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ORIGINAL ARTICLE

Risks factors and outcomes of *Clostridium difficile* infection in patients with cancer: a matched case-control study

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Abstract

Purpose Clostridium difficile infection (CDI) is the leading cause of diarrhoea in hospitalised patients. Cancer populations are at high-risk for infection, but comprehensive evaluation in the current era of cancer care has not been performed. The objective of this study was to describe characteristics, risk factors, and outcomes of CDI in cancer patients.

Methods Fifty consecutive patients with CDI at a large Australian cancer centre (2013–2015) were identified from the hospital pathology database. Each case was matched by ward and hospital admission date to three controls without toxigenic CDI. Treatment and outcomes of infection were evaluated and potential risk factors were analysed using conditional logistic regression.

Results Patients with CDI had a mean age of 59.7 years and 74% had an underlying solid tumour. Healthcare-associated infection comprised 80% of cases. Recurrence occurred in 10, and 12% of cases were admitted to ICU within 30 days. Severe or severe-complicated infection was observed in 32%. Independent risk factors for infection included chemotherapy (odds ratio (OR) 3.82, 95% CI 1.67–8.75; $p = 0.002$), gastro-intestinal/abdominal surgery (OR 4.64, 95% CI 1.20–17.91; $p = 0.03$), proton pump inhibitor (PPI) therapy (OR 2.47, 95% CI 1.05–5.80; $p = 0.04$), and days of antibiotic therapy (OR 1.04, 95% CI 1.01–1.08; $p = 0.02$).

Conclusions Severe or complicated infections are frequent in patients with cancer who develop CDI. Receipt of chemotherapy, gastro-intestinal/abdominal surgery, PPI therapy, and antibiotic exposure contribute to infection risk. More effective CDI therapy for cancer patients is required and dedicated antibiotic stewardship programs in high-risk cancer populations are needed to ameliorate infection risk.

Keywords *Clostridium difficile* · Cancer · Epidemiology · Risks · Severity · Antibiotic stewardship

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Introduction

Clostridium difficile infection (CDI) is the leading cause of healthcare-associated diarrhoea. Patients with malignancy are at increased risk of developing infection, with CDI incidence in some cancer populations estimated to be approximately twofold higher than general hospital patients [1]. CDI may develop as a complication of cancer treatment and may limit cancer care, including delayed delivery of cancer therapies and the need to manage inter-current infections. Additional infection prevention measures, such as patient isolation/cohorting, are required for optimal control in healthcare settings.

In the setting of increasing global incidence of hypervirulent *C. difficile* strains (e.g. B1/NAP1/027) [2], contemporary studies of CDI in cancer populations have focussed upon clusters or outbreaks, or have included haematopoietic stem cell transplantation populations only [3–14]. However, the epidemiology of CDI in Australia is such that a broad range of strain types are responsible for endemic disease [15–17]. Evaluation

of risk factors is necessary in the setting of new chemotherapeutic agents with gastrointestinal toxicities and across a range of underlying malignant conditions. Further, identification of high-risk patients would inform future infection prevention strategies.

Given the need for CDI risks and outcomes to be evaluated in Australian patients receiving current-era cancer therapies, a matched case-control study was conducted at a large tertiary cancer centre with the following objectives: (i) to describe the clinical characteristics of cancer patients acquiring CDI, (ii) to determine risk factors for CDI in cancer patients, and (iii) to evaluate outcomes of CDI in cancer patients.

Methods

Setting

The Peter MacCallum Cancer Centre (PMCC) is an Australian tertiary referral centre providing treatment for a broad range of malignant conditions. A single microbiology laboratory provides diagnostic services for investigation of inpatients and patients managed in ambulatory-care settings. During the study period, a hospital-wide antimicrobial stewardship (AMS) program was operational, with antimicrobial approvals, post-prescription review by a pharmacist or infectious diseases physician, and a standardised clinical pathway for identification and management of sepsis.

