Di Perri[1], Rossana Cavallo[4], Francesco Giuseppe De Rosa[1]

*These authors equally contributed to this work

Affiliations:

[1]Department of Medical Sciences, Infectious Diseases, University of Turin, Turin, Italy.

[2]Department of Anesthesia and Intensive Care Medicine, University of Turin, City of Health and Sciences, Molinette Hospital, Turin, Italy.

[3] Laboratory of Microbiology and Virology, City of Health and Sciences, Molinette Hospital, Turin, Italy.

[4] Department of Public Health and Pediatrics, University of Turin, Laboratory of Microbiology and Virology, Turin, Italy.

Corresponding author:

Silvia Corcione, MD

Department of Medical Sciences

Infectious Diseases

University of Turin

Corso Svizzera 164, 10149 Turin, Italy

tel. +39 011 4393979

fax. +39 011 4393996

Email: corcione.silvia@gmail.com

Abstract:

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.

Highlights:

- *C. difficile* infection (CDI) and of bloodstream infection (BSI) caused by Candida, ESBL-E-producing Enterobacteriaceae (ESBL-E) and carbapenemase-producing *K. pneumoniae* (CP-Kp) are widely represented in the hospital.
- Enteropathogenetic syndromes are defined to highlight the common role of gastrointestinal dysbiosis in diseases such as CDI and BSI caused by Candida, CP-Kp and ESBL-E.

Keyowords: *C. difficile*, candidemia, bloodstream infection, BSI, carbapenemases, CP-Kp, Enterobacteriaceae, ESBL, CRE, epidemiology, mortality, internal medicine wards.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest: none to declare.

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 acronyme “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.

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 ≥20mg/die of prednisone or equivalent. Neutropenia was defined as an absolute neutrophil count <0.5 x 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 hours from the blood culture collection, administered for ≥48h. 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 hours from the stool collection, administered for ≥48h. Moreover, in case of catheter related (CVC)-BSI, CVC removal within 24h, 48h 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.

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.

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). Amongst 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 pancreatits (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).

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).

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).

DISCUSSION

The aims of this study were to describe epidemiology and the risk factors for mortality in patients with CDI, ESBL-E BSI, CP-Kp BSI and candidemia. By an epidemiological point of view, *C. albicans* remained the leading cause of candidemia in our center, as previously published by our group although there is a growing incidence of non-albicans species as described in literature worldwide [12,19-20]. Our data confirmed the European epidemiology recently reported by ECDC, with a predominance of *K. pneumoniae* producing carbapenemases, whilst among ESBL-producing Enterobacteriaceae BSI *E. coli* was predominant [21].

By an internal medicine perspective, there are several considerations: in our study CDI occurred mostly in IMW, highlighting the importance of chronic comorbidities and the severity of underlying diseases as one of the key factors in the development of CDI. Comorbidities had different specific weight on different syndromes: parenteral nutrition, pancreatitis, solid tumor, neurological disease, were more frequently associated with Candida BSI [19], ESBL-E BSI were associated with neutropenia and hematological

diseases, highlighting the importance of medical rather than surgical or critical pattern of risk factors in the development of these infections [22]. Regarding CP-Kp our study confirmed ICU stay and invasive devices as related to CP-Kp BSI and the importance of prolonged antibiotic therapy in the development of invasive infections [23].

In-hospital mortality was higher in CP-Kp group, with a mortality rate similar to those reported in literature (43.7%) may be due to the fact that CP-Kp BSI were more frequently treated with inappropriate antibiotic empirical therapy if compared to other infections [24-26]. Moreover univariate analysis showed the impact of CVC removal on mortality, highlighting the important role of source control in bloodstream infections, to prevent complications and improve the outcome. Medical comorbidities as chronic pulmonary diseases, neutropenia, invasive devices, total parenteral nutrition, creatinine serum level and SIRS were described as independent risk factors for mortality, confirming that the severity of underlying comorbidities leads to a higher patient's frailty, which affects the outcome [24-31]. Moreover, the use of prolonged antibiotic therapy before admission was also associated to a worst outcome: this finding highlights the important role of antibiotic therapy and the associated dysbiosis, promoting intestinal colonization and possibly translocation, with secondary invasive infection.
Fever and abdominal surgery were associated with lower mortality at multivariate analysis, possibly because early suspicion, early blood cultures collection and early source control. Also, the abdominal surgery may lead clinicians to start a broad spectrum antibiotic coverage and to consider these patients as "high risk" for intestinal colonization and translocation or specific and more effective diagnosis and treatment strategies may also apply.

