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ORIGINAL ARTICLE

Risk factors associated with *Clostridium difficile* infection in adult oncology patients

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Abstract
Purpose Clostridium difficile infection (CDI) prevention is particularly important for cancer patients, because diarrhea often results in dose reductions or delays of chemotherapy or radiotherapy. We conducted this study to better ascertain the incidence, susceptibility, and risk factors for CDI in cancer patients receiving chemotherapy at our hospital.
Methods We performed a retrospective study among adult cancer patients admitted at "12 de Octubre" University Hospital between January 2009 through April 2013 who were diagnosed with diarrhea. Inpatient data were available on hospital medical records. We screened by immunochromatography system detecting glutamate dehydrogenase antigen, and *C. difficile* toxins A and B. Later, a polymerase chain reaction for detecting toxin B gene was performed.
Results A total of 225 patients were included in the study, and 39 of them (17.3 %) were diagnosed with CDI. Type of tumor significantly differed between CDI patients, thus relative risk in each type of cancer was calculated after adjusting for age, antibiotic exposure, corticosteroid, and proton-pump inhibitor use. Patients with gastrointestinal tumors were less prone to CDI. Conversely, breast cancer patients have a greater predisposition to CDI. Antibiotic treatment was found to be associated with an increasing risk for CDI in breast cancer patients. Curiously, exposure to proton-pump inhibitors appeared protective in our cohort, except for lung cancer patients. However, we have not been able to find an association between a particular type of chemotherapy and CDI.
Conclusions We underscore the urgent need for early recognition and diagnosis of CDI in cancer patients. Our findings indicate a probable association between antibiotic use and CDI incidence, at least in certain cancer, such as breast cancer.

Keywords Cancer · *Clostridium difficile* infection · Antibiotic use · Risk factors

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Introduction

Clostridium difficile is an opportunistic pathogen predominantly affecting hospitalized patients, although community acquisition has increased in recent years [1–3]. *C. difficile* is a toxin-producing gram-positive anaerobic bacillus that infects the gastrointestinal tract causing a spectrum of disease from asymptomatic colonization to life-threatening toxic megacolon [4]. The capability to form heat-resistant spores is a key feature in its ability to colonize patients and remain in the physical environment for long periods. Whereas the vegetative organism is killed by the acidic gastric environment, the spore form survives. This persistence in a metabolically inactive form facilitates transmission of infection [2, 5].

Advanced age, antibiotic exposure, and comorbidity are independent risk factors described for acquiring *C. difficile* infection (CDI) [6–8]. Thus, cancer patients are at increased risk for CDI, because of their underlying malignancy, exposure to chemotherapy, depressed immune response, and supportive

medications. Furthermore, antibiotics and chemotherapy can each induce alterations of the fecal microbiome [9, 10], and chemotherapeutic agents promote inflammatory changes in the gut, intestinal necrosis, and anaerobic conditions, allowing proliferation of *C. difficile*, whereas leakage of protein into the lumen can inhibit degradation of *C. difficile* toxins [11, 12].

Antineoplasic therapy is a well-documented risk factor for development of CDI, with or without concurrent use of antimicrobials. The incidence of CDI in cancer patients receiving chemotherapy has been reported to be between 2.3 and 7 % with 8.2 % of those cases developing severe enterocolitis [2]. Several specific chemotherapeutic regimens are associated with CDI [13]. Platinum-based chemotherapies, 5-FU, and methotrexate induce severe inflammatory changes in the colonic mucosa, and colonic inflammation causes intestinal necrosis that promotes an anaerobic environment for the *C. difficile* organisms. DNA topoisomerase inhibitors such as irinotecan decrease mucosal epithelium-repairing capacity, and they increase chances of bacterial colonization and frequency of relapsing infections. Moreover, the profound immunological changes due to cancer itself may serve as a risk factor for CDI [14, 15].

