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Bloodstream infections secondary to *Clostridium difficile* infection: risk factors and outcomes

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Running title: BSI subsequent to *C. difficile* infection

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ABSTRACT

Purpose. To determine the incidence, risk factors, and outcomes of bloodstream infections (BSI) subsequent to *Clostridium difficile* infection (CDI).

Methods. Retrospective study of all patients with definite diagnosis of CDI admitted from January 2014 to December 2014 in two large Hospitals in Rome. Two groups of patients were analyzed: those with CDI and subsequent BSI (CDI/BSI+), and those with CDI and no evidence of primary BSI (CDI/BSI-). Data about clinical features, microbiology, treatments and mortality were obtained.

Results. Overall, 393 cases of CDI were included in the final analysis: 72 developed a primary nosocomial BSI while 321 had CDI without microbiological and clinical evidence of BSI. Etiologic agents of BSI were *Candida* species (47.3%), Enterobacteriaceae (19.4%), enterococci (13.9%), and mixed infections (19.4%). In multivariate analysis ribotype 027 (odds ratio [OR] 6.5), CDI recurrence (OR 5.5), severe CDI infection (OR 8.3), and oral vancomycin >500 mg/day (OR 3.1) were recognized as factors independently associated to the development of nosocomial BSI. Compared to controls, 30-day mortality from CDI diagnosis was higher in patients of CDI/BSI+ group (38.9 vs 13.1%, $p<0.001$). Among patients of the CDI/BSI+ group mortality attributable to primary BSI was as high as 57%.

Conclusions. Our findings suggest that severe CDI may be complicated by development of nosocomial BSI. *Candida* and enteric bacteria appear as the leading causative pathogens and are associated with poor outcome.

Keywords: bloodstream infection, *Clostridium difficile* infection, ribotype 027, oral vancomycin, fidaxomicin

INTRODUCTION

Clostridium difficile infection (CDI) is an emerging infection, usually occurring after exposure to broad-spectrum antibiotics [1-2-3]. This infection can be mild and self-limiting, but might progress to severe disease with ileus, toxic megacolon, and, eventually, death. The incidence, severity, and acquisition in people formerly classified as at low risk seem to be increasing, and a hypervirulent, fluoroquinolone-resistant *C. difficile* strain named NAP1/BI/027 is associated with severe symptoms, high recurrence rates, and poor outcome [4-5-6].

The alterations occurring in the intestinal flora, recognized as a microbiome, may promote the translocation of pathogens in the blood and the developing of nosocomial bloodstream infections (BSIs) [7]. Recently, we reported our experience about candidemia subsequent to severe CDI [8-9-10], and we observed an association between *Candida* BSI and CDI, especially if caused by ribotype 027 strains. Also, we reported a case about a severe community onset healthcare-associated CDI complicated by KPC producing *Klebsiella pneumoniae* BSI [11]. Thus, it was hypothesized that antibiotic therapy and/or other clinical characteristics related to CDI (i.e., severity, recurrence, disease caused by a highly virulent strain, etc.) presumably contribute to alterations of the colon indigenous microbiota and eventually predispose patients to BSI [12-13-14].

The aim of our study was to analyze the clinical findings of patients with CDI and primary nosocomial BSI to determine the risk factors and outcomes associated with these infections.

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MATERIALS AND METHODS

Study Design and Study Patients

This was a retrospective study of patients who were admitted from January 2014 to December 2014 in two large Hospitals in Rome: Policlinico Umberto I-"Sapienza" University (1.200 bed and 49.000 admissions/year in 2014) and the San Giovanni-Addolorata Hospital (700 beds and 30.000 admission/year in 2014). All adults (age> 18 years) with a documented CDI infection were initially included in the study. Patients for which was not possible to obtain medical records were excluded from the final analysis. The ethics committee of the Policlinico Umberto I approved the study.

Data were extracted from the medical records of patients and from hospital computerized databases or clinical charts according to a prepared questionnaire. The following data were reviewed: demographics, clinical and laboratory findings, comorbid conditions (like diabetes mellitus, cardiovascular disease, pulmonary disease, renal disease, hepatic disease, central nervous system disease, malignancy, and the overall number of comorbid conditions), microbiological data, duration of hospital stay, incidence of infections during hospitalization, treatments and procedures during hospitalization and/or in the previous 90 days prior to infection (immunosuppressive therapy, placement of a central venous catheter [CVC] or a urinary catheter, dialysis, endoscopic procedures, tracheostomy, surgery, and mechanical ventilation), admission from a long-term care facility or a nursing home, classes of antibiotics received on admission and/or after admission before a positive culture was obtained, the sequential organ failure assessment (SOFA) score at time of infection, side effects and 30-day mortality.