Although medical more than surgical or critical characteristics were identified as independent risk factors for mortality, we decided to include in our analysis all BSI episodes even in surgical and intensive care setting, according to the idea of a same pathogenetic of these eneteropathogenetic syndromes. In fact, gut microbiome alterations can promote the predominance of bacterial species with a nosocomial profile of resistance and it may be favoring colonization or excessive intestinal growth of CP-Kp, Candida or ESBL-E [32-34]. The possibility to restore an healthy microbiome may delay the risk of enteric and also recurrent infections, associated with morbidity and mortality [35].

In conclusion, notwithstanding the limitation of a retrospective study, our data showed that enteropathogenetic syndromes are heterogeneous in the hospital wards and features,

affecting patients with several comorbidities, prolonged hospital stay and treated with prolonged antibiotic courses. In order to reduce the spread of these infections and the antibiotic pressure on the gut microbiome, there is a strong need of a correct antibiotic use, adequate infection control measures and antimicrobial stewardship program implementation, also in internal medicine setting.

REFERENCES

[1] Turnbaugh, P.J., Ley, R.E., Hamady, M., Fraser-Liggett, C.M., Knight, R., Gordon, J.I., 2007. The Human Microbiome Project. Nature 449, 804–810. doi:10.1038/nature06244

[2] The Human Microbiome Project Consortium, 2012. Structure, function and diversity of the healthy human microbiome. Nature 486, 207–214. doi:10.1038/nature11234

[3] Dethlefsen, L., Huse, S., Sogin, M.L., Relman, D.A., 2008. The Pervasive Effects of an Antibiotic on the Human Gut Microbiota, as Revealed by Deep 16S rRNA Sequencing. PLOS Biol. 6, e280. doi:10.1371/journal.pbio.0060280

[4] Prescott, H.C., Dickson, R.P., Rogers, M.A.M., Langa, K.M., Iwashyna, T.J., 2015. Hospitalization Type and Subsequent Severe Sepsis. Am. J. Respir. Crit. Care Med. 192, 581–588. doi:10.1164/rccm.201503-0483OC

[5] Abt, M.C., McKenney, P.T., Pamer, E.G., 2016. Clostridium difficile colitis: pathogenesis and host defence. Nat. Rev. Microbiol. 14, 609–620. doi:10.1038/nrmicro.2016.108

[6] Sidler, J.A., Battegay, M., Tschudin-Sutter, S., Widmer, A.F., Weisser, M., 2014. Enterococci, Clostridium difficile and ESBL-E-producing bacteria: epidemiology, clinical impact and prevention in ICU patients. Swiss Med. Wkly. 144, w14009. doi:10.4414/smw.2014.14009

[7] Harris, A.D., McGregor, J.C., Johnson, J.A., Strauss, S.M., Moore, A.C., Standiford, H.C., Hebden, J.N., Morris, J.G., 2007. Risk Factors for Colonization with Extended-Spectrum β-Lactamase–producing Bacteria and Intensive Care Unit Admission. Emerg. Infect. Dis. 13, 1144–1149. doi:10.3201/eid1308.070071

[8] Nucci, M., Anaissie, E., 2001. Revisiting the source of candidemia: skin or gut? Clin. Infect. Dis. Am. 33, 1959–1967. doi:10.1086/323759

[9] Ling, M.L., Tee, Y.M., Tan, S.G., Amin, I.M., How, K.B., Tan, K.Y., Lee, L.C., 2015. Risk factors for acquisition of carbapenem resistant Enterobacteriaceae in an acute tertiary care hospital in Singapore. Antimicrob. Resist. Infect. Control 4, 26. doi:10.1186/s13756-015-0066-3