The onset of symptoms of CDI may occur immediately after initiation of chemotherapeutic agents, or may be delayed. Fever, abdominal pain, diarrhea, and dehydration commonly seen in patients' post-chemotherapy, period can also be manifestations of CDI, as well. The outbreak of a novel, hypervirulent, resistant strain, NAP-1/027, have further contribute to an increase in prevalence as well as disease severity [16]. Thus, a high index of suspicion for CDI, and early diagnostic and therapeutic interventions are indicated in cancer patients, even without previous antibiotic exposure. Treatment includes general measures such as supportive care and infection control measures. Antibiotic therapy should be initiated as soon as possible. Fecal macrobiota transplantation constitutes another optional treatment for severe/recurrent CDI [17].

Other reported risk factors for CDI include severity of underlying illness, broad-spectrum antibiotic use, administration of proton-pump inhibitors (PPI) [5, 18], neutropenia [19], repeated hospitalizations [20], and steroid treatments [21].

This study aimed to analyze predisposing or associated risk factors for CDI in cancer patients receiving chemotherapy. The identification of potentially modifiable risk factors could lead to a reduction in CDI and most effective interventions in this vulnerable population.

Patients and methods

Patients and clinical data

We performed a retrospective cohort study among hospitalized cancer patients to identify risk factor for CDI. Inpatients at "12 de Octubre" University Hospital between January 2009 through April 2013 who were diagnosed with diarrhea were included. All cancer inpatients with diarrhea (defined as ≥3 stools within a 24-h period that took the shape of a container) underwent testing for the presence of *C. difficile*. Clinical cure was defined as symptom resolution or improved endoscopic findings.

We obtained information regarding patient age, gender, history, pathology, admission diagnosis, medication data, total days of antibiotic therapy, and chemotherapy type. Data were available for all patients on hospital medical records. Chemotherapy exposure 8 to 14 days prior was included in the analysis based on the estimated onset of immunosuppression from those drug exposures.

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by institutional ethics review board.

Laboratory assays

The hospital microbiology laboratory methodology used a 2-stage algorithm: first, we screened by immunochromatography system detecting glutamate dehydrogenase antigen (GDH), and toxins A and B (C. Diff Quik Chek Complete ICT; Inverness Medical Innovations, Inc., Princeton, NJ, USA). The sensitivity and specificity for GDH is 100 and 96.1 %, respectively, and 56.9 and 99.9 % for toxins A and B [22]; later, a polymerase chain reaction for detecting toxin B gene (Xpert C. difficile, Cepheid) was performed when GDH was positive and toxins A and B were negative. This method has a sensibility and specificity up to 99.0 %.

Statistical analysis

Qualitative data were expressed as numbers (percentages) and quantitative data as mean±standard deviation. Univariate analyses were performed using Pearson's χ^2 test or Fisher's exact test when appropriate, and *t*-test was used to analyze continuous variables. To assess whether a given type of cancer, or medical treatment was independently associated with an increased risk (RR) of CDI, Mantel-Haenszel tests were performed to adjust for known or suspected risk factors for CDI, including age, administration of antibiotics, corticosteroid use, and PP inhibitors employ. A P value <0.05 was considered statistically significant.

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software, version 19 (SPSS Inc., Chicago, USA).

Results

Study samples and clinical manifestations

This study included 225 cancer patients admitted for diarrhea to our hospital, from January 2009 through April 2013. Of these patients, 39 (17.3 %) were diagnosed with *C. difficile* infection, six (2.7 %) with *Campylobacter* spp., three (1.3 %) with *Aeromonas* spp., and 4 (1.8 %) with *Salmonella* spp. Clinical characteristics of patients included in this study are described in Table 1.

Patients who suffered more gastrointestinal infections were breast cancer patients (N=19, 35.85 %), and lung cancer patients (N=17, 38.64 %). Clinical findings commonly encountered in all patients include fever (52.4 %), abdominal pain and/or tenderness (37.3 %), and pathological products in stools (mucus, blood, etc.) (9.8 %). These clinical manifestations are not pathognomonic of any single entity, and could be associated with other abdominal conditions.

