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The Gastrointestinal Microbiome and the Enteropathogenetic Syndromes

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1. BACKGROUND:

The role of microbiome in human health is increasingly recognized. **Diet**, **antimicrobial therapy**, environmental changes (i.e., **hospitalization**) and alteration in **host immunity** may contribute to microbiome perturbation.[1-2] These conditions may help the overgrowth of a single opportunistic pathogen. The importance of intestinal dysbiosis in *C. difficile* infection (CDI) has been widely studied; similar alterations may be important for colonization, overgrowth and subsequent bloodstream infection (BSI). The term «enteropathogenetic infectious syndromes» was recently proposed to highlight the **common role of gastrointestinal dysbiosis** in CDI and BSI caused by Candida, Enterobacteriaceae producing extended-spectrum beta-lactamase (ESBL) and *K. Pneumoniae* producing carbapenemase (KPC-Kp).[3]

The incidence of candidemia has increased over the past two decades,[4] as well as CDI which has recently become the most common health-care associated infection.[5] Over the last decade, multidrug-resistant Gram-negative bacteria, including Enterobacteriaceae ESBL- and carbapenemase-producing, have been implicated in severe hospital acquired infections (HAIs) and their occurrence has increased steadily.[6]

2. AIM OF THE STUDY:

Given the rising incidence and the difficult management of these infections, aim of this study is to **describe the epidemiology** and to evaluate **risk factors for in-hospital mortality** in patients with CDI, candidemia, KPC-Kp BSI and ESBL BSI.

3. METHODS:

We conducted a **single center retrospective** study on patients admitted to City of Health and Science Molinette Hospital , Turin, **from January 2013 to April 2015** with CDI or BSI caused by Candida, ESBL-producing Enterobacteriaceae or KPC-Kp. Demographic, clinical and microbiological data were collected for each patient.

Descriptive statistics were used to compare selected categories of pathogen over time (univariate analysis) and to analyze risk factors for in-hospital mortality (univariate and multivariate analysis).

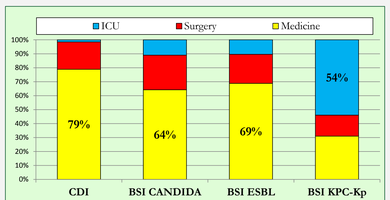
4. RESULTS:

786 cases were analyzed: **398 CDI** (50.6%), **137 Candida BSI** (17.4%), **125 ESBL-producing Enterobacteriaceae BSI** (15.9%) and **126 KPC-Kp BSI** (16%). In **Table 1 demographic data** are reported. **Inhospital mortality** occurred in 23.4%.

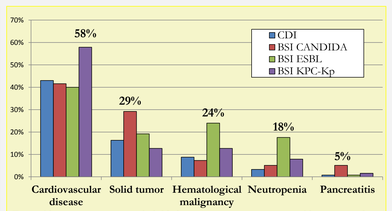
Tab. 1 –Characteristics of patients

	CDI	BSI CANDIDA	BSI ESBL	BSI KPC-Kp	P-VALUE
N. of patients	398	137	125	126	
Ward:					
ICU	6 (1.5%)	15 (11%)	13 (10.4%)	68 (54%)	**<0.0001**
Surgery	78 (19.6%)	34 (24.8%)	26 (20.8%)	19 (15.1%)	0.2628
Medicine	314 (78.9%)	88 (64.2%)	86 (68.8%)	39 (31%)	**<0.0001**
Comorbidities:					
Cardiovascular disease	171 (43%)	57 (41.6%)	50 (40%)	73 (57.9%)	**0.0114**
Solid tumor	65 (16.3%)	40 (29.2%)	24 (19.2%)	16 (12.7%)	**0.0023**
Hematological malignancy	35 (8.8%)	10 (7.3%)	30 (24%)	16 (12.7%)	**<0.0001**
Neutropenia	13 (3.3%)	7 (5.1%)	22 (17.6%)	10 (7.9%)	**<0.0001**
Pancreatitis	3 (0.8%)	7 (5.1%)	1 (0.8%)	2 (1.6%)	**0.0107**
Nutrition:					
EN	28 (0.7%)	22 (16.1%)	16 (12.8%)	64 (50.8%)	**<0.0001**
TPN	73 (18.3%)	107 (78.1%)	18 (14.4%)	36 (28.6%)	**<0.0001**
Pre-ATB					
before admission (6 months)	177 (44.5%)	62 (45.3%)	49 (39.2%)	50 (39.7%)	0.5853
during recovery	311 (78.1%)	119 (86.9%)	97 (77.6%)	118 (93.7%)	**0.0002**
In-hospital mortality	64 (16.1%)	43 (31.4%)	22 (17.6%)	55 (43.7%)	**<0.0001**