[10] Papadimitriou-Olivgeris, M., Marangos, M., Fligou, F., Christofidou, M., Bartzavali, C., Anastassiou, E.D., Filos, K.S., 2012. Risk factors for KPC-producing Klebsiella pneumoniae enteric colonization upon ICU admission. J. Antimicrob. Chemother. 67, 2976–2981. doi:10.1093/jac/dks316

[11] Papadimitriou-Olivgeris, M., Marangos, M., Fligou, F., Christofidou, M., Sklavou, C., Vamvakopoulou, S., Anastassiou, E.D., Filos, K.S., 2013. KPC-producing Klebsiella pneumoniae enteric colonization acquired during intensive care unit stay: the significance of risk factors for its development and its impact on mortality. Diagn. Microbiol. Infect. Dis. 77, 169–173. doi:10.1016/j.diagmicrobio.2013.06.007

[12] Guinea, J., 2014. Global trends in the distribution of Candida species causing candidemia. Clin. Microbiol. Infect. 20, 5–10. doi:10.1111/1469-0691.12539

[13] Miller, B.A., Chen, L.F., Sexton, D.J., Anderson, D.J., 2011. Comparison of the burdens of hospital-onset, healthcare facility-associated Clostridium difficile Infection and of healthcare-associated infection due to methicillin-resistant Staphylococcus aureus in community hospitals. Infect. Control Hosp. Epidemiol. 32, 387–390. doi:10.1086/659156

[14] Tacconelli, E., Cataldo, M.A., Dancer, S.J., Angelis, G.D., Falcone, M., Frank, U., Kahlmeter, G., Pan, A., Petrosillo, N., Rodríguez-Baño, J., Singh, N., Venditti, M., Yokoe, D.S., Cookson, B., 2014. ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients. Clin. Microbiol. Infect. 20, 1–55. doi:10.1111/1469-0691.12427

[15] De Rosa, F.G., Corcione, S., Pagani, N., Di Perri, G., 2015. From ESKAPE to ESCAPE, From KPC to CCC. Clin. Infect. Dis. 60, 1289–1290. doi:10.1093/cid/ciu1170

[16] De Rosa, F.G., Corcione, S., Raviolo, S., Montrucchio, C., Aldieri, C., Pagani, N., Di Perri, G., 2015. Candidemia, and infections by Clostridium difficile and carbapenemase-producing Enterobacteriaceae: new enteropathogenetic opportunistic syndromes? Infez. Med. 23, 105–116

[17] Charlson, M.E., Pompei, P., Ales, K.L., MacKenzie, C.R., 1987. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J. Chronic Dis. 40, 373–383

[18] Quan, H., Li, B., Couris, C.M., Fushimi, K., Graham, P., Hider, P., Januel, J.-M., Sundararajan, V., 2011. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am. J. Epidemiol. 173, 676–682. doi:10.1093/aje/kwq433

[19] De Rosa, F.G., Corcione, S., Filippini, C., Raviolo, S., Fossati, L., Montrucchio, C., Aldieri, C., Petrolo, A., Cavallo, R., Di Perri, G., 2015. The Effect on mortality of fluconazole or echinocandins treatment in candidemia in internal medicine wards. PloS One 10, e0125149. doi:10.1371/journal.pone.0125149

[20] De Rosa FG, D'Avolio A, Corcione S, Baietto L, Raviolo S, Centofanti P, Pasero D, Rinaldi M, Di Perri G. Anidulafungin for *Candida glabrata* infective endocarditis. Antimicrob Agents Chemother. 2012;56(8):4552-3.

[21] European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2015. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). ECDC, Stockholm; 2017. doi 10.2900/6928

[22] Tumbarello, M., Trecarichi, E.M., Bassetti, M., De Rosa, F.G., Spanu, T., Di Meco, E., Losito, A.R., Parisini, A., Pagani, N., Cauda, R., 2011. Identifying patients harboring extended-spectrum-beta-lactamase-producing Enterobacteriaceae on hospital admission: derivation and validation of a scoring system. Antimicrob. Agents Chemother. 55, 3485–3490. doi:10.1128/AAC.00009-11