Given the high incidence of CDI in our cohort, we decided to compare clinical data between cancer patients with CDI (CDI+) and those without CDI (CDI−) (Table 2). With regard to the form of malignancy encountered within the CDI subgroup, four patients (10.3 %) were diagnosed with gastrointestinal cancer, 17 patients (43.6 %) with breast cancer, 11 patients (28.2 %) with lung cancer, three patients (7.7 %) with head and neck cancer, and four patients (10.3 %) with other solid tumors (Fig. 1a). The mean age at the time of admission was 62.7±12.8 years old (range 24 to 85), and the mean age of CDI diagnosed patients were 59.2±14.3 (range 24 to 81). Although the group of patients with CDI was younger, there were no statistically significant differences with all other patients included in this study (t-test, P=0.059). Most of the patients in the study had stage III or IV tumor (97 %).

In our cohort, CDI was more prevalent in women than in men (P=0.045). Type of tumor significantly differed between CDI patients and patients no diagnosed of CDI, finding significant differences in both gastrointestinal and breast tumors, with others cancer patients (Fig. 1b, c). Thus, relative risk

Table 1 Clinical characteristics of 225 cancer patients with diarrhea diagnostic

	Gastrointestinal	Breast	Lung	Head and neck	Others
N (%)	75 (33.3)	53 (23.5)	44 (19.5)	14 (6.2)	39 (17.3)
Age (mean±SD)	63.9±11.4	62.2±12.8	62.4±12.7	64.3±6.4	60.8±16.9
Range	(35.8–81.1)	(32.5–82.6)	(26.5–83.0)	(49.2–74.1)	(24.1–84.7)
Gender (male/female)	49/26	0/53	31/13	13/1	32/7
Fever, *N* (%)	33 (44.0)	32 (60.4)	22 (50.0)	8 (57.1)	23 (59.0)
Abdominal pain, *N* (%)	31 (41.3)	21 (39.6)	11 (25.0)	8 (57.1)	13 (33.3)
Diarrhea grade, *N* (%)					
I+II	36 (48.0)	28 (52.8)	25 (56.8)	9 (64.3)	20 (51.3)
III+IV	39 (52.0)	25 (47.2)	19 (43.2)	5 (35.7)	19 (48.7)
Use of antibiotics, *N* (%)	10 (13.3)	22 (41.5)	6 (13.6)	5 (35.7)	4 (10.3)
Use of corticosteroid, *N* (%)	11 (14.7)	7 (13.2)	16 (36.4)	2 (14.3)	8 (20.5)
Use of PP inhibitors, *N* (%)	41 (54.7)	19 (35.8)	29 (65.9)	6 (42.9)	12 (30.8)
Length of hospital stay (days±SD)	10.4±8.8	10.9±8.8	9.9±4.7	14.6±8.4	15.7±15.2
Infections, N (%)					
CDI+	4 (5.3)	17 (32.1)	11 (25.0)	3 (21.4)	4 (10.3)
Other infections	2 (2.7)	2 (3.8 %)	6 (13.6)	0	3 (7.7)
Chemotherapy, *N* (%)					
Platinum based	0	0	1 (2.3)	2 (14.3)	0
Taxane	1 (1.3)	4 (7.5)	0	0	6 (15.4)
5-FU/capecitabine	10 (13.3)	1 (1.9)	0	0	0
TKIs	2 (2.7)	1 (1.9)	4 (9.1)	0	2 (5.1)
Others	0	4 (7.5)	7 (15.9)	2 (14.3)	5 (12.8)
Combination	58 (77.3)	39 (73.6)	31 (70.5)	8 (57.1)	15 (38.5)
Prior lines of treatments, *N*					
0–2 (CDI+/CDI−)	3/60	9/23	9/28	1/8	3/33
>2 (CDI+/CDI−)	1/11	8/13	2/5	2/3	1/2