Case and control ascertainment

Patients with CDI were identified from a laboratory data extract for the period from May 2013 to May 2015. A matched case-control study was performed to evaluate risks for CDI in cancer patients. The number of cases was determined a *priori* to be 50, and a 1:3 ratio of cases to controls was used as the optimal means of achieving precision [18].

A *case* was defined as any PMCC patient who had confirmation of toxigenic *C. difficile* in a diarrhoeal specimen. If multiple infections had been confirmed for a single patient, only the first CDI episode was analysed. Cases were identified retrospectively and were sequentially selected according to specimen collection dates from May 2013, until a total of 50 cases had been identified.

A *control* patient was defined as having no diarrhoea or having diarrhoea and testing negative for toxigenic *C. difficile*. Controls were matched by ward and time to respective cases.

Diagnostic criteria

Liquid or unformed stool specimens were tested for *C. difficile*, consistent with diagnostic guidelines of the Society for Healthcare Epidemiology of America/Infectious

Diseases Society of America (SHEA/IDSA) and surveillance criteria employed in Australia [15, 19]. To identify toxigenic *C. difficile* isolates, a 3-step diagnostic algorithm was applied. All loose/liquid stool specimens referred for *C. difficile* testing were analysed for the presence of the GDH antigen using the Immunocard® *C. difficile Glutamate Dehydrogenase Antigen* (GDH) Antigen EIA assay (Meridian Bioscience, Inc.). GDH positive specimens were tested using the illumigene® *C. difficile* assay (LAMP – illumigene, Meridian Bioscience, Inc.). Any specimen with discordant results in the previous two steps or illumigene positive results was referred to the state-wide reference laboratory for nucleic acid amplification testing and ribotyping.

Definitions

Consistent with national surveillance methods [20, 21], CDI cases were classified according to the following criteria: 'Healthcare facility (HCF)-associated, HCF-onset'–symptom onset >48 h after admission to HCF; 'HCF-associated, community-onset'–symptom onset within community or within 48 h of admission to HCF, providing onset was within 4 weeks of last discharge from HCF; 'community-associated'–symptom onset in community or within 48 h of admission to HCF providing last admission to HCF was >12 weeks ago; or 'indeterminate'–symptom onset did not fulfil above criteria.

CDI recurrence was defined as an episode of CDI occurring within 8 weeks of onset of a previous episode, provided the previous infection had clinically resolved.

Severity of illness was classified according to SHEA/ISDA criteria: 'mild-moderate', 'severe', and 'severe complicated' [22]. Infections were classified as 'severe' in the presence of a recorded WCC >15,000/μL OR serum creatinine >1.5 times baseline. 'Severe complicated' infections were defined in the presence of hypotension, systemic inflammatory response syndrome (SIRS), or presence of pseudomembranes on colonoscopy.

Data collection

A standardised data collection tool was used to record patient demographics, comorbidities, potential CDI risk factors, severity, and outcomes. Exposure variables recorded for the 30 days prior to the specimen collection date included the following: administration of H_2-receptor antagonists, proton pump inhibitors (PPIs), laxatives, enemas, steroids, and immunosuppressive agents (tacrolimus, mycophenolate, cyclosporin, methotrexate, TNFα inhibitors, rituximab, vorinostat, mTOR inhibitors, etanercept, alemtuzumab, extracorporeal photophoresis, steroid therapy amounting to >0.5 mg/kg prednisolone equivalents daily), and antibiotic therapy (agent/s administered and dates). The following were also recorded if

present on the index date: intercurrent infections, antibiotic therapy, and WHO mucositis grading [23].

Severity markers were captured on the specimen collection date or during the 48-h period after this date if no data were available on the specimen date. Biochemical markers included serum creatinine, serum albumin, and white cell count. The lowest serum creatinine recording for the previous 60 days was recorded as baseline. Clinical severity measures included highest recorded temperature, hypotension (systolic blood pressure <100 mmHg), presence of criteria for SIRS (defined as two or more of the following: temperature of >38 °C or <36 °C, heart rate >90/min, respiratory rate >20/min, white cell count >12,000/μL), and sepsis (defined as SIRS plus microbiological identification of infection).

