To study the contributing factors and outcomes of Clostridioides difficile infection in patients with solid tumors

Kamal Kant Sahua,*, Ajay Kumar Mishra, Vishal Jindal, Ahmad Daniyal Siddiqui, Susan V. George

Hematology & Medical Oncology, Huntsman Cancer Institute, University of Utah, Salt Lake City, 84112, UT, United States
Department of Internal Medicine, Saint Vincent Hospital, Worcester, 01608, MA, United States
Department of Hematology and Oncology, Oakland University William Beaumont School of Medicine, Royal Oak, 48073, MI, United States
Hemat-oncology Division, Department of Internal Medicine, Saint Vincent Hospital, Worcester, 01608, MA, United States

ARTICLE INFO

Keywords:
Clostridioides difficile infection
Cancer
Chemotherapy
Immunotherapy
Antimicrobials

ABSTRACT

Background: Clostridioides difficile infection (CDI) is a considerable healthcare burden, and now identified as the leading cause of acquired diarrheal illness in patients receiving antibiotics. Patients with malignancies are more prone to acquire CDI, owing to their frequent exposure to risk factors.

Objective: This study aims to investigate the factors affecting the outcome of Clostridioides Difficile Infection in patients with solid tumors at our community healthcare center.

Methods: This is a retrospective study that included a total of 59 patients with solid tumors who were hospitalized for Clostridioides difficile infection.

Results: The median age of the study population was 79 years with 39 males and 20 females. The patients had a diagnosis of a malignancy involving the following sites: prostate (25), lung (19), colon (7), bladder (4), breast (3), and renal (1). There were 52 cases of first time and 7 cases of recurrent CDI admissions. 40 patients were detected to have CDI at presentation while 19 patients were diagnosed with CDI after admission. CDI was categorized as follows: non-severe (29), severe (28), and very severe (2). There were 33 patients on chemotherapy and 20 patients undergoing radiotherapy. Twenty-seven patients had a recent history of cancer care-related procedures or interventions. Twenty-nine patients were from either a rehabilitation center or a long-term nursing care facility. There were 39 recent hospitalizations with 29 patients receiving antibiotics. Almost half of the patients were on proton pump inhibitors (29) and 12 were on steroids (20.3%) at the time of developing CDI. Patients with a high-risk qSOFA score of 2 or more (p-value = 0.008) or a high white blood cell count of >15 × 10^9/L (p-value = 0.016) at the time of admission were found to have higher in-hospital mortality. Critical care data suggested that 9 patients required intensive care, 7 patients required vasopressor support, and 6 needed mechanical ventilation. Patients were treated with either vancomycin alone (13), or metronidazole alone (25), or combination therapy with vancomycin + metronidazole (21). The median duration of hospital stay was 6 days with 11 fatalities (18.64%).

Conclusions: CDI causes significant morbidity in patients with malignancies. A high qSOFA score and leukocytosis are significantly associated with high morbidity and thus should be used to prioritize and intensify inpatient care of these patients.

1. Introduction

The last few decades have seen exponential growth in cancer treatment. Newer diagnostic tools and drugs have improved the overall morbidity and mortality of patients with malignancies. Treatment modalities including immunotherapy, targeted therapy, and focused radiation therapy have provided a wide spectrum of the armamentarium for oncologists to treat their patients [1]. Unfortunately, anticancer medications have their associated side effects including the risk of superadded infections [2].

Among the infections, Clostridioides difficile (C. difficile) infection is an extremely lethal infection with increased morbidity and mortality [3].
Data from the United States have shown that amongst the healthcare-associated infections, C. difficile accounts for approximately 15% of all infections [4]. Patients with cancer are at an elevated risk to acquire C. difficile infection because of multiple visits to chemotherapy centers, infusion centers, hospitalizations, and increased chemo-/radiotherapy associated risk factors like myelosuppression and change in gut flora microbiota. These risk factors can be roughly stratified to three major categories-(1) medications/pharmacology related (2) Host related, and (3) Intervention related [5, 6]. Data gathered from the hospitalized adults diagnosed with cancer in United States from 2001–2010 showed overall incidence of C. difficile to be 8.6 discharges per 1000 adult cancer discharges [7, 8].

C. difficile infection not only poses a huge financial burden but also increases the non-cancer-related mortality rates in patients with malignancies.

