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Risk Factors for *Clostridium Difficile* Colitis in Patients Undergoing Treatment for Gynecologic Cancer

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Abstract

Objectives: Clostridium Difficile Associated Diarrhea (CDAD) is a common potentially dangerous complication of treatment for gynecologic cancers and is an important metric for quality of hospital care. We evaluated risk factors associated with CDAD in gynecologic oncology patients.

Design: Retrospective chart review

Setting: Inpatient gynecologic oncology ward

Patients: Women with histological confirmation of a gynecologic malignancy admitted for >24 hours were abstracted at a tertiary referral center over four years. Both surgical and medical admissions included.

Methods: Details regarding health status and treatments were abstracted. Diagnosis of CDAD was made witha positive PCR result. Standard statistical tests were used.

Results: A total of 728 women were included. Fifteen patients had positive PCR proven CDAD (2.01%). In bivariate analysis, cephalosporin exposure (OR 0.21, 95% CI 0.06-0.74) and surgical admission (OR 0.28, 95% CI 0.09- 0.87) were associated with decreased risk of CDAD. Platinum based chemotherapy use (OR 3.61, 95% CI 1.29-10.13), radiation therapy (OR 6.82, 95% CI 1.81-25.7), and early stage (OR 3.59, 95% CI 1.26-10.21) were associated with increased risk of CDAD. In logistic regression analysis, chemotherapy use (aOR 5.7, 95% CI 1.91-17.10) and early stage disease (aOR 5.7, 95% CI 1.22-11.05), were found to be independent predictors of CDAD. Cephalosporin use was independently found to be associated with decreased risk of CDAD (aOR 0.20, 95% CI 0.05-0.75).

Conclusions: Platinum based chemotherapies and early stage disease are significant risk factors for the development of CDAD in gynecologic oncology patients. Attention to these risk factors is warranted to prevent the dangerous sequelae of infection with this organism.

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Introduction

Clostridium Difficile Associated Diarrhea (CDAD) is an increasingly common organism diagnosed in hospital in patient populations and is viewed as an important metric for the quality of hospital care. *C. difficile* is a gram-positive, anaerobic bacillus that forms notably resilient spores with the primary route of transmission via the fecal-oral route. While most carriers of *C. difficile* are asymptomatic, colonization with this microbe can result in CDAD, characterized by pseudomembranous plaques lining the colon and profuse, foul smelling diarrhea. *C. difficile* spores are resistant to many of the hand sanitizers used frequently in hospital settings and susceptible only to thorough hand washing with bactericidal agents.

As of 2007, *C. difficile* was the leading national cause of gastroenteritis-associated deaths [1]. A recent national study showed that in 2011, approximately half a million new cases of *C. difficile* were diagnosed, and this organism was associated with almost 30,000 deaths [2]. *C. difficile* is now the most common hospital acquired infection in the United States [3]. Furthermore, this organism poses a considerable economic burden; increased costs associated with acute care facilities alone in the United States are upwards of 4 billion dollars annually [3,4].

Known factors that increase risk of *C. difficile* infection include age greater than 65, female gender, and white race [2]. Other documented characteristics that increase risk of *C. difficile* infection include prolonged hospital stay, immunocompromised status, and exposure to broad spectrum

Table 1: Risk factors for development of *Clostridium Difficile* Associated Diarrhea (CDAD) in gynecologic cancer patients.

