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Overview of *Clostridium difficile* Infection in Cancer Patients

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Abstract

Clostridium difficile Associated Diarrhoea (CDAD) is the leading cause of nosocomial diarrhoea. *Clostridium difficile* Infections (CDIs) may be induced by medication or medical procedures that disrupt normal bowel flora or interfere with bowel motility. The emergence of hyper-virulent strains of CDI, reports of severe or recurrent CDI in immunocompetent populations, advent of various infection control challenges, and diagnostic and therapeutic dilemmas have contributed to a shift in the disease paradigm. However, there is insufficient data on the risk of CDI in vulnerable cancer patients receiving chemotherapy or who are admitted to health care settings for long periods of time. This review describes the epidemiology, risk factors, pathophysiology, and management of CDIs in cancer patients receiving chemotherapeutic agents.

Keywords: *Clostridium difficile* infection; Cancer patients; Chemotherapy

Introduction

Clostridium difficile (CD) is a gram-positive, spore-forming, anaerobic bacillus recognized as the most common cause of healthcare-associated infectious diarrhoea. Changes in bowel environment and function in cancer patients are common, primarily due to chemotherapy, radiation therapy, and iatrogenic processing. Stress, altered dietary habits, natural patient immunity, and treatment schedules may also play a role in these changes.

Irrelevant to cancer stage and underlying disease, the rates of admission to healthcare units vary according to patient age at diagnosis, co-morbid conditions, and treatment-related complications. Admission rates among cancer patients are also relatively high compared to those in non-oncologic populations. Prolonged or increased frequency of hospital stays are well-known risk factors for *Clostridium difficile* Infection (CDI). Prolonged use of antibiotics or uses of broad spectrum of antibiotics that contribute to co-morbid conditions also play a major role in the development of CDIs [1,2]. Although cancer patients receiving chemotherapy are at high risk for CDIs, diagnosis of CDI is difficult because stool culture and detection of cellular toxicity, both gold-standard diagnostic tools for diagnosis of CDI, are difficult to perform and take too much time. A recently published paper described the use of an Enzyme Immunoassay (EIA) test, which reportedly had low sensitivity (35-85%) and repeat tests reported its low positive predictive value [3,4].

Several articles related to CDI were study designs based on the general population. Even though it is already known that a large portion of high risk group is related to cancer patients and chemotherapy, there are only a few articles that analysed the data. Previous studies were mainly epidemiologic data which come from examination of outbreak rates after conducting single or combined regimen chemotherapy dependent on each cancer patients group. There are only a few studies that compared the degree of CDI outbreaks among chemotherapeutic agents or cancer types, respectively. In some studies, there were reports of CDI outbreaks in hematopoietic stem cell transplantation patients or advanced chronic kidney patients which incur immunocompromised state.

Chemotherapeutic agents, of which CDI outbreaks are highly expected, are introduced to oncology clinician. Also, various situations that may induce CDI in cancer patients which include extent of the immunity, prolonged hospital stay, use of antimicrobial, and more are analysed to help understand the cancer patients in clinical fields. Also this review will be a trailblazer in the field of medical research on various clinical situations or procedures that may induce CDI by introducing general details of CDI in a single risk group, cancer patients or chemotherapeutic agents.

This review presents the most recent data regarding CDI epidemiology, pathophysiology, risk factors, and management among cancer patients at high-risk for infection, a group which includes lung cancer patients receiving chemotherapeutic agents. In addition, the tables analyse previous studies on CDI outbreaks caused by chemotherapeutic agents in cancer patients and also treatment methods that depend on CDI episodes set up until now.

Epidemiology of *Clostridium difficile* Infection (CDI)

The incidence of CDI among hospitalized cancer patients varies nationally, and while the rate changes annually, the overall trend has been increasing. The rate of CDIs in the community doubled between 1996 and 2003, from 31 to 61 per 100,000 person-years, respectively. Between 2000 and 2010, there were about 15 cases per 1,000 hospital discharges and 20 cases per 100,000 person-years in the community [2,5-7]. In 2010, the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) published the "Clinical practice guidelines for *Clostridium difficile* infection in adults" [8]; however, data on the incidence or epidemiology among cancer patients undergoing chemotherapy received patients, a group at high risk for CDI, were not included. In a study by Henrich et al. 46.9% of 336 patients had malignancies, 39% of which had experienced *Clostridium difficile* Associated Disease (CACD) [7]. In addition, Chopra et al. reported a nine fold and 1.4 fold

higher incidence of CDI among hematopoietic stem cell transplantation recipients and other oncology patients, respectively, compared to non-oncogenic patients. CDI, including the BI/NAP1/027 strain, first emerged in Western Europe and North America [5]. Increased severity or mortality associated with CDI has been linked to discovery of North American pulsed field gel electrophoresis type 1 (NAP-1), Polymerase Chain Reaction (PCR) ribotype 027, toxinotype III, also known as new virulent strain and restriction endonuclease analysis type BI [9].