2. Methodology

2.1. Patients and methodology

Search strategy: This is a retrospective study conducted at a community hospital, Worcester, Massachusetts, United States that included all hospital admissions for C. difficile infection in cancer patients who presented to us between January 2009 to December 2019. This is a 381 bedded hospital which is one of the busiest community hospitals in Central Massachusetts. It has a full-fledged inpatient service including an intensive care unit and associated outpatient cancer wellness centre. The detection method for C. difficile infection in our hospital was done by using stool sample with Nucleic Acid Amplification Test (NAAT). The study was approved by the institutional review board (IRB# 2019-102).

2.1.1. Selection and inclusion criteria

All adult (age greater than 18 years) patients with malignancies namely solid tumors who presented to our hospital and were diagnosed with C. difficile were included in this retrospective analysis. Oncology patients with diagnoses other than C. difficile infection were excluded from the study (Figure 1).

Data extraction: All selected patients’ case records were thoroughly reviewed, data were extracted and entered in a predefined excel sheet. For the defined period of the study: age of the patient, risk factors for infection, details on the usage of anti-microbiological agents in recent past, first versus recurrence C. Difficile infection, duration of hospital stay, hemodynamic instability, the requirement of vasopressors, type of treatment, mortality and outcome were recorded retrospectively.

Data analysis: Statistical analysis was done using SPSS, version 16. Means and percentages were reported for continuous and categorical

Figure 1. Synopsis of the selection of patients, their cancer types, the severity of infection with the outcome.
variables, respectively. Laboratory results (worst value documented in the hospital) were tabulated, and variables were studied with in-hospital mortality as the primary outcome. To compare the differences between categorical patient variables, chi-square test was used. A p value of less than 0.05 was considered statistically significant. We studied other variables in our patient set for their impact on mortality. We stratified patients for greater risk for a poor outcome using the qSOFA score system which is a bedside prompt that may identify patients with suspected infection who are outside the intensive care unit (ICU). It comprises of three criteria scoring system, with one point each for hypotension (SBP ≤100 mmHg), tachypnea (>22 breaths per min), or impaired mentation (GCS score <15). 41 patients fell into the low-risk category (0–1 score), while 18 patients fell into the high risk (2–3 score) category. The qSOFA score was calculated on the day of diagnosis of C. Difficile was made.  

Stratification of C. difficile: Patients with C. difficile infection were divided into categories (non-severe, severe, and very severe) based on the following established criteria: Non-severe is defined as patients with white blood cell count less than 15.00 × 10^9/L and serum creatinine less than 1.5 mg/dL. Severe C. difficile infection was defined as white blood cell count more than 15.00 × 10^9/L or serum creatinine equal or more than 1.5 mg/dL. Very severe/fulminant colitis was defined as patients with shock, ileus, or megacolon [9].

3. Results

3.1. Demographics of patients and cancer descriptions

A total number of 59 patients were found to have solid cancers and C. difficile infection. The median age of the study population was 79 years with 39 males and 20 females. The patients were suffering from malignancies located at the following sites: prostate (25 patients), lung (19 patients), colon (7 patients), bladder (4 patients), breast (3 patients), and renal (1 patient).

Data on C. difficile infection: We reviewed the electronic medical records and found 52 cases with the first episode of C. difficile infection-related admissions. The other 7 cases had 2 or more C. difficile infection-related admissions.

Amongst the 59 patients, 40 patients were detected to have C. difficile infection at presentation while the remaining 19 patients were diagnosed with C. difficile infection after admission and during the course of hospitalization (Table 1). Among the 19 patients, who developed infection during hospitalization, our review showed that 7 patients had hospital acquired infections (that is the occurrence of symptoms were after 3 days of admission to hospital). In our patient dataset, based on the above-mentioned criteria, we had non-severe (29 cases), severe (28 cases), and very severe/fulminant (2 cases). There were 33 patients and 20 patients actively receiving chemotherapy and radiotherapy, respectively. Six patients were not on any treatment at the time of admission. Table 2 mentions descriptive data of the cohort including age, gender, and proportions of variables that were evaluated as risk factors.

Associated comorbidities: We also studied our patients for the various comorbidities. The most commonly associated comorbidities were COPD (15 cases), congestive heart failure (11 cases), chronic kidney disease (10 cases), diabetes mellitus (5 cases), inflammatory bowel disease, asthma (2 cases), and interstitial lung disease (1 case). We did not compare these factors with the mortality outcome due to the small sample size.