Variable	CDAD n=15 Mean +/-SD or %	No CDAD n=713 Mean +/-SD or %	OR (95% CI) or P value
Age (years)	62.7 +/- 11.1	60.0 +/- 11.6	0.863
Body mass index (kg/m2)	27.5+/- 6.0	27.0 +/- 8.1	0.950
Malignancy diagnosis			0.036
Cervical	20.0%	10.8%	--
Uterine	60.0%	31.5%	--
Ovarian/fallopian tube/peritoneal	20.0%	54.0%	--
Vulvar/vaginal	0%	3.6%	--
Early stage (I-II)	**60.%**	**29.5%**	**3.6 (1.26-10.2)**
Comorbidities			
Hypertension	53.3%	49.5%	1.17 (0.42-3.25)
Diabetes mellitus	6.7%	15.6%	0.39 (0.05-2.98)
Coronary artery disease	0%	6.3%	--
Asthma	13.3%	14.9%	0.88 (0.20-3.0)
Gastroesophageal reflux	66.7%	39.4%	3.08 (1.04-9.09)
Rheumatologic disease	0.0%	6.6%	--
Chronic kidney disease	6.7%	39.4%	1.11 (0.14-8.67)
Hepatic disease	13.3%	3.8%	3.91 (0.84-18.2)
Coagulopathy	26.7%	11.8%	2.72 (0.85-8.74)
Hypothyroidism	6.7%	6.0%	1.11 (0.14-8.67)
Anemia	40.0%	22.2%	2.34 (0.82-6.70)
Hyperlipidemia	26.7%	21.9%	1.30 (0.41-4.13)
Ulcerative colitis	0%	0.6%	--
Crohn's disease	6.7%	0.4%	17.0 (1.70-172.7)
Hospitalization factors			
NG tube	26.7%	19.7%	1.46 (0.47-4.74)
Hospital admission number	2.0+/- 1.3	2.0+/-2.2	0.355
Surgical admission	**26.7%**	**56.9%**	**0.28 (0.09-0.87)**
Radiation within the past month	**20.0%**	**3.5%**	**6.82 (1.81-25.7)**
Neutropenic	6.7%	6.5%	1.03 (0.13-8.02)
Colostomy present	20.0%	12.1%	1.82 (0.50-6.58)
Total parenteral nutrition	13.3%	8.7%	1.61 (0.36-7.32)

antibiotics, cytotoxic drugs, and proton pump inhibitors [5]. The additional morbidity imposed by *C. difficile* infection is potentially devastating, especially when imposed on patients that are at a baseline compromised health status. One of the most severe complications of *C. difficile* infection is toxic megacolon requiring colectomy. A recent study found that the number of colectomies due to *C difficile* colitis is increasing nationally, and the mortality associated with these procedures is 30% [6].

Gynecologic oncology patients are at especially high risk for infection with *C. difficile* due to the presence of many of these known risk factors. However, while there is no shortage of literature on *C. difficile* infection in various hospital populations, there is little data specific to women diagnosed with gynecologic malignancies. The purpose of this study was to identify aspects of care that increase risk for developing *C. difficile* cololitis in order to enable us to modify our standards of care to reduce risk in our gynecologic oncology inpatient population.

Methods

Institutional review board approval was obtained through the Colorado Multiple Institutional Review Board (COMIRB). A retrospective chart review of all inpatient admissions to the gynecologic oncology service in a single institution from September 2011 through March 2015 was conducted. Both medical and surgical admissions were included. Exclusion criteria included absence of biopsy proven malignancy, admission for less than 24 hours, and lack of laboratory confirmation of *C. difficile* infection. A team of medically trained researchers conducted a detailed review of individual charts. Specific definitions for each variable collected were distributed to each research assistant prior to initiation of data collection. Data was abstracted for elements of care including patient demographic, admission, disease and treatment information.

Basic demographic information and details regarding patients' overall state of health were collected for each individual patient. Age,

Table 2: Medication exposure as a risk factor for *Clostridium Difficile* Associated Diarrhea (CDAD) in gynecologic cancer patients.

Variable	CDAD	No CDAD	OR (95% CI)
Proton pump inhibitor	93.3%	73.8%	5.0 (0.65-38.1)
Corticosteroid	13.3%	20.3%	0.60 (0.13-2.70)
Antimicrobials°			
Cephalosporins	20.0%	54.7%	0.21 (0.60-0.74)
Penicillin	6.7%	10.8%	0.59 (0.78-4.55)
Fluoroquinolone	26.7%	11.9%	2.69 (0.84-8.62)
Carbanepenem	6.7%	1.8%	3.85 (0.47-31.50)
Vancomycin	26.7%	15.0%	2.06 (0.64-6.69)
Clindamycin	6.7%	9.4%	0.70 (0.90-5.32)
Sulfonamide	6.7%	6.9%	1.0 (0.13-7.50)
Nitrofurantoin	26.7%	13.9%	2.25 (0.70-7.22)
Chemotherapeutics§			
Platinum	46.7%	19.5%	3.61 (1.23-10.13)
Taxane	20.0%	16.8%	1.24 (0.34-4.44)
Avastin	6.7%	3.4%	2.05 (0.26-16.24)

° -Antimicrobials including monobactams, macrolides, tetracyclines, fluconazole, and linezolid were associated with 0% of CDAD cases.