Data on antibiotic therapy in the previous 30 days as well as other risk factors for multidrug-resistant (MDR) organisms were derived from the following sources: a) history taken from patients and/or relatives; b) discharge letters and summaries if patients were previously hospitalized in other facilities, and c) electronic charts if patients were previously hospitalized or seen in the clinics involved in the study.

Study Definitions

CDI was defined as 1) presence of diarrhea, defined as passage of three or more unformed stools in 24 or fewer consecutive hours; 2) a stool test result positive for the presence of toxigenic *C. difficile* or its toxins or colonoscopic or histopathologic findings demonstrating pseudomembraneous colitis [15]. The same criteria were used to diagnose recurrent CDI. BSI was defined according to the standard definitions of the Centers for Disease Control and Prevention (CDC) [16]. If common skin contaminants (ie, diphtheroids, *Bacillus* [not *B. anthracis*] spp, *Propionibacterium* spp, coagulase-negative staphylococci [including *S. epidermidis*], viridans group streptococci, *Aerococcus* spp, *Micrococcus* spp), bacteremia was considered clinically significant if at least two blood cultures were positive associated with at least two signs or symptoms of systemic inflammatory response [16]. Candidemia was defined as the isolation of microorganism in one or more separate blood culture with clinical evidence of infection [17].

Severe sepsis was defined as sepsis with sepsis-induced organ dysfunction or tissue hypoperfusion (manifesting as hypotension, elevated lactate, or decreased urine output); septic shock as severe sepsis plus persistently low blood pressure following the administration of intravenous fluids [18]. The CVC was considered the likely source of infection if blood culture obtained from the lumen of the catheter was positive in a time <2 hours compared to peripheral veins, and/or culture of catheter was positive [19]. Primary BSI was defined as BSI occurring in patients without a recognized source of infection. Patients with secondary BSI (defined as BSI with a documented source of infection including intravascular device, urinary tract infection, pneumonia, intra-abdominal infection, skin and soft tissue infection, localized abscess, central nervous system infection, infective endocarditis) were excluded from the final analysis.

BSI was defined as a nosocomial infection if it occurred more than 48 h after admission to the hospital and if no signs or symptoms of infection were noted at the time of hospital admission. *Candida* colonization at time of admission was defined as positive culture for fungal species from any of tested surveillance sites, and colonization was considered, respectively, unifocal or

multifocal when *Candida* species were isolated from one focus or simultaneously from various non-contiguous foci [20].

Severe CDI was defined as: white blood cell count >15.000 cells/μL or a serum creatinine level ≥ 1.5 times the premorbid level [15]. Time at risk is a measure of the risk of developing some new condition within a specified period of time: time at risk for CDI was considered the median of the time between hospitalization and clinical development of CDI; time at risk for CDI recurrence was considered the median of the time between the first CDI and the recurrence of infection; time at risk for BSI was considered the median of the time between CDI and BSI. MDR pathogens were defined according to the standard definitions [21-22]. Data of all patients were entered in an electronic database.

Study Groups, Endpoints and Measurement of Outcomes

All patients with definite diagnosis of CDI were divided in two groups: those developing a primary BSI within 30 days from initial diagnosis of CDI (CDI/BSI+ group) and patients with CDI and no evidence of primary BSI (CDI/BSI- group). The attainable records of all patients belonging to the CDI/BSI+ and CDI/BSI- groups were compared.

The clinical endpoints of our study were the assessment of risk factors for development of BSI and the evaluation of 30-day mortality [23] rates in both groups. All the outcomes in the two groups were measured after the main acute event during hospitalization: the first CDI, the recurrence of CDI, and primary BSI (only in patients of CDI/BSI+ group).

Outcomes of primary BSI episodes were assessed as follows: (i) cure, in the case of complete disappearance of clinical, radiological and microbiological signs (repeated negative cultures) of infection at the time of hospital discharge; and (ii) attributable mortality, in the case of BSI-related death due to clinical evidence of infection at the time of death without an alternative cause of death, or autopsy evidence of tissue infection [24].