Predisposing risk factors: In our study, we found that 27 patients had a recent history of cancer care-related procedures or interventions done within 3 months of admission to our hospital. 29 patients were from either a rehabilitation center or resident of a long-term nursing facility. There were 39 recent hospitalizations (<90 days) with 29 patients receiving antibiotics for various reasons (during prior hospitalization or as outpatient treatment). Almost half of the patients were on proton pump inhibitors (29 patients) and 12 were on steroids (20.3%) at the time of developing C. difficile infection.

Laboratory data: We also studied various laboratory parameters in our study population. Mean WBC count of the patients was 16.95 × 10^9/L (59 patients, Range: 0.5 to 40.3 × 10^9/L). Mean hemoglobin value was 9.66 g/dL (59 patients, Range: 6.2–14.9 g/dL). The mean platelet count was 210,650 per microlitre (59 patients, Range 9000 to 435,000 per microlitre). Analysis of the CBC data suggested that the impact of leukocytosis (59 patients, WBC >15 × 10^9/L) was significant with higher in-hospital mortality (P value: 0.016, CI: 0.030–0.815). There was no significant impact of anemia (defined as < 9 g/dL) and thrombocytopenia (defined as < 150,000 per microliter) on the survival outcome of our patients.

### Table 1. Indication of the hospitalization of C. difficile patients.

| Reason for admission       | Count |
|----------------------------|-------|
| C. difficile related        | 40    |
| Pneumonia                  | 7     |
| Dehydration, chemotherapy side effects | 4     |
| Urinary tract infection     | 4     |
| Congestive heart failure   | 2     |
| COPD                       | 2     |
| Total patient              | 59    |

### Table 2. Descriptive data of the cohort including age, gender, and proportions of variables that were evaluated as risk factors.

| Median Age | 79 years |
|------------|----------|
| Patient population | Total | 59 |
|             | Males | 39 |
|             | Females | 20 |
| Malignancy types | Prostate | 25 |
| Lung        | 19    |
| Colon       | 7     |
| Bladder     | 4     |
| Breast      | 3     |
| Renal       | 1     |
| C. Difficile severity | Non-Severe | 29 |
| Severe      | 28    |
| Very Severe | 2     |
| Treatment   | Chemotherapy | 33 |
| Radiotherapy | 20    |
| Variables   | Cancer related procedures | 27 |
| Nursing home residents | 29 |
| Recent hospitalizations | 39 |
| Recent Antibiotic use | 29 |
| Proton Pump use | 29 |
| Steroid use | 12    |
| Comorbidities | COPD | 15 |
| Chronic Kidney Disease | 10 |
| Diabetes mellitus | 5     |
| Inflammatory bowel disease | 2     |
| Asthma       | 2     |
| Intestinal Lung disease | 1     |
| Laboratory Data | Parameters | Mean value |
| WBC count    | 16.95 × 10^9/L |
| Hemoglobin   | 9.66 gm/dL    |
| Platelet count | 210,650/microlitre |
| Creatinine   | 1.41 mg/dL    |
| Albumin      | 2.56 gm/dL    |
| Lactate level | 2.45 mmol/L    |
Table 3. Analyzing various laboratory and clinical parameters with the in-hospital mortality.

### Impact of ICU stay on mortality

| Required ICU stay | Survived | Died | Marginal Row Totals | P value |
|-------------------|----------|------|----------------------|---------|
| Yes               | 7 (7.32) [0.01] | 2 (1.68) [0.06] | 9 | 0.764 |
| No                | 41 (40.68) [0] | 9 (9.32) [0.01] | 50 | |
| Marginal Column Totals | 48 | 11 | 59 (Grand Total) | |

### Impact of hospital stay on mortality

| Hospital stay | Alive | Died | Marginal Row Totals | P value |
|---------------|-------|------|----------------------|---------|
| <5 days       | 20 (18.71) [0.09] | 3 (4.29) [0.39] | 23 | 0.370 |
| >5 days       | 28 (29.29) [0.06] | 8 (6.71) [0.25] | 36 | |
| Marginal Column Totals | 48 | 11 | 59 (Grand Total) | |