Previous studies have reported that patients with solid cancers and hematologic malignancies, as well as post-chemotherapy patients, who have reduced immunity, are at high risk for CDIs [10,11]. However, little data are available regarding the epidemiology of CDI in this high risk population. The incidence CDI in gynaecologic cancer patients undergoing chemotherapy is 2.3-7%, and 8.2% developed severe enterocolitis [12,13]. However, reports on CDI in patients with lung cancer, the leading cause of cancer-related mortality, are scant [1]. One of the biggest reasons is a debate regarding diagnostic tools [14]. CDI is typically diagnosed using an EIA test for toxins A and B as well as stool culture. However, while the toxin A and B EIA test has good specificity (98%), its low sensitivity (79-80%) is problematic. Stool culture has a higher sensitivity than the toxin EIA test, but adequate culture using medium is not practiced domestically, which results in low culture rates. However, even if bacteria are cultured in stool, the toxin producing strain may not grow under these conditions. Cell toxin tests combined with cell culture as a standard diagnostic method has a reported sensitivity and specificity ranging from 56-100% and 90-100%, respectively, but its complexity limits its practical use [3,4]. Stool direct real time offers superior sensitivity (93%) than existing toxin EIA tests, but insufficient data means that additional verification is required. CDI is major side effect in cancer patients, and chemotherapy places this population at high risk for opportunistic infection. It is necessary to understand the epidemiology and treatment of CDI; thus, research on a large scale is of great importance.

Pathophysiology of CDI in Cancer Patients

The diverse clinical manifestations of CDI range from asymptomatic colonization to fulminant colitis. However, compared to the relatively well-established knowledge of the pathogenesis of antibiotic-associated CDI, the pathogenesis of cancer or chemotherapy-related CDI is not well understood. However, its status as a well-known risk factor in this population indicates the urgent need for pathological and molecular biological studies. The proposed mechanisms are similar to those of antibiotic-associated CDI, including changes in bowel environment. *Clostridium difficile* is spread via the oral-faecal route through oral ingestion of spores, which are resistant in the environment as well as tolerant to acid, heat, and antibiotics. The spores, typically blocked by the barrier properties of the faecal micro biota, are plentiful in health care facilities, found at low levels in the environment and food supply, which may lead to nosocomial transmission. In the small intestine, the ingested spores germinate to the vegetative form [15-18]. In addition, *Clostridium difficile* may produce a number of other virulence factors, binary toxin (CDT), Fibronectin binding protein A (FbpA), fimbriae, Surface-layer protein A (SlpA), cysteine protease 84 and 66 (Cwp84 and Cwp66), and Cell Wall Protein (CWP) adhesions. Use of antimicrobial or chemotherapeutic agents may disrupt to the normal colonic bacteria and gut mucosa, leading to *Clostridium difficile* colonization of the large intestine [19].

Boukhettala et al. reported that methotrexate, an antineoplastic agent, induced villus atrophy associated with epithelial necrosis in the gut in an animal model, which resulted in decreased mucosal protein synthesis and mucin contents via a mechanism similar to that of antimicrobial agents [20]. In other proposed mechanism, chemotherapeutic agents induce severe inflammatory change, incur anaerobic gut environment by intestinal necrosis, decrease degradation of CDI toxin, and finally induce delayed reestablishment of normal flora [21-23].

The *Clostridium difficile* organism itself is non-invasive, and CDI outside the colon is rare. However, two factors affect clinical manifestations, including the virulence of the infecting strain as well as host immunity. Malignancy and/or chemotherapeutic agents can affect both of these factors. As mentioned previously, the BI/NAP1/027 strain has characteristically high levels of fluoroquinolone resistance, efficient sporulation, and markedly high toxin production [2,9]. As a result, its clinical manifestation and mortality rate are three times higher than those of less virulent strains, such as the 001 or 014 ribotypes [24]. A study on host immunity reported higher serum Immunoglobulin (IgG) titer, and the presence of antitoxin of Toxin A (TcdA, an enterotoxin) and Toxin B (TcdB, a cytotoxin), means higher asymptomatic colonization proportion in antibiotics used hospitalized patients [25].

Cancer and Chemotherapy to Risk Factors of CDI

There have been several reports on the influence of chemotherapy on the incidence of CDI in cancer patients that do not use antibiotics. Anand et al. excluded cancer patients that used antibiotics in order to examine the CDI incidence rate of chemotherapeutic agents [16]. A case report described a CDI that occurred after using carboplatin and paclitaxel, both platinum-based chemotherapeutic agents used in patients with lung cancer. Similarly, there has been additional case reports of hospitalizations due to CDIs associated with chemotherapy or antimicrobial use in patients with various cancers [21,22,26]. However, unlike for antimicrobial agents, incidence rates for CDIs associated with use of chemotherapeutics have not yet been established. These chemotherapeutic agents, including 5-Fluorouracil (FU), cyclophosphamide, doxorubicin, cisplatin, carboplatin, paclitaxel, and vinorelbine, are used to treatment of various cancers, and are also known to induce CDIs as shown in Table 1 [21,22,27,28].

There have been no reports of CDI itself induced by cancer. Until now, end-stage cancer patients that refuse chemotherapy are thought to have increased risk of CDI due to reduced immunity, old age, poor oral intake, and prolonged admission to healthcare settings [17,29]; however, reports are scarce, possibly because most cancer patients are exposed to chemotherapy, radiation therapy, and antibiotics. The limited data on this subject lack significant statistical value.