§ -Chemotherapies including pegylated liposomal doxorubicin, topotecan, and gemcitabine were associated with 0% of CDAD cases.

body mass index, histologic diagnosis, and disease stage and status were noted. Medical comorbidities were also examined in detail. Comorbidities were collected based on the patient's diagnoses as per admission problem list at time of admission. If a comorbidity, such as anemia, had previously existed but resolved during dates of admission, it was not listed as positive in the patient's data for that particular admission. Other variables relevant to patient disease and health outcomes, such as albumin level, were also extracted.

Elements of treatment and care during inpatient admissions were also collected. Variables extracted were duration of admission, surgical versus medical admission, and chief complaint or reason for admission. Aspects of treatment during course of care noted were inpatient administration of proton pump inhibitors, total parenteral nutrition and corticosteroids, use of nasogastric tube, and recent exposure to chemotherapy or radiation therapy. Antimicrobial therapy was recorded according to drug class. Diagnosis of *C. Difficile* toxin presence was documented only if there was a laboratory confirmed positive polymerase chain reaction result in the institution's electronic medical record system and associated symptoms of diarrhea.

The primary outcome was to examine the elements of treatment, health and disease status, and inpatient admission that independently predicted infection with *C. difficile* in gynecologic oncology patients. Statistical analysis was performed with IBM SPSS statistics version 21. Statistical significance was estimated with chi-square tests for dichotomous and categorical variables and Student's t-tests were used to compare continuous variables. Multivariable analyses were used to determine factors that were independently associated with positive *C. difficile* infection. Variables significant in bivariate analyses were included in the multivariable model. For all tests, a p value of <.05 was considered statistically significant.

Results

A total of 728 women fit inclusion criteria and were included in the analysis (mean age 60, range 21-87). Demographic data are shown in (Table 1). A total of 15 patients had positive PCR proven *C. difficile* infection (2.01%). In terms of demographic and clinical characteristics, neither age nor BMI were associated with increased risk of diagnosis with CDAD.

Cancer diagnoses included cervical (11.0%), uterine/endometrial (32.1%), ovarian/fallopian tube/primary peritoneal (53.3%), and vulvar/vaginal (3.5%).

Early stage disease was significantly associated with increased risk of CDAD (p <0.005; OR 3.60, CI 1.26-10.2). Exposure to treatments for malignancy including chemotherapeutics and radiation was analyzed. Notably, platinum agents (p<0.01; OR 3.61, 95% CI 1.29-10.13) were associated with increased risk of CDAD. Neither taxanes nor bevacizumab were associated with increased risk of CDAD. Pelvic radiation within a month of admission was also associated with increased risk of developing CDAD (p <0.02; OR 6.82, 95% CI1.81-25.7).

Exposure to different classes of medication was also analyzed. Neither use of PPI or corticosteroid exposure was associated with increased risk of hospital acquired CDAD. Multiple different classes of antibiotics were examined independently. Cephalosporins were the most commonly represented antibiotics, and they were associated with decreased risk of CDAD (p <0.01; OR 0.21, 95% CI 0.06-0.74). Penicillins, fluoroquinolones, carbanepenems, vancomycin, clindamycin, sulfonamides, and nitrofurantoin were not statistically associated with increased risk of CDAD.

Multiple medical comorbidities were extracted, and none of the comorbidities examined were associated with increased risk of CDAD. Gastroesophageal reflux disease was not associated with CDAD at a statistically significant level (p = 0.058; OR 3.08, CI 1.04-9.09) although 66.7% of patients positive for CDAD in our study did carry this diagnosis. Other gastrointestinal comorbidities including Crohn's disease or presence of a colostomy were also not statistically associated with CDAD. Cardiovascular comorbidities such as hypertension and hyperlipidemia were not associated with increased risk for CDAD. Diabetes mellitus, chronic kidney disease, and hepatic disease were not found to be statistically associated with CDAD. Neutropenia was also not found to be a statistically significant risk factor for acquisition of CDAD.

Other aspects of inpatient hospital admission thought to potentially have an impact on risk of acquiring CDAD were also analyzed. Neither hospital admission number nor length of stay was associated with increased risk of CDAD. Surgical admission did show a protective association towards CDAD (p = 0.032; OR 0.28, 95% CI 0.09-0.87). Neither use of total parenteral nutrition nor nasogastric tube showed increased association with CDAD.