The following outcomes and treatment-related factors were recorded: 30-day all-cause mortality, admission to ICU within 30 days, and CDI recurrence. Cause of death, death attributed to CDI, unplanned readmission within 30 days, change in cancer treatment intent following diarrhoeal episode, surgery for complications of CDI, treatment for CDI, and response to treatment at 10-days post specimen collection date were recorded.

Ethics approval

Approval for the study was obtained from the PMCC Human Research Ethics Committee (No. 16/33R).

Statistical analysis

Univariate conditional logistic regression was used to determine odds ratios (ORs) for individual risk factors potentially associated with *C. difficile*. Multivariable analysis was performed to determine adjusted odds ratios. Potential risk factors with a *p* value of <0.20 on univariate analysis were included stepwise in the multivariate model. All analyses were performed using RStudio Version 0.99.902 (RStudio, Inc., Boston, MA, USA).

Results

Fifty cases of CDI fulfilled criteria for study inclusion, comprising 33 unique strains of *C. difficile* with no infections caused by the B1/NAP1/027 strain. Of these cases, 40 were healthcare-associated, nine were community-associated and one was of indeterminate source. In 74% of cases, the underlying malignancy was a solid tumour and infection occurred at a median of 5.5 days (range 0–24 days) following hospital admission. Twenty-eight of the 50 cases (56%) were aged 60–80 years. Characteristics of cases are summarised in Table 1. During the study period, the rate of healthcare-associated CDI episodes was 6.1 (95% confidence interval 4.7–7.7) per 10,000 occupied bed days.

Baseline characteristics, including underlying disease and prior healthcare contact, were comparable in case ($N = 50$) and control groups ($N = 150$) (Table 1). Exposure to cancer and other therapies with potential to influence CDI risk is summarised for cases and controls in Table 2. Antibiotic and chemotherapy exposure in the previous 30 days were significantly higher in cases than controls, and laxative therapy was more frequently administered to control patients (Table 2). Penicillins followed by cephalosporins were the most commonly prescribed antibiotics, administered in 60 and 40% of CDI cases, respectively. Fluoroquinolone exposure in cases was low (12%). Piperacillin-tazobactam was prescribed in 42% of cases. Antibiotic exposure was high in the subgroup of patients who had gastro-intestinal/abdominal surgery—91.6% received antibiotics (median 9 antibiotic days of therapy (DOT), range 0–34 DOT). In comparison, 69.5% of all other patients received antibiotics (median 4.5 antibiotic DOT, range 0–49 DOT). PPIs were prescribed for 80% of cases and 66.7% of control patients. Cases received the following cancer therapies: radiotherapy (20%), surgery (30%), and chemotherapy (68%).

The majority of patients with CDI (68%) had 'mild-moderate' disease, while 16% were classified as 'severe', and 16% as 'severe complicated'. All patients classified as having 'severe' or 'severe complicated' disease had a healthcare-associated infection.

Metronidazole was the most commonly administered monotherapy for CDI treatment ($N = 33$, 66%). When combination therapy was used, this most frequently consisted of metronidazole with oral vancomycin ($N = 14$, 28%). Overall response to therapy was 75.5% (Table 3). Recurrent CDI developed in five cases (10%). One patient required surgery for *C. difficile*-related complications, and three subjects had a change in the treatment intent for their cancer following infection. Six patients (12%) were admitted to ICU within 30 days of CDI, and the 30-day all-cause mortality rate for CDI cases was 16%.

The following variables were significantly associated with CDI on univariate analysis: chemotherapy within the previous 30 days, gastro-intestinal/abdominal surgery within the previous 30 days, autologous stem cell transplantation within the previous 30 days, antibiotic therapy within the previous 30 days, and antibiotic DOT. Chemotherapy (OR 3.82, 95% CI 1.67–8.75; *p* = 0.002), gastro-intestinal/abdominal surgery (OR 4.64, 95% CI 1.20–17.91; *p* = 0.03), antibiotic DOT (OR 1.04, 95% CI 1.01–1.08; *p* = 0.02), and PPI therapy (OR 2.47, 95% CI 1.05–5.80; *p* = 0.04), were retained as independent risk factors for CDI on multivariate analysis. Crude and adjusted odds ratios for developing CDI are provided in Table 4.