[23] Tumbarello, M., Trecarichi, E.M., Tumietto, F., Bono, V.D., De Rosa, F.G., Bassetti, M., Losito, A.R., Tedeschi, S., Saffioti, C., Corcione, S., Giannella, M., Raffaelli, F., Pagani, N., Bartoletti, M., Spanu, T., Marchese, A., Cauda, R., Viscoli, C., Viale, P., 2014. Predictive Models for Identification of Hospitalized Patients Harboring KPC-Producing Klebsiella pneumoniae. Antimicrob. Agents Chemother. 58, 3514–3520. doi:10.1128/AAC.02373-13

[24] Corcione, S., Cardellino, C.S., Calcagno, A., Fossati, L., Costa, C., Cavallo, R., Di Perri, G., De Rosa, F.G., 2014. Healthcare-Associated Klebsiella pneumoniae carbapenemase Producing K. pneumoniae Bloodstream Infection: The Time Has Come. Clin. Infect. Dis. 59, 321–322. doi:10.1093/cid/ciu294

[25] Tumbarello, M., Trecarichi, E.M., De Rosa, F.G., Giannella, M., Giacobbe, D.R., Bassetti, M., Losito, A.R., Bartoletti, M., Del Bono, V., Corcione, S., Maiuro, G., Tedeschi, S., Celani, L., Cardellino, C.S., Spanu, T., Marchese, A., Ambretti, S., Cauda, R., Viscoli, C., Viale, P., 2015. Infections caused by KPC-producing Klebsiella pneumoniae: differences in therapy and mortality in a multicentre study. J. Antimicrob. Chemother. 70, 2133–2143. doi:10.1093/jac/dkv086

[26] Tumbarello, M., Viale, P., Viscoli, C., Trecarichi, E.M., Tumietto, F., Marchese, A., Spanu, T., Ambretti, S., Ginocchio, F., Cristini, F., Losito, A.R., Tedeschi, S., Cauda, R., Bassetti, M., 2012. Predictors of Mortality in Bloodstream Infections Caused by Klebsiella pneumoniae Carbapenemase–Producing K. pneumoniae: Importance of Combination Therapy. Clin. Infect. Dis. 55, 943–950. doi:10.1093/cid/cis588

[27] Trecarichi, E.M., Cauda, R., Tumbarello, M., 2012. Detecting risk and predicting patient mortality in patients with extended-spectrum β-lactamase-producing Enterobacteriaceae bloodstream infections. Future Microbiol. 7, 1173–1189. doi:10.2217/fmb.12.100

[28] Palacios-Baena, Z.R., Gutiérrez-Gutiérrez, B., De Cueto, M., Viale, P., Venditti, M., Hernández-Torres, A., Oliver, A., Martínez-Martínez, L., Calbo, E., Pintado, V., Gasch, O., Almirante, B., Antonio Lepe, J., Pitout, J., Akova, M., Peña-Miralles, C., Schwaber, M.J., Tumbarello, M., Tacconelli, E., Origüen, J., Prim, N., Bou, G., Giamarellou, H., Bermejo, J., Hamprecht, A., Pérez, F., Almela, M., Lowman, W., Hsueh, P.-R., Navarro-San Francisco, C., Torre-Cisneros, J., Carmeli, Y., Bonomo, R.A., Paterson, D.L., Pascual, Á., Rodríguez-Baño, J., 2017. Development and validation of the INCREMENT-ESBL-E predictive score for mortality in patients with bloodstream infections due to extended-spectrum-β-lactamase-producing Enterobacteriaceae. J. Antimicrob. Chemother. 72, 906–913. doi:10.1093/jac/dkw513

[29] Trecarichi, E.M., Tumbarello, M., Spanu, T., Caira, M., Fianchi, L., Chiusolo, P., Fadda, G., Leone, G., Cauda, R., Pagano, L., 2009. Incidence and clinical impact of extended-spectrum-beta-lactamase (ESBL-E) production and fluoroquinolone resistance in bloodstream infections caused by Escherichia coli in patients with hematological malignancies. J. Infect. 58, 299–307. doi:10.1016/j.jinf.2009.02.002