Microbiological Analysis

Microbiological diagnosis of *C. difficile* disease was performed by using enzyme immunoassays (EIAs) combining detection of *C. difficile* glutamate dehydrogenase (GDH) and toxin A/B antigens in stool specimens, through the commercial methods TechLab C. Diff Quik Chek Complete or Meridian Bioscience Immunocard *C. difficile* GDH and Vidas *C. difficile* Toxin A/B, according to the testing algorithms established at the individual study sites. Stool specimens were also tested by the Cepheid Xpert *C. difficile*/Epi assay, which is a multiplex real-time PCR that detects *tcdB*, the binary toxin gene (*cdt*), and the *tcdC* gene deletion at nt 117, to identify the PCR-ribotype 027 strain, also called 027/NAP1/BI strain [25].

To detect bacteria and/or fungi, blood specimens were obtained for culture (from a peripheral venipuncture and/or intravascular catheter), and processed using the automated BACTEC system (Becton Dickinson Diagnostic Instruments, Sparks, MD, USA). For bloodstream isolates, species identification was performed by micromorphology analysis and biochemical tests, according to standard procedures.

Statistical analysis

All data were statistically analyzed using a commercially available statistical software package (SPSS, version 20.0; SPSS Inc, Chicago, Illinois). Continuous variables were compared using Student t test for independent samples. Categorical variables were evaluated using the $\chi 2$ test or Fisher exact test, when appropriate. All tests were 2-tailed and a P value $< .05$ was considered statistically significant. Results were expressed as mean ± standard deviation (SD) for continuous normally distributed variables or as percentage for categorical variables. Multivariate analysis was used to identify independent predictors of mortality and predictors of BSI. Matched bivariate analyses were conducted using a conditional logistic regression model, incorporating all variables found to be significant at univariate analysis ($p<0.05$) with a stepwise method. The final selected model was tested for confounding factors (like underlying severity of illness, comorbidities, antibiotic use). If a covariate affected the ß-coefficient of a variable in the model by >10%, then the

confounding variable was maintained in the multivariable model. CI (95%) was calculated. Multi-collinearity was assessed according to the condition index of the multivariate model: a condition index <10 denotes weak collinearity, 10–30 denotes moderate collinearity, and >30 denotes strong collinearity.

RESULTS

During the study period 440 patients fulfilled criteria for CDI: out of these 19 patients with secondary BSI and 28 patients with non-obtainable medical records were excluded from the final analysis. The final cohort of study comprised 393 patients. The incidence of CDI was 6.1 per 1000 admissions in Policlinico Umberto I, and 4.5 per 1000 admissions in San Giovanni-Addolorata Hospital. The majority of patients with CDI were hospitalized in medical wards (63%), followed by intensive care unit (ICU) (18%), and surgery (19%). Seventy-two patients (18.3%) developed a primary nosocomial BSI within 30 days from the CDI episode (CDI/BSI+ group), and these were compared to 321 patients with CDI but no evidence of primary BSI during hospitalization (CDI/BSI- group). As regards to the ward of hospitalization, there were no significant differences between the two study groups (medical wards 63% Vs 62%, p=0.8, ICU 19% Vs 17%, p=0.7, surgical wards 18% Vs 21%, p= 0.3 in CDI/BSI+ and CDI/BSI-, respectively).

Table 1 reports the pathogens causing BSI in patients of CDI/BSI+ group: the most common etiology was *Candida* species (47.3%), followed by Enterobacteria (19.4%), mixed infections (19.4%), and enterococci (13.9%). Among patients with monomicrobial or polymicrobial bacterial BSI, a MDR phenotype was detected in 26 out of 38 cases (68.4%), with 11 cases of extended-spectrum beta-lactamases (ESBL) producing Enterobacteriaceae, 8 cases of carbapenemase–producing *Klebsiella pneumoniae*, and 7 cases of vancomycin-resistant enterococci (VRE).

Demographics and clinical features of CDI patients with or without nosocomial BSI are summarized in **Table 2**. No differences were detected in term of age, sex, and comorbidities (calculated also as Charlson score) between the two study groups. Compared to CDI/BSI- group, patients included in the CDI/BSI+ group were more frequently affected by a severe CDI (100% Vs 46.7%, p<0.001), had a higher rate of *C. difficile* recurrence (83.3% Vs 29.6%, p<0.001), a higher frequency of ≥ 1 recurrence (33.3% Vs 7.1%, p<0.001), and a higher median SOFA score (3.6 Vs 1.7, p<0.001). Compared to patients of the CDI/BSI- group, those included in the CDI/BSI+ group had a higher frequency of ribotype 027 infection, (84.7% Vs 33.9%, p<0.001); patients with CDI

due to ribotype 027 had a high likelihood of developing BSI during the first 2 weeks (94% Vs 21%) from the initial CDI diagnosis.