### Impact of qSOFA stratification on mortality

| qSOFA risk category | Survived | Died | Marginal Row Totals | P value |
|---------------------|----------|------|----------------------|---------|
| Low risk (0–1 score)| 37 (33.36) [0.4] | 4 (7.64) [1.74] | 41 | 0.008 OR-0.636 (CI:0.041–0.689) Significant |
| High risk (2–3 score) | 11 (14.64) [0.91] | 7 (3.36) [3.96] | 18 | |
| Marginal Column Totals | 48 | 11 | 59 (Grand Total) | |

### Impact of cancer type on mortality

| Cancer type | Survived | Died | Marginal Row Totals | P value |
|-------------|----------|------|----------------------|---------|
| Colon cancer | 6 (5.69) [0.02] | 1 (1.31) [0.07] | 7 | |
| Cancers other than colon cancer | 42 (42.31) [0] | 10 (9.69) [0.01] | 52 | 0.107 |
| Marginal Column Totals | 48 | 11 | 59 (Grand Total) | |

### Impact of severity of C. difficile on mortality

| C. difficile severity | Survived | Died | Marginal Row Totals | P value |
|-----------------------|----------|------|----------------------|---------|
| Non severe            | 26 (23.59) [0.25] | 3 (5.41) [1.07] | 29 | 0.752 |
| Severe/Very Severe    | 22 (24.41) [0.24] | 8 (5.59) [1.04] | 30 | |
| Marginal Column Totals | 48 | 11 | 59 (Grand Total) | |

### Impact of severity of chemotherapy on mortality

| Chemotherapy | Survived | Died | Marginal Row Totals | P value |
|--------------|----------|------|----------------------|---------|
| Yes          | 29 (26.85) [0.17] | 4 (6.15) [0.75] | 33 | 0.147 |
| No           | 19 (21.15) [0.22] | 7 (4.85) [0.96] | 26 | |
| Marginal Column Totals | 48 | 11 | 59 (Grand Total) | |

### Impact of rehab/nursing facility stay on mortality

| Rehab/Nursing facility | Survived | Died | Marginal Row Totals | P value |
|------------------------|----------|------|----------------------|---------|
| Yes                    | 22 (23.59) [0.11] | 7 (5.41) [0.47] | 29 | 0.286 |
| No                     | 26 (24.41) [0.1] | 4 (5.59) [0.45] | 30 | |
| Marginal Column Totals | 48 | 11 | 59 (Grand Total) | |

### Impact of recent hospitalization stay on mortality

| Recent hospitalization | Survived | Died | Marginal Row Totals | P value |
|------------------------|----------|------|----------------------|---------|
| Yes                    | 29 (31.73) [0.23] | 10 (7.27) [1.02] | 39 | 0.053 |
| No                     | 19 (46.27) [0.46] | 1 (3.73) [2] | 20 | |
| Marginal Column Totals | 48 | 11 | 59 (Grand Total) | |

### Impact of recent antibiotics use on mortality

| Recent antibiotic use | Survived | Died | Marginal Row Totals | P value |
|-----------------------|----------|------|----------------------|---------|
| Yes                   | 21 (23.59) [0.29] | 8 (5.41) [1.24] | 29 | 0.082 |
| No                    | 27 (24.41) [0.28] | 3 (5.59) [1.2] | 30 | |
| Marginal Column Totals | 48 | 11 | 59 (Grand Total) | |

### Impact of recent proton pump inhibitors use on mortality

| Proton pump inhibitors | Survived | Died | Marginal Row Totals | P value |
|------------------------|----------|------|----------------------|---------|
| Yes                    | 23 (23.59) [0.01] | 6 (5.41) [0.07] | 29 | 0.691 |
| No                     | 25 (24.41) [0.01] | 5 (5.59) [0.06] | 30 | |
| Marginal column totals | 48 | 11 | 59 (Grand Total) | |

### Impact of leukocytosis (WBC >15 x10^9/L) on mortality

| WBC >15 x10^9/L | Survived | Died | Marginal Row Totals | P value |
|-----------------|----------|------|----------------------|---------|
| WBC <15         | 28 (24.41) [0.53] | 2 (5.59) [2.31] | 30 | 0.016 OR-0.1587 (CI: 0.030–0.815) Significant |
| WBC >15         | 20 (23.59) [0.55] | 9 (5.41) [2.39] | 29 | |
| Marginal Column Totals | 48 | 11 | 59 (Grand Total) | |