Established and Recent Management of CDI

Treatment of CDI in patients with cancer or receiving chemotherapeutic agents is similar to that in immunocompromised populations. Treatment regimens or methods are typically based on current SHEA and IDSA guidelines given in Table 2 [2,5,18,30-35]. The factors that influence treatment regimens include the frequency of recurrence and severity of clinical manifestation, based on laboratory parameters including white blood cell counts and serum creatinine levels [36].

Author (year)	Chemotherapeutic agents	Malignancy	No. of confirmed CDAD	Patients outcome
Emoto et al.	Cisplatin	Ovarian cancer	2	Treated
Paterson	Topotecan	Ovarian cancer	1	Treated
Husain et al.	Paclitaxel	Gynaecologic malignancies	24	- (do not checked)
Wong et al.	Carboplatin, vinorelbine	Bronchoalveolar cancer	1	Death
Maeda et al.	Paclitaxel	Lung cancer	1	Treated
Morales Chamorro et al.	5-flourouracil(FU)	Colorectal cancer	1	Treated
Yang et al.	Paclitaxel and carboplatin	Lung cancer	1	Treated
Ansari et al.	Vinorelbine	Breast cancer	1	Death
Kim et al.	Cisplatin, gemcitabine, pemetrexed, gefitinib, erlotinib	Lung cancer	44	Treated (89%) Relapsed (9%)

Table 1. Studies of chemotherapeutic agents associated with *Clostridium difficile* infection.

Number of episode	Treatment option	Dose (regimen)	Duration
Initial episode or first recurrence	Mild: Metronidazole	500 mg (orally)	3 times daily for 10 to 14 days
	Moderate: Vancomycin	125 mg (orally)	4 times daily for 10 to 14 days
	Severe: Colectomy may be needed		Early surgical consultation is recommended
	Vancomycin	125 mg (orally)	4 times daily for 14 days, then twice daily for 7 days, then once daily for 7 days, then once every 2 days for 8 days, then once every 3 days for 15 days
Second recurrence	Fidaxomicin	200 mg (orally)	Twice daily for 10 days
	Vancomycin taper followed by rifaximin	400 mg (orally)	2 times daily for 14 days
Third recurrence	Immunoglobulin	400 mg/kg (Intravenous)	Once every 3 weeks a total of 2 to 3 doses
	Faecal transplantation	(Oral or rectal intubation)	

Table 2. Summary of treatment for *Clostridium difficile* infection.

Metronidazole or vancomycin is generally used for 10-14 days for recurrent infections, with a repeat course, resulting in a successful treatment rate of about 50% [36-40]. Cure rates following second and higher recurrences drop remarkably, and fidaxomicin (200 mg twice daily for 10 days) or a vancomycin regimen involving tapered and pulsed dosing is typically used [30]. Recent data suggest that fidaxomicin may be more effective than vancomycin at preventing further episodes of CDI after an initial recurrence [31]. However, treatment options for severe colitis resistant to both vancomycin and fidaxomicin are limited. The mortality rate for emergency colectomy due to fulminant colitis is over 80%, and diverting ileostomy and colonic lavage with vancomycin may offer an effective alternative treatment method. Other antibiotics used for treatment of recurrent CDIs include rifaximin, nitazoxanide, ramoplanin, teicoplanin, and tigecycline. However, due to insufficient data, high cost, and adverse effects, their use is recommended only for recurrent CDI related to standard therapy associated unacceptable adverse effects [32,40]. In addition, tolevamer, a toxin binding agent; *Saccharomyces boulardii*, and *Lactobacillius rhamnosus*, two types of probiotics, IgG, an immunologic agent; monoclonal antibodies; and toxoid vaccines have also been used in clinical trials for treatment of recurrent CDI [19].

Faecal microbial transplantation was first reported in 1958. This method has recently reappeared as an acceptable, safe, and effective treatment option for recurrent CDIs. Oral or rectal transplantation of faeces from a healthy, pretested donor and simultaneous cessation of all antibiotic use in the recipient are successful in treating more than 90% of patients with CDI. To date, no significant adverse effects or infectious complications due to faecal microbial transplantation have been reported. A 2013 randomized, controlled trial reported superior cure rate, relapse rate, and safety in the transplantation group that had received vancomycin following transplantation via naso-duodenal tube compared to vancomycin alone [33-35].

Conclusion

CDI in cancer patients and those undergoing chemotherapy is an issue that can no longer be overlooked. CDI often occurs in cancer patients and may progress to a severe clinical course. However, most information about CDIs is based on data from non-oncologic populations. More data on gastrointestinal tract environment changes as well as immunity-lowering factors in cancer patients, such as underlying disease, Performance Status (PS) scale scores, poor oral intake, and prolonged hospitalization, are needed to better understand the pathophysiology and epidemiology of CDI in immunocompromised hosts. Additional studies on CDI disease progression and incidence rates, as well as on changes to the gut environment associated with solid tumors themselves or with chemotherapeutic agents individually, are also necessary.

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