The **Table 3** describes antibiotic regimens and outcomes of patients with CDI. All patients were initially treated with vancomycin or metronidazole monotherapy; during hospital stay an escalation therapy including oral vancomycin plus metronidazole was recorded in 34.7% of patients of the CDI/BSI+ group, and in 29.6% of those of the CDI/BSI- group. Overall, a dosage of oral vancomycin >500 mg/day was used in 51 (70.8%) patients of the CDI/BSI+ group, compared to 100 (31.1%) patients of the control group ($p<0.001$). Among patients receiving increased vancomycin dosages the following regimens were adopted: 250 mg tid in 87 cases and 250 mg qid in 64 patients. Patients of the CDI/BSI+ group had also a higher ICU (16.9 Vs 9.1, $p<0.001$) and hospital length of stay (62.2 Vs 29.3, $p<0.001$). Of interest, patients of CDI/BSI+ group showed a lower time at risk for CDI recurrence (20.4 Vs 35.1 days, $p <0.001$). The median time at risk for primary BSI in the CDI/BSI+ group was 14.8 ± 2.9 days.

Overall, 30-day mortality was 17.8% among all patients with CDI; compared to controls, 30-day mortality from CDI diagnosis was higher in patients of CDI/BSI+ group (38.9 vs 13.1%, $p<0.001$), and in 41 (56.9%) patients of CDI/BSI+ group mortality was attributable to primary BSI. BSI-attributable mortality was 51.1% in patients with bacterial infection, 67.6% in those with *Candida* infection, and 50% in those with mixed infection analysis. Thirty-day mortality in patients with CDI due to ribotype 027 was 71% in patients of CDI/BSI+ group and 26% in patients of CDI/BSI- group.

Finally, **Table 4** shows results of the multivariate analysis, and ribotype 027, CDI recurrence, severe CDI infection, and oral vancomycin >500 mg/day resulted risk factors independently associated to the development of BSI after CDI.

DISCUSSION

Our study is the first describing an association between CDI and nosocomial BSI. The novel message is that a significant percentage of patients with CDI may develop a primary BSI, mostly caused by *Candida* or enteric bacteria, and that mortality associated with this complication is very high, exceeding 50%.

From a clinical standpoint, our findings reveal that clinicians should be very diligent in diagnosing and treating a BSI during the first 2-4 weeks after CDI diagnosis, since this complication is associated with an excess of mortality. In a multicenter cohort study CDI mortality was 13% after 30 days and 37% after 1 year [26]. We observed a slightly higher mortality in our population (17.8%), probably because we included elderly patients with multiple comorbidities, and with high frequency of CDI recurrence. This finding may be explained by the fact that the hospitals involved in this study provide assistance to patients following transfer from various nursing homes, long-term care facilities and community-hospitals of our region, and probably we analyzed a setting of severely ill and frail patients with multiple risk factors for infection and high frequency of previous antibiotic therapy.

We have recently demonstrated that patients with CDI may suffer of subsequent *Candida* BSI [10]. The alterations of the intestinal mucosa and resident flora occurring in patients with CDI may predispose to translocation of pathogens from the intestinal lumen to the blood, particularly in patients with severe CDI and/or CDI recurrences, as consequence of two main factors: 1) the severe mucosal damage associated with ribotype 027 *C. difficile* strains, and 2) impairment of the normal intestinal microbiota due to prolonged vancomycin therapy. As a matter of fact, the receipt of high oral vancomycin dosages and ribotype 027 infection were independent risk factors for developing a BSI.

Of importance, all cases of primary BSI were caused by enteric pathogens like *Candida*, Enterobacteriaceae, or enterococci. Since patients with other documented foci of infection were excluded, microbial translocation from the gut was the likely source of infection in all cases. Three

conditions are usually necessary for hematogenous spread of microorganism residents in the gut: alterations of the normal integrity of the mucosal epithelium, impairment of mucosal immunity (particularly neutrophils, which play a crucial role in clearing gastrointestinal candidiasis), and colonization of gastrointestinal mucosa. Among patients with severe CDI, all the above conditions are frequently co-existing: mucosal damage is sustained by an intense host inflammatory response, particularly in those with 027 ribotype [27-28], and this condition frequently persists despite the administration of appropriate antibiotic therapy [29]. Moreover toxins production exerts mucosal immunity impairment also by modification of neutrophils morphology and function [30]. Moreover, a significant number of patients of the CDI/BSI+ group received immunosuppressive therapies, especially steroids, and this factor can also be involved in an increased susceptibility to invasive infections.