PP proton pump, *TKIs* tyrosine kinase inhibitors

Table 2 Clinical characteristics of patients with (+) and without (−) *Clostridium difficile* infection (CDI)

Variable	CDI−, No. of patients (%), *N*=186	CDI+, No. of patients (%), *N*=39	
Gender (male/female)	109/77	16/23	*P*=0.045
Age (>65)	90 (48.4 %)	15 (38.5 %)	*P*=0.292
Length of hospital stay (days±SD)	11.09±9.64	14.08±10.33	*P*=0.083
Tumor			
Gastrointestinal	71 (38.2 %)	4 (10.3 %)	*P*=0.001
Breast	36 (19.4 %)	17 (43.6 %)	*P*=0.003
Lung	33 (17.7 %)	11 (28.2 %)	*P*=0.181
Head and neck	11 (5.9 %)	3 (7.7 %)	*P*=0.715
Others	35 (18.8 %)	4 (10.3 %)	*P*=0.249
Symptom			
Fever	93 (54.4 %)	25 (67.6 %)	*P*=0.200
Abdominal pain	69 (40.6 %)	15 (40.5 %)	*P*=0.996
Pathological products in stools	17 (9.1%)	5 (12.8%)	*P*=0.557
Antibiotic use	31 (16.7 %)	16 (41.0 %)	*P*=0.005
Corticosteroid use	34 (20.0 %)	10 (27.0 %)	*P*=0.377
PP inhibitor use	95 (51.1 %)	12 (30.8 %)	*P*=0.018
Severe complications	34 (18.3 %)	13 (33.3 %)	*P*=0.050
Chemotherapy (Monotherapy or combination)			
Irinotecan	19 (10.7 %)	1 (2.6 %)	*P*=0.136
Platinum	77 (43.5 %)	20 (51.3 %)	*P*=0.381
Taxane	49 (27.7 %)	16 (41.0 %)	*P*=0.123
5-FU/capecitabine	33 (18.6 %)	3 (7.7 %)	*P*=0.152
TKI	49 (27.7 %)	8 (20.5 %)	*P*=0.426
Chemotherapy			
Irinotecan monotherapy	0	0	
Irinotecan combination	19 (10.2 %)	1 (2.6 %)	
Platinum monotherapy	31 (16.7 %)	6 (15.4 %)	*P*=0.450
Platinum combination	46 (24.7 %)	14 (35.9 %)	
Taxane monotherapy	14 (7.5 %)	4 (10.3 %)	*P*=0.782
Taxane combination	35 (18.8 %)	12 (30.8 %)	
5-FU, monotherapy	4 (2.2 %)	0	*P*=0.522
5-FU, combination	29 (15.6 %)	3 (7.7 %)	
TKI monotherapy	17 (9.1 %)	6 (15.4 %)	*P*=0.051
TKI combination	32 (17.2 %)	2 (5.1 %)	

PP proton pump, *TKIs* tyrosine kinase inhibitors

(RR) of CDI in each type of cancer was calculated. Tables 3, 4, and 5 show relative risk of CDI in gastrointestinal, breast, and lung cancer patients, respectively, after adjusting for age, antibiotic exposure, corticosteroid, and PP inhibitor use. Surprisingly, patients with gastrointestinal tumors were less prone to CDI. Moreover, our results show that these patients seem protected against CDI (Table 3). Conversely, breast cancer patients have a greater predisposition to CDI (Table 4). But these results should be taken with caution because of the higher number of gastrointestinal and breast cancer patients included in the study.

CDI patients had more severe complications than patients without this infection, but there was only a borderline statistical significance (*P*=0.05, Table 2).

There were 15 deaths resulting from any cause in our cohort of patients, and five of them were diagnosed as having CDI. Only one death could be attributed to CDI in a patient diagnosed with head and neck carcinoma, who developed toxic megacolon. However, it is especially difficult to objectively determine precise CDI-related mortality rates because of factors such as underlying patient condition.