Discussion

Identification of risk factors for CDI in cancer patients is an important step to enable targeting of preventative measures.

Table 1 Baseline characteristics of *Clostridium difficile* cases and matched controls

Characteristic	CDI cases (N = 50)	Controls (N = 150)
Male sex (% total)	23 (46%)	88 (59%)
Age, mean (SD)	59.7 (15.5)	60.3 (15.8)
Charlson comorbidity index, mean (SD)	4.5 (2.2)	4.1 (2.2)
Days hospitalised prior to specimen collection, median (range)	5.5 (−1–24)	N/A
Total length of stay, median (range)	14.5 (0–99)	13(1–80)
Underlying cancer diagnosis (%)		
Solid tumour	37 (74%)	113 (75.3%)
Haematological malignancy	13 (26%)	37 (24.7%)
Leukaemia	3 (6%)	9 (6%)
lymphoma	7 (14%)	22 (14.7%)
Multiple myeloma	3 (6%)	5 (3.3%)
Other	0 (0%)	1 (0.7%)
Relapsed/refractory malignancy (%)	28 (56%)	85 (56.7%)
No. of previous hospital admissions in last 12 months, mean (SD)	2.0 (1.3)	2.0 (1.5)
No. of days hospitalised in last 12 months, mean (SD)	14.6 (10.9)	18.1 (19.6)

CDI Clostridium difficile infection, *IQR* inter-quartile range, *SD* standard deviation

Previous studies have analysed risk factors for CDI within general hospital populations or within haematology patients [24]. The current study, however, evaluated risks and outcomes of CDI across the spectrum of malignant conditions. Importantly, we identified patients undergoing gastro-intestinal/abdominal surgery, and those receiving chemotherapy, PPI therapy, or antibiotics in the previous 30 days as being at significantly higher risk for developing CDI.

Findings of this study demonstrate the burden of illness associated with CDI in cancer patients. In patients with CDI, relapse of infection was observed in 10, and 12% of patients required admission to ICU within 30 days of infection. We also observed moderate response to standard therapy (75.5% overall), acknowledging that severe disease predisposes to refractory infection, and that a large proportion of studied patients had mild disease. Recurrence has previously been reported in 11% of patients undergoing haematopoietic stem cell transplantation, [6], and this is consistent with outcomes observed in our study. Notably, fidaxomicin and faecal microbiota transplantation (FMT) have been shown to be efficacious for treatment of CDI in cancer populations [25, 26]. However, fidaxomicin was not routinely available at our centre during the study period, and only one patient underwent FMT. Our findings therefore apply predominantly to patients managed with metronidazole and/or vancomycin therapy.

We observed a range of severity of CDI illness, spanning mild disease (68%) to severe or complicated infection (32%). Grading of CDI severity is challenging because accepted tools for scoring have not generally been developed or validated in cancer populations [24]. Previously, severe disease has been reported variably (2–57%), depending on the underlying cancer diagnoses in studied populations [3, 4]. Consistent with

our findings, a recent study of haematology/oncology patients reported severe illness in 19.7% of CDI episodes and ICU admission in 6.6% of cases [27]. Furthermore, five patients in our study required admission to ICU, and one patient required surgery, underscoring the severity of illness in this high-risk cohort.

With respect to antibiotic exposure, we observed each day of cumulative antibiotic therapy to incur an approximate 4% increase in the odds for development of CDI. This effect is likely to be multiplied if numerous antibiotics are administered and highlights the importance of antibiotic stewardship for patients with cancer, where agents may be concurrently administered for prophylaxis and treatment. Previously reported risks for developing CDI include increasing cumulative dose, number of antibiotics, and days of antibiotic exposure [28]. Looking ahead, antibiotic stewardship programs in cancer populations must determine if early review of therapy to facilitate timely cessation can be employed to reduce CDI risk associated with cumulative antibiotic exposure. This is consistent with recommendations provided by the SHEA/IDSA for implementing antibiotic stewardship programs generally in hospitalised patients [29].