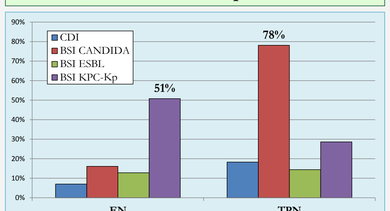
Abbreviation: CDI: *C. difficile* infection; BSI: bloodstream infection; ESBL: (Enterobacteriaceae producing) extenden-spectrum beta-lactamase; KPC-Kp: *Klebsiella pneumoniae* carbapenemase-producing; ICU: intensive care unit; EN: enteral nutrition; TPN: total parenteral nutrition; ATB: antibiotic (administration)



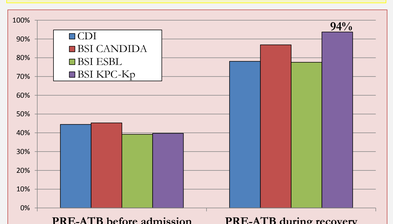
CDI and BSI caused by Candida and Enterobacteriaceae ESBL-producing were most common in Medical Wards, while more than a half of KPC-Kp BSI where diagnosed in ICU. **Annual incidence** of **CDI in medical wards** was **0.9%**, vs. **5.7%** of **KPC-Kp BSI in ICU**.



Leading comorbidities were cardiovascular diseases (44.7%), especially among KPC-Kp BSI (57.9%). Hematologic malignancies were documented in 24% of ESBL-producing Enterobacteriaceae BSI, while solid tumors were especially found in Candida BSI (29.2%).



Total parenteral nutrition is a well known risk factor for candidemia and invasive candidiasis. Enteral nutrition was more frequent in patients that developed a KPC-Kp BSI but, given the highest incidence in ICU, it would be useful a multivariate analysis.



Antibiotics were administered **before admission in 43%** while, **during the recovery**, previous antimicrobial therapy was observed in **82.1%**, with higher percentage among KPC-Kp BSI (93.7%).

Independent risk and protective factors for in-hospital mortality are reported in **Table 2**.

Tab. 2 – RISK FACTORS FOR IN-HOSPITAL MORTALITY

	OR	CI 95%
Comorbidities:		
Chronic pulmonary disease	1.578	1.022-2.436
IBD	0.160	0.029-0.864
Neutropenia	3.481	1.567-7.732
Abdominal surgery	0.470	0.254-0.867
TPN	2.083	1.290-3.364
Urinary catheter	2.227	1.405-3.528
KPC-Kp BSI vs CDI	3.164	1.729-5.790
Pre-ATB before admission (6 months)	1.520	1.012-2.284
Clinical features:		
Albuminemia (g/dL) at admission	0.508	0.424-0.795
Fever (>38°C)	0.455	0.255-0.812
SIRS	4.808	2.872-8.049
Creatininemia (mg/dL)	1.216	1.047-1.412

IBD and previous abdominal surgery result as **independent protective factors** for in-hospital mortality, probably because of the highest index of suspicion in these patients, with early diagnosis and appropriate therapy. Also fever, red flag for the diagnosis, and higher serum albumina levels were protective. In addition to comorbidity (chronic pulmonary disease, neutropenia) and worst clinical condition (SIRS and higher creatininemia), TPN and antibiotic administration before admission were **independent risk factors.**

5. CONCLUSION:

The gastrointestinal alterations are well recognized key players in promoting intestinal colonization, overgrowth and diseases by opportunistic microrganisms. Our study shows the **different epidemiologic features** of the four infections, highligting **not only their importance as risk factors, but also as prognostic factors**: TPN and antibiotic administration before admission result as independent risk factors for in-hospital mortality. These results may suggest that longer or more severe microbiome perturbations may result in more severe enteropathogenetic infectious syndromes. Thus, to reduce the opportunity of enteropathogenetic infectious syndromes, there is a strong need of a correct antibiotic use and adequate infection control measures.

6. REFERENCES:

1. Dethlefsen, L., Huse, S., Sogin, M. L. & Relman, D. A. The pervasive effects of an antibiotic on the human gut microbiota, as revealed by deep 16S rRNA sequencing. *PLoS Biol.* 6, e280 (2008).
2. Prescott, H. C., Dickson, R. P., Rogers, M. A. M., Langa, K. M. & Iwashyna, T. J. Hospitalization Type and Subsequent Severe Sepsis. *Am. J. Respir. Crit. Care Med.* 192, 581–588 (2015).
3. De Rosa, F. G. *et al.* Candidemia, and infections by Clostridium difficile and carbapenemase-producing Enterobacteriaceae: new enteropathogenetic opportunistic syndromes? *Infez. Med.* 23, 105–116 (2015).
4. Guinea, J. Global trends in the distribution of Candida species causing candidemia. *Clin. Microbiol. Infect.* 20 (Suppl 6), 5–10 (2014).
5. Miller, B. A., Chen, L. F., Sexton, D. J. & Anderson, D. J. 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 (2011).
6. Tacconelli, E. *et al.* 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 (Suppl 1), 1–55 (2014).