(continued on next page)
Similarly, we studied the comprehensive metabolic profile of our patients. Mean creatinine value was noted to be 1.41 mg/dL (59 patients, Range: 0.39–7.02 mg/dL). The mean serum albumin was 2.56 g/dL (49 patients, Range 1.4–4.1 g/dL). The mean serum lactate was 2.45 mmol/L (32 patients, Range 0.6–14.1 mmol/L). Analysis of the comprehensive metabolic profile data suggested that there was no impact of lactic acidosis, deranged renal function, or hypoalbuminemia on the survival outcome of our patients.

**Other parameters:** We found that patients with a high-risk qSOFA score of 2 or more (p-value = 0.008) were found to have higher inhospital mortality. Recent hospitalization, use of proton pump inhibitors, and steroids, staying in rehabilitation/nursing home were not associated with clinically significant mortality (Table 3).

### 3.2. Treatment and outcome

Critical care data suggested that 9 patients required intensive care therapy, 7 patients required vasopressor support, and 6 needed mechanical ventilation. Patients were treated per guideline-directed therapy (following Infectious Diseases Society of America guidelines; https://www.idsociety.org/practice-guideline/clostridium-difficile/) with either oral vancomycin alone (13 patients), or intravenous metronidazole alone (25 patients), or combination therapy with oral vancomycin and intravenous metronidazole (21 patients). The median duration of hospital stay was 6 days with 11 fatalities (18.64%). None of the patients were given fidaxomicin or fecal transplant treatment.

### 4. Discussion

Clostridioides difficile is the most common cause of nosocomial diarrhea [10]. It is associated with significant mortality and morbidity especially in old, frail individuals who are immunocompromised and have multiple comorbidities. As per the latest data from the Centers for Disease Control and Prevention (CDC), nearly half a million Clostridioides difficile infections are reported just from the United States. Of these, 15,000 deaths were assessed to be causally related to C. difficile infections [11]. In addition, recurrence rate is significantly high which adds to both health care and financial burden. Musher et al is their study of 207 patients reported a recurrence rate of 28% [12]. The problem of recurrence worsens in patients with cancer than non-cancer patients and this was reported by Chung et al in their recent study [13]. Unfortunately, with the advent of newer therapies like immunotherapy, cellular therapy and various target molecules, the incidence of opportunistic and nosocomial infections are expected to rise further [14, 15].

Studies in the recent past have suggested that patients with malignancies have higher mortality and longer duration of hospital stay as compared to patients without cancer [8, 16]. Delgado et al studied the data of Clostridioides difficile hospital discharges from 2001 to 2010. They found that cancer patients had 9.4% mortality rates as compared to non-cancer patients (7.5%, p < 0.0001). Also, the hospital stay was longer in patients with malignancies than those without that diagnosis (9 days vs. 4 days, p < 0.0001) [7]. We did not do a similar comparative study between cancer and non-cancer patients due to the small sample size.

### Table 3 (continued)

| Impact of anemia (< 90 g/L) on mortality | Survived | Died | Marginal Row Totals | P value |
|----------------------------------------|----------|------|---------------------|---------|
| Yes                                    | 19 (18.71) [0] | 4 (4.29) [0.02] | 23 | 0.843 |
| Marginal Column Totals                 | 24 8 32   |      | 59 (Grand Total)    |         |

| Impact of renal dysfunction (S. creatinine >1.5 mg/dL) on mortality | Survived | Died | Marginal Row Totals | P value |
|------------------------------------------------------------------|----------|------|---------------------|---------|
| S. creatinine                                                    |          |      |                     |         |
| <1.5                                                             | 33 (33.36) [0] | 8 (7.64) [0.02] | 41 | 0.796 |
| >1.5                                                             | 15 (14.64) [0.01] | 3 (3.36) [0.04] | 18 |         |
| Marginal Column Totals                                           | 48       | 11   | 59 (Grand Total)    |         |