Non-antibiotic pharmacotherapy in cancer patients also contributes to risk for developing CDI. Receipt of chemotherapy has previously been reported as a risk for CDI [11, 12, 30–33], and our findings confirm these reports. Two large meta-analyses in general hospital patient populations have demonstrated an association between gastric acid suppression and the development of CDI [34, 35]. Studies in cancer populations, however, have demonstrated an inconsistent relationship. For example, Alonso et al. and Garzotto et al. found that PPI use was protective, while Liu et al. demonstrated that

Table 2 Cancer and other therapies with potential risk for *Clostridium difficile* infection in cases and matched controls

Exposure category	CDI cases (N = 50)	Controls (N = 150)	p value
Any antibiotic administered in previous 30 days (%)[a]	43 (86%)	104 (69.3%)	0.04
Penicillins (%)	30 (60%)	68 (45.3%)	0.10
Cephalosporins (%)[b]	20 (40%)	47 (31.3%)	0.34
Carbapenems (%)	1 (2%)	5 (3.3%)	1.00
Fluoroquinolones (%)	6 (12%)	11 (7.3%)	0.46
Aminoglycosides (%)	2 (4%)	8 (5.3%)	1.00
Glycopeptides (%)	8 (16%)	19 (12.7%)	0.72
Antibiotics administered on index date	32 (64%)	73 (48.7%)	0.09
Number of antibiotics, median (range)	2 (0–9)	1 (0–7)	0.16
No antibiotic administered (%)	7 (4%)	45 (30%)	0.04
1 antibiotic administered (%)	13 (26%)	39 (19.3%)	0.85
2 antibiotics administered (%)	14 (28%)	23 (15.3%)	0.07
>2 antibiotics administered (%)	16 (32%)	43 (28.7%)	0.79
Antibiotics days of therapy, median (range)	7 (0–5)	4 (0–49)	0.03
Radiotherapy in previous 30 days (%)	10 20%)	34 (22.7%)	0.84
Surgery in previous 30 days (%)	15 (30%)	37 (24.7%)	0.58
Gastro-intestinal/abdominal surgery in previous 30 days (%)	13 (26%)	23 (15.3%)	0.14
Chemotherapy in previous 30 days (%)	34 (68%)	65 (43.3%)	0.00
Severe mucositis (grade 3/4)	5 (10%)	6 (4%)	0.21
ASCT in previous 30 days (%)	4 (8%)[c]	2 (1.3%)	0.06
Proton pump inhibitors in previous 30 days (%)	40 (80%)	100 (66.7%)	0.11
H_2-receptor antagonists in previous 30 days (%)	9 (18%)	25 (16.7%)	1.00
Laxative therapy (%)	18 (36%)	86 (57.3%)	0.01
Enemas (%)	3 (6%)	19 (12.7%)	0.30

CDI Clostridium difficile infection, *IQR*, inter-quartile range, *SD*, standard deviation, *ASCT* autologous stem-cell transplantation

[a] Agents with anti-pseudomonal activity (ticarcillin-clavulanate, piperacillin-tazobactam, ceftaxidime, cefepime, cefoperazome, ciprofloxacin, levofloxacin, aztreonam, imipenem, meropenem, doripenem, gentamicin, tobramycin, amikacin, or colistin) were administered to 25 patients with CDI (50%) and 60 control patients (40%) (p = 0.28)

[b] Third or fourth generation cephalosporins were administered to nine patients with CDI (18%) and 19 control patients (12.7%) (p = 0.48)

[c] ASCT recipients who developed CDI had underlying conditions of diffuse large B-cell lymphoma (n = 2) and multiple myeloma (n = 2), with CDI onset at median of 7-days post-ASCT (range 0–11)