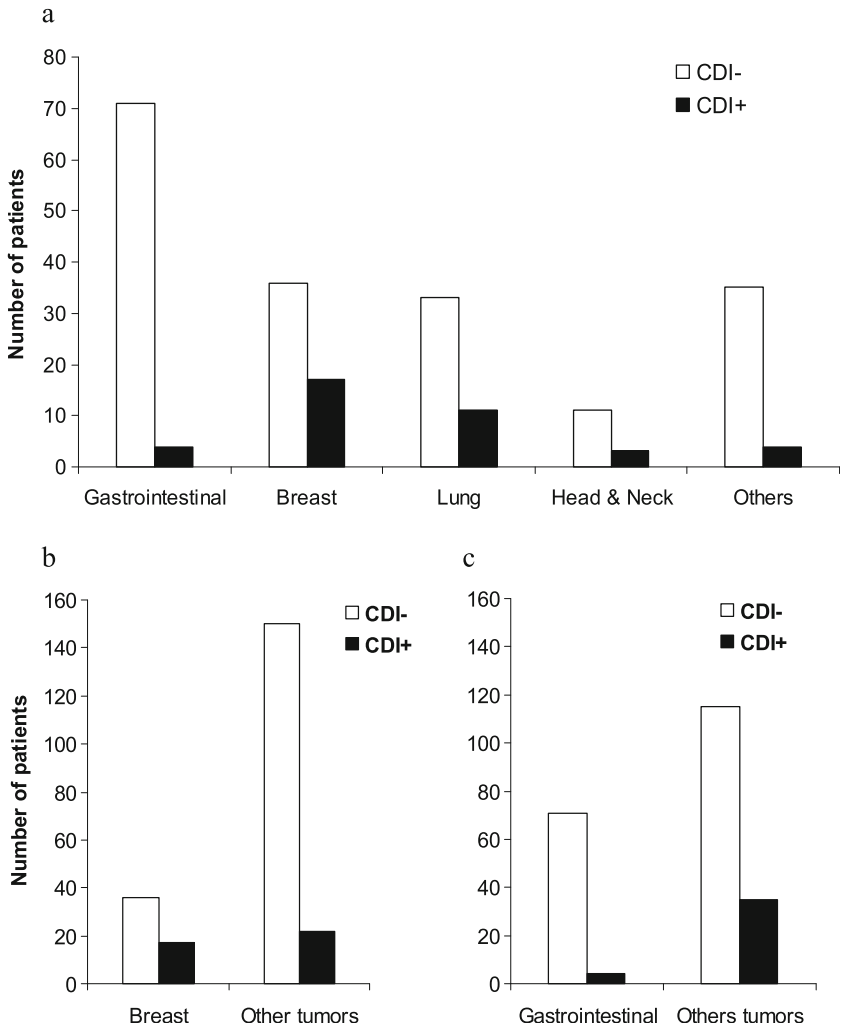

Fig. 1 **a** Incidence of CDI among patients diagnosed with different types of cancer. **b** Incidence of CDI in breast cancer patients as compared to patients with other cancers, and **c** in patients with gastrointestinal tumors

Antibiotics pretreatment and CDI

Patients with breast, and head and neck cancers were more frequently treated with broad-spectrum antibiotics (41.5 and 35.7 %, respectively), compared with other cancer patients (Table 1). Types of antibiotics used and duration of antibiotic consumption did not differ significantly among groups of patients ($P<0.05$). However, antibiotic treatment within 30 days prior to CDI testing was found to be associated with an increasing risk for CDI, with a RR of 3.48 (95 % confidence interval (CI)=1.65–7.31) (Table 2).