[30] Tumbarello, M., Sanguinetti, M., Montuori, E., Trecarichi, E.M., Posteraro, B., Fiori, B., Citton, R., D'Inzeo, T., Fadda, G., Cauda, R., Spanu, T., 2007. Predictors of Mortality in Patients with Bloodstream Infections Caused by Extended-Spectrum-β-Lactamase-Producing Enterobacteriaceae: Importance of Inadequate Initial Antimicrobial Treatment. Antimicrob. Agents Chemother. 51, 1987–1994. doi:10.1128/AAC.01509-06

[31] Viale, P., Giannella, M., Lewis, R., Trecarichi, E.M., Petrosillo, N., Tumbarello, M., 2013. Predictors of mortality in multidrug-resistant Klebsiella pneumoniae bloodstream infections. Expert Rev. Anti Infect. Ther. 11, 1053–1063. doi:10.1586/14787210.2013.836057

[32] Guastalegname, M., Russo, A., Falcone, M., Giuliano, S., Venditti, M., 2013. Candidemia Subsequent to Severe Infection Due to Clostridium difficile: Is There a Link? Clin. Infect. Dis. 57, 772–774. doi:10.1093/cid/cit362

[33] Papadimitriou-Olivgeris, M., Spiliopoulou, A., Fligou, F., Manolopoulou, P., Spiliopoulou, I., Vrettos, T., Dodou, V., Filos, K.S., Anastassiou, E.D., Marangos, M., Christofidou, M., 2014. Association of KPC-producing Klebsiella pneumoniae colonization or infection with Candida isolation and selection of non-albicans species. Diagn. Microbiol. Infect. Dis. 80, 227–232. doi:10.1016/j.diagmicrobio.2014.07.012

[34] Cole, G.T., Halawa, A.A., Anaissie, E.J., 1996. The Role of the Gastrointestinal Tract in Hematogenous Candidiasis: From the Laboratory to the Bedside. Clin. Infect. Dis. 22, S73–S88. doi:10.1093/clinids/22.Supplement_2.S73.

[35] Giacobbe, D.R., Bono, V.D., Bruzzi, P. et al., 2017. Previous bloodstream infections due to other pathogens as predictors of carbapenem-resistant Klebsiella pneumoniae bacteraemia in colonized patients: results from a retrospective multicentre study. Eur. J. Clin. Microbiol. Infect. Dis. 36, 663–669. doi:10.1007/s10096-016-2843-1

Highlights:

- *C. difficile* infection (CDI) and of bloodstream infection (BSI) caused by Candida, ESBL-E-producing Enterobacteriaceae (ESBL-E) and carbapenemase-producing *K. pneumoniae* (CP-Kp) are widely represented in the hospital.
- Enteropathogenetic syndromes are defined to highlight the common role of gastrointestinal dysbiosis in diseases such as CDI and BSI caused by Candida, CP-Kp and ESBL-E.

Keyowords: *C. difficile*, candidemia, bloodstream infection, BSI, carbapenemases, CP-Kp, Enterobacteriaceae, ESBL, CRE, epidemiology, mortality, internal medicine wards.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest: none to declare.

Table(s)

Table 1 – Characteristics of patients with CDI, Candida BSI, ESBL-E-producing Enterobacteriaceae BSI and carbapenemase producing *K. pneumonia* BSI.

(Abbreviations: CDI: *C. difficile* infection; BSI: bloodstream infection; ESBL-E: extendend-spectrum beta-lactamase; CP-Kp: carbapenemase producing *K. pneumonia*e; IBD: inflammatory bowel disease; SOT: solid organ transplant; HSCT: hematopoietic stem cell transplant; HIV: human immunodeficiency virus; ICU: intensive care unit; CVC: central venous catheter; iv: intravenous; ATB: antibiotic; WBCs: white blood cells; SIRS: systemic inflammatory response syndrome)