Table 3 Response to treatment for *Clostridium difficile* infection

CDI treatment	Total no. receiving therapy	Clinical response N (%)[c]	Persisting CDI symptoms N (%)[c]
Metronidazole monotherapy[a]	33[d]	25 (75.7%)	3 (9.2)
Oral vancomycin monotherapy	2	2 (100%)	0 (0%)
Combination therapy[b]	14	10 (71.4%)	4 (28.6%)
Faecal transplant	1	1 (100%)	0 (0%)
All treatment	49[d]	37 (75.5%)	7 (14.3%)

[a] Oral or intravenous metronidazole

[b] Oral and/or intravenous metronidazole together with oral vancomycin

[c] Response assessed at 10 days of therapy

[d] Response not evaluable in five cases (transferred to other healthcare facility or not clinically reviewed following commencement of CDI therapy)

Table 4 Univariate and multivariate analyses of potential risk factors for *Clostridium difficile* infection

Potential risk factor for CDI[a]	Crude OR (95% CI)	*p* value	Adjusted OR (95% CI)	*p* value
Age	0.997 (0.974–1.020)	0.788		
Sex (male)	0.603 (0.316–1.150)	0.125		
Number of admissions in previous 12 months	0.990 (0.792–1.238)	0.932		
Haematological malignancy	1.171 (0.392–3.499)	0.777		
Relapsed/refractory malignancy	0.973 (0.508–1.864)	0.934		
Charlson comorbidity index	1.085 (0.928–1.269)	0.306		
Severe mucositis (grade 3/4)	2.708 (0.772–9.494)	0.120		
Autologous stem cell transplantation	10.18 (1.114–93.020)	0.040		
Administration of chemotherapy	3.383 (1.570–7.291)	0.002	3.822 (1.670–8.745)	0.002
Rituximab	2.269 (0.683–7.538)	0.181		
HIPEC	3.937 (0.912–17.000)	0.066		
Cisplatin	2.708 (0.772–9.494)	0.120		
Radiotherapy	0.844 (0.373–1.910)	0.683		
Immunosuppression[b]	2.448 (0.880–6.809)	0.086		
Gastro-intestinal/abdominal surgery	3.733 (1.118–12.460)	0.032	4.636 (1.200–17.906)	0.026
Proton pump inhibitors	2.018 (0.921–4.424)	0.079	2.467 (1.050–5.798)	0.038
H_2-receptor antagonists	1.157 (0.404–3.310)	0.786		
Laxative therapy	0.374 (0.183–0.763)	0.007		
Antibiotic days of therapy	1.034 (1.001–1.069)	0.042	1.044 (1.006–1.084)	0.023
15–30 antibiotic days of therapy	2.789 (1.085–7.717)	0.033		
>30 antibiotic days of therapy	4.609 (1.087–19.533)	0.038		
Any Antibiotic	2.687 (1.131–6.382)	0.025		
Penicillins	1.917 (0.963–3.815)	0.064		
Cephalosporins	1.542 (0.754–3.153)	0.236		
Fluoroquinolones	1.675 (0.603–4.651)	0.322		
Carbapenems	0.600 (0.070–5.136)	0.641		
Glycopeptides	1.682 (0.520–3.670)	0.517		

CDI Clostridium difficile infection, *OR* odds ratio, *HIPEC* hyperthermic intraperitoneal mitomycin C + IV 5-fluorouracil

[a] 'Severe mucositis' variable are not included in multivariate model because of collinearity with 'administration of chemotherapy'; covariates '15–30 antibiotic days of therapy' and '>30 antibiotic days of therapy' are not included in multivariate model because of collinearity with 'antibiotic days of therapy'