Curiously, four (40 %) of 10 patients with gastrointestinal tumors who were pretreated with antibiotic suffered CDI, and nevertheless, there were no gastrointestinal tumor patients with CDI and without antibiotic pretreatment. Of the patients pretreated with antibiotic (N=47), seven of 22 (31.8 %) breast

Table 3 Relative risk of *C. difficile* infection (CDI+) in gastrointestinal cancer patients compared to patients with other cancers

Adjusted for	Gastrointestinal cancer		Other cancer		
	CDI−, *N* (%)	CDI+, *N* (%)	CDI−, *N* (%)	CDI+, *N* (%)	RR (95 % CI)
None (unadjusted)	71 (94.7 %)	4 (5.3 %)	115 (76.7 %)	35 (23.3 %)	0.18 (0.06–0.54)
Age (>65)	35 (94.6 %)	2 (5.4 %)	55 (80.9 %)	13 (19.1 %)	0.19 (0.06–0.55)
Antibiotic exposure	6 (60.0 %)	4 (40.0 %)	25 (67.6 %)	12 (32.4 %)	0.21 (0.07–0.64)
Corticosteroid use	9 (81.8 %)	2 (18.2 %)	25 (75.8 %)	8 (24.2 %)	0.20 (0.07–0.59)
PP inhibitor use	40 (97.6 %)	1 (2.4 %)	55 (83.3 %)	11 (16.7 %)	0.19 (0.06–0.57)

PP proton pump

Table 4 Relative risk of *C. difficile* infection (CDI+) in breast cancer patients compared to patients with other cancers

Adjusted for	Breast cancer		Other cancer		
	CDI−, *N* (%)	CDI+, *N* (%)	CDI−, *N* (%)	CDI+, *N* (%)	RR (95 % CI)
None (unadjusted)	36 (67.9 %)	17 (32.1 %)	150 (87.2 %)	22 (12.8 %)	3.22 (1.55–6.81)
Age (>65)	16 (59.3 %)	11 (40.7 %)	80 (86.0 %)	13 (14.0 %)	3.29 (1.58–6.84)
Antibiotic exposure	15 (68.2 %)	7 (31.8 %)	16 (64.0 %)	9 (36.0 %)	2.25 (1.07–4.72)
Corticosteroid use	6 (85.7 %)	1 (14.3 %)	28 (75.7 %)	9 (24.3 %)	3.12 (1.46–6.66)
PP inhibitor use	14 (73.7 %)	5 (26.3 %)	81 (92.0 %)	7 (8.0 %)	2.73 (1.27–5.87)

PP proton pump

cancer patients, three of six (50 %) lung cancer patients, and one of five (20 %) head and neck cancer patients were diagnosed with CDI. In the whole cohort, relative risk of CDI in patients pretreated with antibiotics was 3.48 (95 % CI=1.65–7.33), compared with no antibiotic exposure. Relative risk of CDI in gastrointestinal, breast, and lung cancer patients adjusted by antibiotic exposure is shown in Table 3 (RR=0.21, 95 % CI=0.07–0.64), Table 4 (RR=2.25, 95 % CI=1.07–4.72), and Table 5 (RR=2.21, 95 % CI=0.96–5.06), respectively.

Acid suppression and CDI

Hypochlorhydria has been implicated in the transmission of *C. difficile*. In our cohort, there were significant differences between patients exposed and no exposed to gastric acid suppression and CDI (Table 2). But curiously, exposure to PP inhibitors appeared protective (RR=0.41, 95 % CI=0.19–0.86). However, only 12 (30.8 %) of 39 patients who developed CDI were exposed to acid suppression, and six patients of those exposed to acid suppression who developed CDI had also received antibiotic pretreatment.

The use of PPI was more frequent among lung cancer patients (65.9 %) and gastrointestinal cancer patients (54.7 %). Curiously, only in lung cancer patients the relative risk of CDI was increased when adjusted by use of PP inhibitors (Table 5, RR=2.62, 95 % CI=1.11–6.15).