| Impact of hypoalbuminemia on mortality | Survived | Died | Marginal Row Totals | P value |
|---------------------------------------|----------|------|---------------------|---------|
| S. albumin level (g/dL)               |          |      |                     |         |
| <3 g/dL                               | 27 (28.69) [0.1] | 10 (8.31) [0.35] | 37 | 0.177 |
| >3 g/dL                               | 11 (9.31) [0.31] | 1 (2.69) [1.07] | 12 |         |
| Marginal Column Totals                | 38       | 11   | 49 (Grand Total)    |         |

| Impact of lactic acidosis on mortality | Survived | Died | Marginal Row Totals | P value |
|--------------------------------------|----------|------|---------------------|---------|
| S. Lactate (mmol/L)                  |          |      |                     |         |
| <2                                   | 16 (15.75) [0] | 5 (5.25) [0.01] | 21 | 0.829 |
| >2                                   | 8 (8.25) [0.01] | 3 (2.75) [0.02] | 11 |         |
| Marginal Column Totals               | 24       | 8    | 32 (Grand Total)    |         |
more than 60 years as risk factors for postoperative C. difficile-associated colitis [29]. It is being postulated that there may be a potential change in intestinal microbiota following colorectal surgery which could predispose to develop C. colitis [28].

Almost half of our study population were (29/59) patients who were either from a rehabilitation center or long-term care nursing facility. Also, there was a significant number of recent hospitalizations (39 hospitalization events in total <90 days). Twenty-nine patients received a recent course of antibiotics for various reasons. These findings are in alignment with the established data on predisposing/risk factors for Clostridioides difficile infection in non-cancer patients. These findings were also confirmed in the recent study conducted in nine hospitals from seven European countries. In this study by Czepiel et al, a total of 624 patients were included. The frequency of co-morbidities was studied. The importance of early recognition, diagnosis, and treatment of Clostridioides difficile infection. They did not find any association between specific chemotherapy and risk to develop Clostridioides difficile infection. Interestingly, they found that patients with breast cancer had a greater predisposition to Clostridioides difficile infection. In contrast, patients with gastrointestinal malignancy had a lesser predisposition [23].

Leukocytosis (WBC >15 x 10⁹/L), and high Q SOFA score (High risk, 2–3 score) were the only two factors noted in our patient study group which was associated with an inpatient mortality. In our patients, the treatment protocol was decided by the infectious disease specialists depending on the severity of the disease and guideline-directed treatment protocols. The use of fecal microbiota transplantation (FMT) in cancer patients has also recently been explored. However, the major challenge remains the risk of donor-derived infection in the recipients [33].

4.1. Limitation of the study

We acknowledge a few potential shortcomings of the study due to the design of a retrospective model and associated potential confounders. Other important limitation noted was in determining symptomatic severity of CDI and temporal association with risk factors. In addition, the details of cancer treatment of our patients could not be retrieved. Of importance, the study design was a retrospective model and associated potential confounders. In our patient data, we could not retrieve detailed information regarding the chemotherapy/immunotherapy protocols used due to the inaccessibility to patient oncological treatment charts.

Another important fact to note is the wide differentials of gastrointestinal symptoms that an oncology patient can have; chemotherapy-induced mucositis, immune colitis, and non-Clostridioides difficile colitis. Garzotto et al did a retrospective study on 225 patients with solid tumors who were hospitalized with diarrhea. They found 39 of 225 patients (17.3 %) were subsequently diagnosed with Clostridioides difficile infection. They did not find any association between specific chemotherapy and risk to develop Clostridioides difficile infection. Interestingly, they found that patients with breast cancer had a greater predisposition to Clostridioides difficile infection. In contrast, patients with gastrointestinal malignancy had a lesser predisposition [23].

In our patients, the treatment protocol was decided by the infectious disease specialists depending on the severity of the disease and guideline-directed treatment protocols. The use of fecal microbiota transplantation (FMT) in cancer patients has also recently been explored. However, the major challenge remains the risk of donor-derived infection in the recipients [33].

5. Conclusion

Clostridioides difficile remains a major hurdle to improve the overall survival of patients with cancer. This interrupts the normal cycles of chemotherapy and radiotherapy and hence can have a serious impact on achieving or maintaining remission. Through this study, we emphasize the importance of early recognition, diagnosis, and treatment of Clostridioides difficile infections in patients with malignancies.

Declarations

Author contribution statement

Kamal Kant Sahu: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Susan George: Performed the experiments; Wrote the paper.