	OVER ALL N=786	**CDI N=398 (50.6%)**	**BSI CANDIDA N=137 (17.4%)**	**BSI ESBL-E N=125 (15.9%)**	**BSI CP-Kp N=126 (16%)**	**P-value**
Patient variables						
Male	437 (55.6%)	203 (51.6%)	74 (54%)	80 (64%)	80 (63.5%)	**0.0162**
Age (years)	69 (±16)	70 (±16)	70 (±15)	67 (±13)	62 (±16)	**<0.0001**
Comorbidity						
Cardiovascular diseases	351 (44.7%)	171 (43%)	57 (41.6%)	50 (40%)	73 (57.9%)	**0.0114**
Chronic pulmonary disease	224 (28.5%)	123 (30.9%)	46 (33.6%)	22 (17.6%)	33 (26.2%)	**0.0149**
Neurologic diseases	234 (29.8%)	113 (28.4%)	50 (36.5%)	29 (23.2%)	42 (33.3%)	0.0831
Diabetes	184 (23.4%)	97 (24.4%)	29 (21.2%)	29 (23.2%)	29 (23%)	0.8956
Chronic renal failure	193 (24.6%)	109 (27.4%)	26 (19%)	26 (20.8%)	32 (25.4%)	0.1701
Hepatic cirrhosis	68 (8.7%)	41 (10.3%)	7 (5.1%)	10 (8%)	10 (8%)	0.2964
Acute pancreatitis	13 (1.7%)	3 (0.8%)	7 (5.1%)	1 (0.8%)	2 (1.6%)	**0.0107**
Diverticulosis/diverticulitis	72 (9.2%)	37 (9.3%)	10 (7.3%)	13 (10.4%)	12 (9.5 %)	0.8423
IBD	33 (4.2%)	18 (4.5%)	5 (3.7%)	5 (4%)	5 (4%)	0.9717
Solid tumor	145 (18.5%)	65 (16.3%)	40 (29.2%)	24 (19.2%)	16 (12.7%)	**0.0023**
Solid abdominal tumor	69 (8.8%)	32 (8%)	16 (11.7%)	13 (10.3%)	8 (6.4%)	0.3841
Hematological malignancy	91 (11.6%)	35 (8.8%)	10 (7.3%)	30 (24%)	16 (12.7%)	**<0.0001**
SOT	47 (6%)	20 (5%)	7 (5.1%)	11 (8.8%)	9 (7.1%)	0.4071
HSCT	30 (3.8%)	16 (4%)	2 (1.5%)	8 (6.4%)	4 (3.2%)	0.2095
HIV	1 (0.1%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	0.1547
Neutropenia	52 (6.6%)	13 (3.3%)	7 (5.1%)	22 (17.6%)	10 (7.9%)	**<0.0001**
Charlson score	3 (±2)	3 (±2)	3 (±2)	3 (±2)	3 (±2)	0.7318
Age-adjusted Charlson score	6 (±3)	6 (±3)	6 (±3)	5 (±3)	5 (±3)	**0.0454**
Characteristics of index hospitalization						
Previous hospitalization (6 months)	519 (66%)	122 (69.4%)	74 (54%)	87 (69.6%)	82 (65.1%)	**0.0092**
Previous long term care facility	99 (12.6%)	69 (17.3%)	10 (7.3%)	13 (19.4%)	7 (5.6%)	**0.0005**
Total length of hospital stay (days)	27 (16; 48)	21 (13;34)	38 (23; 70)	24 (16;40)	42 (23;78)	**<0.0001**
Time from hospital admission to diagnosis (days)	12 (4; 22)	8 (2;16)	18 (10; 34)	11 (2;20)	23 (11;39)	**<0.0001**
Ward of microbiological isolation						
Medicine	527 (67.1%)	314 (78.9%)	88 (64.2%)	86 (68.8%)	39 (31%)	**<0.0001**
Surgery	157 (20%)	78 (19.6%)	34 (24.8%)	26 (20.8%)	19 (15.1%)	0.2628
ICU	102 (13%)	6 (1.5%)	15 (11%)	13 (10.4%)	68 (54%)	**<0.0001**