Chemotherapy and CDI

The majority of patients (90.22 %) included in this study had received chemotherapy within 2 weeks prior to their inpatient diarrhea, and also most of patients CDI diagnosed (92.31 %). However, we have not been able to find an association between a particular type of chemotherapy and CDI (Table 2). Most patients with CDI had receiving platinum and taxane-based therapies (51.3 and 41.0 %, respectively). Curiously, it appears that the use of tyrosine-kinase inhibitors (TKIs) in combination with cytotoxic drugs have a weak protective effect (RR=0.177, 95 % CI=0.03–0.97).

Discussion

We have investigated CDI risk factors in patients with cancer. Despite a potential decrease in the incidence of CDI in recent decades, this infection still contributes substantially to morbidity and possibly mortality in this vulnerable patient population [8]. Rapid and sustained resolution of CDI is particularly important for cancer patients, because diarrhea often results in dose reductions or delays of chemotherapy or radiotherapy [2, 23, 24]. The diagnosis of CDI is not always simple and is based on a combination of clinical symptoms and laboratory finding. Diarrhea is the most common manifestation of CDI. Fever, cramping, and abdominal discomfort are

Table 5 Relative risk of *C. difficile* infection in lung cancer patients compared to patients with other cancers

Adjusted for	Lung cancer		Other cancer		
	CDI−, *N* (%)	CDI+, *N* (%)	CDI−, *N* (%)	CDI+, *N* (%)	RR (95 % CI)
None (unadjusted)	33 (75.0 %)	11 (25.0 %)	153 (84.5 %)	28 (15.5 %)	1.82 (0.83–4.02)
Age (>65)	20 (74.1 %)	7 (25.9 %)	76 (81.7 %)	17 (18.3 %)	1.76 (0.79–3.89)
Antibiotic exposure	3 (50.0 %)	3 (50.0 %)	28 (68.3 %)	13 (31.7 %)	2.21 (0.96–5.06)
Corticosteroid use	11 (68.8 %)	5 (31.3 %)	23 (82.1 %)	5 (17.9 %)	1.80 (0.79–5.01)
PP inhibitor use	25 (86.2 %)	4 (13.8 %)	70 (89.7 %)	8 (10.3 %)	2.62 (1.11–6.15)

PP proton pump

common [25]; however, they occur in less than 50 % of patients, in our cohort.

Similarly to other works [20], we did not find poor outcomes from CDI among cancer patients. Women were more affected with CDI (P=0.045), but this is probably a bias due to the large group of women with breast cancer included in this study.

Although there were differences in CDI susceptibility according to type of cancer (gastrointestinal and breast mainly), samples sizes were too small to draw conclusions. Also, the number of gastrointestinal and breast cancer patients is high compared with other cancer patients included in our cohort, which may be a confounding factor in the statistical analysis, and these results should be taken with caution. The lower CDI incidence in gastrointestinal cancer patients may be due to better or special care of the digestive tract in these patients. On the other hand, the number of gastrointestinal cancer patients may be increased due to the inclusion criteria of the study and the special features of this disease (site-specific tumor, prior surgery, etc.).

Like others [6–8, 10, 26], we also identified an increased risk of CDI associated with exposure to antibiotics. However, up to 80 % of cancer patients in our cohort do not have documented antibiotic exposure prior to presentation of CDI.

Surprisingly, a decreased risk for CDI associated with exposure to PPIs was found in our cohort, except in the subgroup of lung cancer patients. We must point out that lung cancer patients were the subgroup greatest exposed to PP inhibitors (65.9 %). Although most studies have shown that exposure to PP inhibiting agents increases the likelihood of developing CDI [18], the data has been ambiguous. Two separates meta-analyses of observational studies examining the risk of CDI from PPI use have been published recently [26, 27]. In both revisions, substantial statistically and clinically significant heterogeneity among the studies included was found that was not explained by subgroup or sensitivity analyses. Thus, although PPI use has been described as a risk factor for CDI, the strength of the association was weak and was based on observational studies of lower quality with potentially unmeasured comorbidity and risk factors in PPI-treated patients and a risk for confounding by indication [28].