CDI may promote colonization by *Candida* and other microorganisms: Raponi et al [31] showed that CDI is significantly associated with *Candida* colonization. Furthermore, Nerandzic and coworkers found high rates of stool colonization by *Candida* spp and/or vancomycin-resistant enterococci after oral vancomycin therapy [12]. Of interest, the majority of our patients with bacterial BSI had a MDR etiology (mostly ESBLs and carbapenemase–producing *K. pneumoniae*), a fact highlighting the role of intestinal tract as a reservoir of MDR organisms in patients with multiple healthcare contacts [32]. On this line, our data confirm the recent experience of Amit et al who found CDI as a predisposing factor for Gram-negative BSI [33].

Another crucial point of our study is the association between BSI and ribotype 027 infection. During last years an increasing incidence of 027 ribotype has been reported in our geographic area [34], and there is epidemiological evidence of a recent spread of this organism in our hospital [35]. In our study, CDI due to ribotype 027 is associated to an increased risk of BSI during the first 30 days after diagnosis and increased 30-day mortality. This finding support the hypothesis that the hypervirulent 027 strains might cause a major damage to integrity of intestinal mucosa, favouring translocation of microbes to the blood. Furthermore, oral vancomycin, especially if higher dosages

Antimicrobial Agents and Chemotherapy

are used, may also cause delayed intestinal tissue injury, that may act as an additional driver for microbial translocation [36]. Our data suggest to avoid the use of increased oral vancomycin dosages, and confirm previous observations [37].

There are four important limitations in our observations: first, the retrospective nature of the study does not allow definitive conclusions and future large trials will be necessary to confirm our data; second, the possible microbial colonization preceding CDI was not assessed in the population; third, it is possible that the association between severe CDI and nosocomial BSI may be detected in an old and frail patient population, as depicted by the present study, but our findings cannot be generalized to all patients with CDI; fourth, the significantly higher use of immunosuppressive therapy in the CDI/BSI+ group may make these patients susceptible to invasive infections. However, despite these limitations, our analyses provide a strong rationale for a possible link between severe CDI and BSI.

In conclusion, it is possible to hypothesize an increased risk of BSI in patients with severe or relapsing CDI. The evidence from our study highlights the leading role of 027 strains and higher oral vancomycin dosages in promoting nosocomial BSI. Our findings confirm the need of further and more comprehensive approaches to patients with CDI.

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TABLE 1. Etiologies of BSI

Pathogens*	**CDI/BSI+ n= 72**
Enterobacteriaceae	14 (19.4%)
***Enterococcus* species**	10 (13.9%)
***Candida* species**	34 (47.3%)
- *C. albicans*	15 (44.1%)
- *C. glabrata*	9 (26.5%)
- *C. tropicalis*	5 (14.7%)
- *C. parapsilosis*	3 (8.9%)
- *C. krusei*	1 (2.9%)
- *C. guilliermondii*	1 (2.9%)
Mixed BSI**	14 (19.4%)
- *C. albicans* + *E. faecalis*	6 (42.9%)
- *E. faecalis* + *K. pneumoniae*	3 (21.5%)
- *C. glabrata* + *K. pneumoniae*	2 (14.3%)
- *C. tropicalis* + *K. pneumoniae*	1 (7.1%)
- *E. faecium* + *K. pneumoniae*	1 (7.1%)
- *C. tropicalis* + *E. faecium*	1 (7.1%)

Legend. BSI: bloodstream infections.

*Multidrug-resistant pathogens are summarized in: 8 strains of carbapenemase–producing *K. pneumoniae;* 7 strains of vancomycin-resistant enterococci; among ESBL isolates, 6 strains of *K. pneumoniae*, 4 strains of *E. cloacae*, and 1 strain of *E. coli.* **Isolation of bacteria plus fungi.