Pre-infection healthcare interventions						
Surgery	304 (38.7%)	131 (33%)	63 (46%)	45 (36%)	65 (51.6%)	**0.0005**
Abdominal surgery	140 (17.8%)	65 (23.4%)	32 (16.3%)	18 (14.4%)	25 (19.8%)	0.1853
Dialysis	76 (9.7%)	21 (5.3%)	8 (5.8%)	14 (11.2%)	33 (26.2%)	<**0.0001**
Nutrition						
Enteral	130 (16.5%)	28 (7%)	22 (16.1%)	16 (12.8%)	64 (50.8%)	**<0.0001**
Parenteral	234 (29.8%)	73 (18.3%)	107 (78.1%)	18 (14.4%)	36 (28.6%)	**<0.0001**
Invasive mechanical ventilation	83 (10.6%)	6 (1.5%)	19 (13.9%)	8 (6.4%)	50 (39.7%)	**<0.0001**
Indwelling invasive devices						
CVC	467 (59.4%)	166 (41.8%)	114 (83.2%)	72 (57.6%)	115 (91.3%)	**<0.0001**
Bladder catheter	427 (54.3%)	184 (46.2%)	88 (64.2%)	56 (44.8%)	99 (78.6%)	**<0.0001**
Treatment administered						
Chemotherapy	100 (12.7%)	41 (10.3%)	15 (11%)	29 (23.2%)	15 (11.9%)	**0.0019**
Radiotherapy	25 (3.2%)	10 (2.5%)	11 (8%)	2 (1.6%)	2 (1.6%)	**0.0129**
Corticosteroids	136 (17.3%)	69 (17.3%)	22 (16.1%)	21 (16.8%)	24 (19.1%)	0.9321
Immunosuppressive drugs	86 (10.9%)	41 (10.3%)	12 (8.8%)	18 (14.4%)	15 (11.9%)	0.4769
Previous antibiotic administration (iv)						
Before admission (6 months)	338 (43%)	177 (44.5%)	62 (45.3%)	49 (39.2%)	50 (39.7%)	0.5853
During current admission	645 (82.1%)	311 (78.1%)	119 (86.9%)	97 (77.6%)	118 (93.7%)	**0.0002**
Total days	10 (4;19)	7 (3;12)	16 (9;28)	8 (2;18)	20 (8;30)	**<0.0001**
≥3 categories of ATB	233 (29.6%)	60 (15.1%)	59 (43.1%)	29 (23.2%)	85 (67.5%)	**<0.0001**
Clinical features						
Serum albumin (g/dL) at admission	3.1 (±0.7)	3 (±0.7)	2.9 (±0.7)	3.3 (±0.7)	3.1 (±0.7)	**0.0070**
Fever	338 (43%)	45 (11.3%)	108 (78.8%)	98 (78.4%)	87 (69.1%)	**<0.0001**
WBCs/mm³	11000 (±8.200)	11.390 (±7.571)	10450(±6.630)	9.030 (±8.450)	12470 (±10.680)	**0.0006**
SIRS	350 (44.5%)	82 (20.6%)	96 (70.1%)	83 (66.4%)	89 (70.6%)	**<0.0001**
Serum creatinine (mg/dL)	1.34 (±1.2)	1.33 (±1.24)	1.16 (±0.99)	1.41 (±1.14)	1.46 (±1.33)	0.1677
Treatment variables						
Adequate empiric antimicrobic treatment	201 (21.6%)	40 (10.1%)	58 (42.3%)	66 (52.8%)	37 (29.4%)	**<0.0001**
Targeted therapy	463 (59%)	319 (80.2%)	58 (42.3%)	45 (36%)	42 (33.3%)	**<0.0001**
Therapeutic delay (hours)	24 (12; 54)	12 (10; 24)	72 (48;108)	72 (48;120)	72 (48;108)	**<0.0001**
CVC removal (within 5 days)	169 (36.1%)	-	75 (65.8%)	29 (40.3%)	65 (56.5%)	**<0.0001**
Within 48 hours	88 (18.8%)	-	42 (36.9%)	15 (20.8%)	31 (27%)	**<0.0001**
Within 24 hours	51 (10.9%)	-	28 (24.6%)	5 (6.9%)	18 (15.7%)	**<0.0001**
In-hospital death	184 (23.4%)	64 (16.1%)	43 (31.4%)	22 (17.6%)	55 (43.7%)	**<0.0001**
At 14 days	122 (15.5%)	40 (10.1%)	29 (21.2%)	15 (12%)	38 (30.2%)	**<0.0001**

Table2 – Univariate analysis of factors associated with in-hospital mortality

(Abbreviations: CDI: *C. difficile* infection; BSI: bloodstream infection; ESBL-E: extendend-spectrum beta-lactamase; CP-Kp: carbapenemase producing *K. pneumonia*e; IBD: inflammatory bowel disease; ICU: intensive care unit; CVC: central venous catheter; iv: intravenous; WBCs: white blood cells; SIRS: systemic inflammatory response syndrome)