Ahmad Danial Siddiqui: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Ajay Mishra and Vishal Jindal: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

Acknowledgements

None.

References

[1] K.K. Sahu, A. Mishra, I. Chastain, Novel anticancers and dermatological adversities: old rivals but new challenges, BMJ Case Rep. 11 (1) (2018 Dec 14).
[2] S. Ghanein, C.J. Kim, D. Dutta, M. Salifu, S.H. Lim, Antimicrobial therapy during cancer treatment: beyond antibacterial effects, J. Intern. Med. (2020 Dec 29).
[3] A.R. Marra, E.N. Perencevich, R.E. Nelson, M. Samore, K. Khader, H.-Y. Chiang, et al., Incidence and outcomes associated with Clostridium difficile infections: a systematic review and meta-analysis, JAMA Netw Open 3 (1) (2020 Jan 3) e1917597.
[4] D. Dutta, F. Jafri, D. Suhr, B.M. Knoll, S.H. Lim, A contemporary review of Clostridioides difficile infections in patients with haematologic disorders, J. Intern. Med. (2020 Sep 10).
[5] L.M. Legenza, S.G. Barnett, W.E. Rose, Vaccines in development for the primary prevention of Clostridium difficile infection, J. Am. Pharm. Assoc. JAPHA 57 (4) (2017 Aug) 547–549.
[6] P. Eze, E. Balsells, M.H. Kyaw, H. Nair, Risk factors for Clostridium difficile infections - an overview of the evidence base and challenges in data synthesis, J. Glob. Health 7 (1) (2017 Jun). 010417.
[7] A. Delgado, L.A. Reveles, F.T. Cabello, K.R. Reveles, Poorer outcomes among cancer patients diagnosed with Clostridium difficile infections in United States community hospitals, BMC Infect. Dis. [Internet] 17 (2017 Jun 23) [cited 2021 Jan 16]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5481960/.
[8] M. Ramboj, C. Son, S. Cann, R.P. Chemaly, J. Dickman, E. Dubberke, et al., Hospital-onset Clostridium difficile infection rates in persons with cancer or hematopoietic stem cell transplant: a CBIC network report, Infect. Control Hosp. Epidemiol. 33 (11) (2012 Nov) 1162–1165.
[9] M. Kachrimanidou, N. Malisiovas, Clostridium difficile infection, J. Am. Pharm. Assoc JAPHA 57(4) (2017 Aug) 547–549.
[10] A. Lal, R. Davaro, A.K. Mishra, K.K. Sahu, G.M. Abraham, Detection of coexisting toxigenic Clostridium difficile and nontoxigenic Salmonella in a healthcare worker with diarrhea: a therapeutic dilemma, J. Fam. Med. Prim. Care 8 (8) (2019 Aug) 2724–2727.
[11] CDC Press Releases [Internet], CDC, 2016 [cited 2021 Jan 16]. Available from: http://www.cdc.gov/media/releases/2015/p0225-clostridium-difficile.html.
[12] D.M. Musher, S. Ablam, N. Logan, S. Nallscheru, I. Bhaila, F. Borchert, et al., Relatively poor outcome after treatment of Clostridium difficile colitis with metronidazole, Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 40 (11) (2005 Jun 1) 1586–1590.
[13] M.S. Chung, J. Kim, J.O. Kang, H. Pai, Impact of malignancy on Clostridium difficile infection, Eur. J. Clin. Microbiol. Infect. Dis. Off. Publ. Eur. Soc. Clin. Microbiol. 35 (11) (2016 Nov) 1771–1776.

[14] K.K. Sahu, K. Mahagoekar, B. Patel, D. Winokur, S. Suzuki, J.S. Daly, et al., Strongyloides stercoralis hyperinfection syndrome in mantle cell lymphoma in post-transplant setting, Ann. Hematol. (2020 May 6).

[15] A.K. Mishra, K.K. Sahu, A. James, Disseminated herpes zoster following treatment with benralizumab, Clin. Res. J. 13 (3) (2019 Mar) 189–191.

[16] K. Neemann, A. Freifeld, Clostridium difficile-associated diarrhea in the oncology patient, J. Oncol. Pract. 13 (1) (2017 Jan) 25–30.