Unnecessary use and overuse of PPIs have been well-documented in adults [5, 29], and it is biologically plausible that an increase in barrier function of the gastric environment could put one at risk for CDI. But, exposure to acid suppression may be under-reported due to its availability as an over-the-counter product. On the other hand, antibiotics appear to act synergistically with PPIs [5]. Our study supports the possibility of a protective effect from exposure to PPIs although the reason for the effect is not clear. Further investigations should focus on trying to delineate a mechanism for this differential effect of acid reducing agents on the risk for CDI.

Chemotherapy has been shown to perturb fecal microbiota, leading to conditions that promote the incidence and severity of CDI and simultaneously hinder its resolution [9, 11, 12]. The great majority of patients included in this study were exposed to chemotherapy before the onset of diarrhea symptoms. But, our analysis did not show that exposure to a particular chemotherapy agent increased the risk of CDI. Conversely, the use of TKIs in combination with cytotoxic chemotherapy showed a protective trend for CDI. Whether cancer alone, without chemotherapy can lead to CDI is unknown. The profound immunological changes due to cancer itself may serve as a risk factor [14, 15]. In a number of systemic review [2, 30], several chemotherapeutic regimens are linked to the development of CDI, such as 5-fluorouracil, DNA topoisomerase inhibitors, cisplatin, paclitaxel, and carboplatin, among others. Regarding the treatment, most patients with CDI underwent platinum and taxane-based therapies (Table 2), however, and similar to others [15, 25], no significant differences were found compared with patient without CDI, in our study. Regardless of this, clinicians caring for patients with solid tumors who receive these and other mucositis-producing agents should consider CDI in their differential diagnosis when the patients present with diarrhea.

How chemotherapeutic agents modulate the risk of broad spectrum antibiotics promoting CDI development is uncertain factor that may unequally affect certain cancer patients more than others [20]. Treatment of post-chemotherapy patients who develop CDI is complicated by their generalized illness, presence of oral/gastrointestinal mucositis, and nausea after chemotherapy.

Furthermore, not only can chemotherapy cause diarrhea, but also non-CDC opportunistic infections are an additional frequent etiology. In our reports, there were 13 patients (5.78 %) with other enteric infections, creating a clinical scenario very similar to CDI. Thus, testing such patients for *C. difficile* represents the safest care plane.

Other potentially important risk factors, such as a history of CDI, laboratory-defined neutropenia or clinically defined mucositis, and the use of radiation were not available and should be investigated in future studies. On the other hand, variability in host factors may explain the wide spectrum of symptoms and course of CDI in cancer patients.

Our study has several limitations, including its retrospective nature and several methodological limitations. It should be noted that retrospective analysis such as this are hypothesis-generating, and causality of associations cannot be determined. In addition, there is a possibility that selection bias influenced the significance of our findings. When interpreting the findings of this study, it is necessary to consider the influence of confounding factors that were not included in the analytical models. Our study is from a single institution and has a small sample size, which limits the extension of our findings to the general population. Others authors have found

that a *C. difficile* diagnosis based on laboratory results alone overestimates the incidence of CDI [31]. Further research including a larger sample size and prospective methodology, assessment of additional risk factors for CDI in cancer patients, are necessary.

Our findings suggest that reduced exposure to antibiotics, a well-known and potentially modifiable risk factor, might lead to reduced CDI in cancer patients. By modifying certain risk factors among cancer patients, we may then reduce morbidity, and possibly also expense and mortality, from CDI.

We would like to emphasize the importance of judicious use of antibiotics even in a population at high risk for invasive bacterial infection. Additional studies also are necessary to further investigate the role of immunosuppression to confirm the variation in risk for CDI associated with acid blockade agents, to identify potential interventions for reducing CDI risk after chemotherapy administration, and to compare the effectiveness of newer *C. difficile* active agents in patients with cancer.

Conflict of interest The authors have no conflicts of interest to disclose.

The authors have had full control of all primary data for the study, and they agree to allow the journal to review their data if requested.

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