[b] Receipt of tacrolimus, mycophenolate, cyclosporine, methotrexate, TNFα inhibitors, rituximab, vorinostat, mTOR inhibitors, etanercept, alemtuzemab, extracorporeal photophoresis, or steroid therapy >0.5 mg/kg prednisolone equivalent

chronic gastric acid suppression was associated with risk for developing CDI [5, 10, 14]. Our findings support the latter study, confirming an association between CDI risk and PPI use in cancer populations. Notably, the AMS program at our centre did not include review of PPI therapy during the study period. Given the high prevalence of PPI use in patients with malignancy [36], further evaluation of indications for PPI prescribing is required to determine if there is a role for rationalising PPI therapy to mitigate CDI risk. Future AMS programs for cancer patients should incorporate review of PPI indications with cessation in the absence of a documented clinical indication, in order to reduce CDI risk.

Our observation that gastro-intestinal/abdominal surgery was associated with development of CDI in patients with malignancy has not previously been reported. In our series, the most frequently performed surgical procedures prior to onset of CDI included laparotomy with hyperthermic intraperitoneal mitomycin C and IV 5-fluorouracil (5/13 cases), gastro-oesophageal procedures (3/13 cases), and cystectomy with formation of ileal conduit (2/13 cases). Although absolute numbers were limited in the current study, these surgical populations reflect high-risk groups for targeting of clinician education/awareness and early identification of CDI. For these high-risk patients, clinicians should commence empiric CDI therapy while awaiting diagnostic results for *C. difficile*.

Prior studies of upper and lower gastrointestinal surgical procedures for malignancy have reported variable rates of CDI (0–6.8%) [37], with significantly increased mortality

and prolonged hospitalisation in the presence of infection [38]. During the study period, guidelines at our centre recommended the use of cefoxitin or cefazolin plus metronidazole for prophylaxis prior to gastro-intestinal/abdominal surgery. Others have shown that pre-operative prophylactic antibiotic exposure per se does not contribute to risk for developing CDI [39]. We observed a median of 9 days of antibiotic exposure in patients who underwent gastro-intestinal/abdominal surgical procedures, which far exceeds recommendations for prophylactic regimens (24–48 h). Inappropriately extended post-operative antibiotic courses contributing to infection risk should therefore be a focus for AMS programs.

Limitations of our study include the retrospective study design, common to all case-control studies. Although detailed review of medical records was conducted, some clinical indices (e.g. mucositis grading) were difficult to assess retrospectively, being reliant upon adequacy of documentation. Antibiotics prescribed by clinicians outside of the study centre were not routinely recorded, meaning that our data may be an under-estimate of true antibiotic exposure. Our study was also limited in size, preventing meaningful comparison of CDI according to individual disease, chemotherapy, or antibiotic classes. Single-centre experience may not be applicable to all centres managing patients with cancer. In particular, the context for our study was endemic *C. difficile*, unrelated to an outbreak or predominant hypervirulent clone, and the majority of patients (83%) managed at PMCC during the study period had solid tumours. A small number of cases ($n = 5$) were not able to be followed to determine response to therapy, and this may have contributed to reporting bias in study outcomes. Laboratory diagnosis of CDI at our centre employed GDH antigen detection as a sensitive screen, followed by DNA amplification assay to detect the presence of a toxigenic strain. False negative results are negligible when this approach is taken, although this algorithm may result in enhanced case-detection compared to instances where stool culture (not routinely used at our centre) is used for diagnosis. Notwithstanding these limitations, findings are relevant to the current era of cancer therapy and provide insights into CDI epidemiology and burden of illness.

Conclusions

C. difficile infection is an important cause of diarrhoea in patients with malignant disorders, with severe or complicated infections comprising a significant burden of illness. Non-modifiable risk factors associated with infection include receipt of chemotherapy and gastro-intestinal/abdominal surgery; modifiable risk factors include proton pump inhibitor therapy and antibiotic exposure. Study outcomes reveal the potential for risk stratification within the broad group of patients with malignancy and allow effective targeting of preventative measures. Our findings demonstrate the need for more effective CDI therapy in cancer patients and support the need for dedicated antibiotic stewardship programs, especially in cancer patients requiring gastro-intestinal/abdominal surgery.

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