[17] S. Sharma, P. Singh, K.K. Sahu, A. Rajwanshi, P. Malhotra, S. Naseem, Histoplasmosis in pleural effusion in a 23-year-old man with mixed-phenotype acute leukemia, Lab. Med. 48 (3) (2017 Aug 1) 249–252.

[18] I.C. Djuikoue, E. Tambo, G. Tazemda, O. Njajou, D. Makoudjou, V. Sokeng, et al., Evaluation of inpatients Clostridium difficile prevalence and risk factors in Cameroon, Infect. Dis. Poverty 9 (1) (2020 Aug 31) 122.

[19] D.N. Gerding, S. Johnson, Advances in pathogenesis, diagnosis and management of CDI, Nat. Rev. Gastroenterol. Hepatol. 8 (2) (2011 Feb) 67–68.

[20] A.N. Ananthakrishnan, Clostridium difficile infection: epidemiology, risk factors and management, Nat. Rev. Gastroenterol. Hepatol. 8 (1) (2011 Jan) 17–26.

[21] M.G. Hautmann, M. Hipp, O. Kölbl, Clostridium difficile-associated diarrhea in radiooncology: an underestimated problem for the feasibility of the radiooncological treatment? Radiat. Oncol. 6 (1) (2011 Aug 1) 89.

[22] A.M. Stringer, Interaction between Host cells and microbes in chemotherapy-induced mucositis, Nutrients 5 (5) (2013 May) 1488–1499.

[23] A. Rodríguez Garzotto, A. Mérida García, N. Muñoz Unceta, M.M. Galera Lopez, M.A. Orellana-Miguel, C.V. Díaz-García, et al., Risk factors associated with Clostridium difficile infection in adult oncology patients, Support. Care Cancer 23 (6) (2015 Jun 1) 1569–1577.

[24] R.V. McCaleb, A.S. Gandhi, S.M. Clark, A.B. Clemmons, Clinical outcomes of Acid suppressive therapy use in hematology/oncology patients at an academic medical center, Ann. Pharmacother. 50 (7) (2016 Jul 1) 541–547.

[25] K.D. Bishop, J.J. Castillo, Risk factors associated with Clostridium difficile infection in adult oncology patients with a history of recent hospitalization for febrile neutropenia, Leuk. Lymphoma 53 (8) (2012 Aug 1) 1617–1619.

[26] A. Anand, A.E. Glatt, Clostridium difficile infection associated with antineoplastic chemotherapy: a review, Clin. Infect. Dis. 17 (1) (1993 Jul 1) 109–113.

[27] J. Czepli, M. Krutova, A. Mizrahi, et al., Mortality following Clostridiodes difficile infection in Europe: a retrospective multicenter case-control study, Antibiotics (Basel) 10 (3) (2021) 299.

[28] I. Koliarakis, E. Athanasakis, M. Sgantzos, et al., Intestinal microbiota in colorectal cancer surgery, Cancers (Basel) 12 (10) (2020) 3011.

[29] C.H. Yeom, M.M. Cho, S.K. Baek, O.S. Bae, Risk factors for the development of Clostridium difficile-associated colitis after colorectal cancer surgery, J. Korean Soc. Coloproctol. 26 (5) (2010) 329–333.

[30] X.B. Lin, L.A. Diederman, A. Ketabi, I. Bibova, M.B. Sawyer, H. Xue, et al., Irinotecan (CPT-11) chemotherapy alters intestinal microbiota in tumour bearing rats, PLoS One 7 (7) (2012 Jul 26), e39764.

[31] I von Bültzingslowen, I. Adlerberth, A.E. Wold, G. Dahlen, M. Jontell, Oral and intestinal microflora in 5-fluorouracil treated rats, translocation to cervical and mesenteric lymph nodes and effects of probiotic bacteria, Oral Microbiol. Immunol. 18 (5) (2003) 278–284.

[32] N.A. Babacan, T. Tanwetyan, Superimposed Clostridium difficile infection during checkpoint inhibitor immunotherapy-induced colitis, J. Immunother. Hagerstown Md. 42 (9) (1997) 350–353, 2019 Dec.

[33] A. Sabus, M. Merrow, A. Heiden, J. Boster, J. Koo, A.R.K. Franklin, Fecal microbiota transplantation for treatment of severe Clostridioides difficile colitis in a pediatric patient with non-Hodgkin Lymphoma, J. Pediatr. Hematol. Oncol. (2020 Dec 2),