TABLE 2. Clinical characteristics of patients with CDI/BSI compared to controls

Variable	CDI/BSI+ n= 72	CDI/BSI– n= 321	p
Age years	74.4 ± 4.3	74.1 ± 5	0.8
Male sex	35 (48.6%)	153 (47.6%)	0.8
Presence of at least 2 comorbidities	72 (100%)	295 (91.9%)	0.07
COPD	30 (41.6%)	121 (37.7%)	0.2
Heart failure	27 (37.5%)	101 (31.4%)	0.08
Diabetes mellitus	31 (43%)	124 (38.6%)	0.07
Neoplasm	15 (20.8%)	63 (19.6%)	0.9
Chronic liver disease	7 (9.7%)	37 (11.5%)	0.8
Neurological disease	24 (33.3%)	93 (28.9%)	0.09
Immunosuppressive therapy			
- Steroids	36 (50%)	79 (24.6%)	**0.001**
- Chemotherapy	5 (6.9%)	16 (5%)	0.3
Chronic renal disease	29 (40.3%)	123 (38.3%)	0.8
IBD	7 (9.7%)	15 (4.7%)	0.05
Severe CDI infection	72 (100%)	150 (46.7%)	**<0.001**
CDI recurrence	60 (83.3%)	95 (29.6%)	**<0.001**
Number of recurrence >1	24 (33.3%)	23 (7.1%)	**<0.001**
Ribotype 027	61 (84.7%)	109 (33.9%)	**<0.001**
Antibiotic therapy (previous 30 days)	62 (86.1%)	275 (85.7%)	0.1
Mean duration of previous antibiotic therapy (days)	10.3 ± 2.6	10.1 ± 3.1	0.6
Antifungal therapy (previous 30 days)	10 (13.9%)	39 (12.1%)	0.7
Mean duration of previous antifungal therapy (days)	6 ± 1.7	5.4 ± 1.3	0.1
Removable intravascular devices			
- CVC	31 (43%)	123 (40.5%)	0.08
- Pacemaker	9 (12.5%)	38 (11.8%)	0.7
Multifocal *Candida* colonization	6 (8.3%)	15 (4.6%)	**0.03**
Abdominal surgery	5 (6.9%)	31 (9.6%)	0.2
TPN	29 (40.3%)	109 (33.9%)	0.08
PPIs therapy	72 (100%)	321 (100%)	1.0
Charlson Comorbidity Index median	3.7 ± 1.5	3.3 ± 1.6	0.1
SOFA score median	3.6 ± 0.8	1.7 ± 0.7	**<0.001**

Legend. BSI: bloodstream infections; COPD: chronic obstructive pulmonary disease; IBD: inflammatory bowel disease; CVC: central venous catheter; CDI: *Clostridium difficile* infection; MDR: multi-drug resistant; ICU: intensive care unit; TPN: total parental nutrition; PPIs: proton pump inhibitors; SOFA: sequential organ failure assessment.

374 **TABLE 3**. Initial antibiotic regimen and outcomes of patients with CDI/BSI compared to controls

Variable	CDI/BSI+ n= 72	CDI/BSI– n= 321	p
Oral vancomycin	61 (84.7%)	262 (81.6%)	0.7
Metronidazole	11 (15.3%)	59 (18.4%)	0.4
Escalation to oral vancomycin + metronidazole	25 (34.7%)	95 (29.6%)	0.1
Oral vancomycin > 500 mg/day	51 (70.8%)	100 (31.1%)	**<0.001**
Transfer to ICU	14 (19.5%)	29 (9%)	**0.002**
Days of ICU stay	16.9 ± 4.4	9.1 ± 4.9	**<0.001**
Days of hospital stay	62.2 ± 21.9	29.3 ± 13.2	**<0.001**
Time at risk for CDI (days)	9.5 ± 1.4	11.1 ± 2.3	0.2
Time at risk for CDI recurrence (days)	20.4 ± 3.3	35.1 ± 6.2	**<0.001**
Severe sepsis or Septic shock	61 (84.7%)	50 (15.7%)	**<0.001**
30-day mortality from CDI diagnosis	28 (38.9%)	42 (13.1%)	**0.001**
Attributable mortality to BSI	41 (56.9%)	-	-
All causes in-hospital mortality	55 (76.3%)	70 (21.8%)	**<0.001**

375 **Legend.** BSI: bloodstream infections; CDI: *Clostridium difficile* infection; ICU: intensive care unit.
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403 **TABLE 4.** Multivariate analysis of factors associated to primary BSI during CDI.

Variable	P	OR	CI (95%)
Ribotype 027	<0.001	6.5	3.99-9.12
CDI recurrence	<0.001	5.5	3.11-11.23
Severe CDI infection	<0.001	8.3	4.76-14.12
Oral vancomycin > 500 mg/day	<0.001	3.1	1.57-4.67

404 **Legend.** BSI: bloodstream infections; CDI: *Clostridium difficile* infection.
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