Following logistic regression analysis, platinum agents (p = 0.02; aOR5.7, 95% CI 1.91-17.10), early stage disease (p <0.01; aOR 5.7, 95% CI 1.22-11.05), and cephalosporins (p = 0.02; aOR 0.20, 95% CI 0.05-0.75) all retained their significant associations.

Discussion

The purpose of this study was to examine factors independently associated with inpatient diagnosis of *C. difficile* infection, and information was abstracted regarding both intrinsic and modifiable factors. The aim of our study was to identify components of care that put our patients at increased risk for this potentially devastating

condition in order to enable us to modify our standards of care to reduce risk in our gynecologic oncology inpatient population.

Many modifiable risk factors have been identified in patient populations outside of gynecologic oncology. Administration of several classes of medications has been specifically associated with higher rates of *C. difficile* infection. Antibiotic and PPI exposure are frequently cited as a risk factor for acquisition of *C. difficile* infection [7-10]. Notably, our study found antibiotic exposure to have either a protective or insignificant effect, depending on class. Although the majority of patients with CDAD had been prescribed PPIs while inpatients, there was not a statistically significant association between these agents and CDAD amongst our population. Anti-neoplastics have also been shown to increase risk for CDAD [9,11]. Exposure to chemotherapeutics is a common risk factor amongst gynecologic patients. Carboplatin and paclitaxel, the two most common agents used in gynecologic oncology, have been associated with especially morbid presentations of CDAD [12]. The findings in our study were consistent with those of many others in that platinum agents were significantly associated with a higher risk of CDAD. While platinum agents will remain as an integral component of the care we provide our gynecologic cancer patients, this finding serves to reinforce a high index of suspicion for CDAD in women who present with diarrhea after receiving chemotherapy. Our study also found that radiation within the past month is associated with increased risk of CDAD. This association has not previously been demonstrated amongst cancer patients receiving radiation with the exception of occasional case reports [13] and those with head and neck malignancies [14]. A well-known potential side effect of pelvic radiation is diarrhea or radiation proctitis; however, findings of our study indicate that there should also be a high index of suspicion for CDAD in patients who have recently been treated with radiation. Other than early stage disease, our study found that most intrinsic risk factors, such as medical comorbidities, were not associated with increased risk of CDAD.

Investigation into both intrinsic and iatrogenic factors leading to increased risk of acquiring *C. difficile* infection during inpatient admission is relevant because this hospital acquired infection is becoming increasingly prevalent in hospitals across the country. Inpatient populations are at unacceptably high risk for colonization with the organism. Studies have shown that bacterial spores which are acquired via fecal-oral transmission can be detected in greater than 50% of patients hospitalized for 4 weeks in an inpatient facility [15]. The national estimated incidence of asymptomatic colonization of *C. difficile* is 2%; however, the estimated rate of colonization in patients with exposure to health care facilities is much higher at approximately 25% [16]. The 2% infection rate documented amongst the patients followed in our study was much lower than the national average for healthcare associated *C. difficile* colonization; however, only symptomatic patients were screened for the microbe. Additionally, many *C. difficile* infections are diagnosed in an outpatient community setting, even if the infection was initially acquired during an inpatient admission. One of the weaknesses of this study is that we did not capture the patients presenting with CDAD outside of the inpatient admission [2,17].

This study was designed as a retrospective review of a specific population at a single institution, which enabled us to analyze treatment course and outcomes with a rare degree of detail. Some of the benefits of performing a study at a single institution include consistency amongst the physician providers as well as a presumed baseline equivalent risk of colonization with *C. difficile*, an important consideration when the primary outcome is related to an infectious agent. However the design of this study did result in an overall statistical under-powering due to the rare nature of our primary outcome. The overall rate of colonization amongst patients tested was much lower than anticipated based on national statistics. While this is a testament to infection control at the institution studied, the results might not be generalizable to populations with a higher incidence of infection or exposure to a more virulent strain of *C. difficile*.

Overall, this study lends important insight into factors that might affect risk of acquiring CDAD in gynecologic oncology inpatient populations. Providers are encouraged to continue to carefully consider the risks and benefits of pharmacologics used during admissions. Patients who are noted to be at especially high risk of contracting CDAD include those that have been exposed to platinum agents and radiation and those with early stage disease. Awareness of increased risk amongst certain populations can enable preemptive measures to avoid infection, such as emphasizing hand washing with soap and water prior to any interaction with these patients.

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