	Non-survivors N=184 (23.4%)	**Survivors N=602 (76.6%)**	**P-value**
Comorbidity			
Cardiovascular diseases	66 (56.5%)	247 (41%)	**0.0002**
Chronic pulmonary diseases	66 (35.9%)	158 (26.3%)	**0.0114**
IBD	2 (1.1%)	31 (5.2%)	**0.0162**
Neutropenia	19 (10.3%)	33 (5.5%)	**0.0207**
Ward			
Medicine	112 (60.9%)	415 (68.9%)	**0.0416**
Surgery	25 (13.6%)	132 (21.9%)	**0.0133**
ICU	47 (25.5%)	55 (9.1%)	**<0.0001**
Pre-infection healthcare interventions			
Abdominal surgery	20 (10.9%)	120 (19.9%)	**0.0049**
Dialysis	26 (14.1%)	50 (8.3%)	**0.0193**
Nutrition			
Enteral	46 (25%)	84 (14%)	**0.0004**
Parenteral	77 (41.9%)	157 (26.1%)	**<0.0001**
Invasive mechanical ventilation	41 (22.3%)	42 (7%)	**<0.0001**
Indwelling invasive devices			
CVC	136 (73.9%)	331 (55.1%)	**<0.0001**
Urinary catheter	136 (73.9%)	291 (48.3%)	**<0.0001**
Previous antibiotic administration (iv)			
Before admission (6 months)	94 (51.1%)	244 (40.5%)	**0.0114**
Before microbiological isolation	166 (90.2%)	479 (79.6%)	**0.0010**
Microbiological isolation			
CDI	64 (34.8%)	334 (55.5%)	
Candida BSI	43 (23.4%)	94 (15.6%)	**<0.0001**
Enterobacteriaceae ESBL-E+ BSI	22 (12%)	103 (17.1%)	
CP-Kp BSI	55 (29.9%)	71 (11.8%)	
Clinical features			
Serum albumin (g/dL) at admission	2.9 (±0.6)	3.1 (±0.7)	**0.0002**
Fever	91 (49.5%)	247 (41%)	**0.0433**
WBCs/mm^3	12.750 (±9.750)	10.500 (±7.600)	**0.0015**
SIRS	129 (70.1%)	221 (36.7%)	**<0.0001**
Serum creatinine (mg/dL)	1.55 (±1.31)	1.27 (±1.16)	**0.0010**
Treatment variables			
Targeted therapy	82 (44.6%)	382 (63.5%)	**<0.0001**
CVC removal (within 5 days)	39 (28.7%)	130 (39.2%)	**0.0321**

Table 3 – Multivariate analysis of factors associated with in-hospital mortality.

(Abbreviations: CDI: *C. difficile* infection; BSI: bloodstream infection; ESBL-E: extendend-spectrum beta-lactamase; CP-Kp: carbapenemase producing *K. pneumonia*e; IBD: inflammatory bowel disease; iv: intravenous; SIRS: systemic inflammatory response syndrome)

	OR	95% CI
Comorbidity		
Chronic pulmonary diseases	1.578	1.022-2.436
IBD	0.160	0.029-0.864
Neutropenia	3.481	1.567-7.732
Antibiotic administration (iv)		
Before hospital admission	1.520	1.012-2.284
Pre-infection healthcare interventions		
Abdominal surgery	0.470	0.254-0.867
Total parenteral nutrition	2.083	1.290-3.364
Urinary catheter	2.227	1.405-3.528
Microbiological isolation		
Candida BSI vs CDI	1.343	0.677-2.665
Enterobacteriaceae ESBL-E+ BSI vs CDI	1.060	0.527-2.131
CP-Kp BSI vs CDI	3.164	1.729-5.790
Clinical features		
Serum albumin (g/dL) at admission	0.580	0.424-0.795
Fever	0.455	0.255-0.812
SIRS	4.808	2.872-8.049
Serum creatinine (mg/dL)	1.216	1.047-1.412