**Clostridium Difficile** Infection Retreatment Based on Initial Therapy in Patients with Cancer

Anastasia Finn, PharmD, MBA, BCOP; Jesse Young, PharmD; Kathy Edwards, PharmD, BCPS, BCOP; Andy Perez, PharmD, BCOP; Shawn MacVane, PharmD, BCPS

**BACKGROUND:** Limited recommendations exist for treating *Clostridium difficile* infection in patients with cancer, and the optimal treatment remains unclear. Studies have identified potential issues with current *C difficile* infection severity classification criteria in patients with cancer that may affect therapy selection.

**OBJECTIVES:** To evaluate treatment practices and retreatment rates for hospitalized patients with cancer at our institution who have *C difficile* infection and to assess the most effective treatment.

**METHODS:** This was a single-center, retrospective cohort study of hospitalized patients with cancer and *C difficile* infection between May 2011 and May 2014. Clinical severity was classified according to the Society for Healthcare Epidemiology of America (SHEA)/Infectious Diseases Society of America (IDSA) guidelines. We used descriptive statistics to assess the efficacy of initial antibiotic treatment by quantification of 90-day retreatment and mortality rates.

**RESULTS:** A total of 79 adult patients received treatment for an initial episode of *C difficile* infection. The majority (82%) of infections were classified as mild to moderate according to the SHEA/IDSA criteria. Patients received monotherapy consisting of metronidazole (67.0%), oral vancomycin (26.6%), or combination regimens (6.3%). Overall, 16 (20.3%) patients required retreatment for *C difficile* infection within 90 days. Retreatment rates were similar regardless of antibiotic exposure, fluoroquinolone prophylaxis, neutropenia, and hematologic versus nonhematologic malignancy. Receipt of active chemotherapy was associated with a higher rate of retreatment versus patients who were not receiving active cancer treatment (*P* = .016). Ninety-day retreatment rates were 26% in patients who received metronidazole monotherapy compared with 5% in patients who received oral vancomycin (*P* = .053).

**CONCLUSION:** At our institution, initial metronidazole monotherapy led to higher *C difficile* infection retreatment rates in patients with cancer compared with oral vancomycin. In the absence of more sensitive markers of *C difficile* infection severity, oral vancomycin may be a more appropriate initial treatment of *C difficile* infection in this patient population.

Treatment of *Clostridium difficile* infection presents a unique challenge in patients with cancer. *C difficile* infections are often related to the use of antibiotics and to hospitalizations, and patients undergoing chemotherapy treatment may be at a particularly high risk for infection. Limited recommendations exist for treating *C difficile* infection in patients with cancer, but most sources favor managing patients with cancer similar to patients without cancer in the absence of studies indicating otherwise. However, studies have identified potential issues with current classification criteria in determining the severity of *C difficile* infection in patients with hematologic malignancies, which may affect potential therapy choices. Wang and colleagues demonstrated that patients with hematologic malignancies were less likely to meet criteria for having severe *C difficile* infection based on common assessments, such as serum creatinine and white blood cell (WBC) count, suggesting that traditional classification of *C difficile* infection based on these parameters may not be accurate in patients with cancer.

Current *C difficile* infection treatment guidelines published by the Society for Healthcare Epidemiology of America (SHEA)/Infectious Diseases Society of America (IDSA) recommend the use of antibiotic therapies based on the severity of infection, which is stratified based on WBC count, serum creatinine level, and the presence of systemic complications, such as shock, hypotension, or ileus. The SHEA/IDSA guidelines recommend the use of oral metronidazole for patients who have nonsevere disease, and oral vancomycin in patients with severe or severe and complicated infections.
At the Medical University of South Carolina (MUSC), Charleston, the SHEA/IDSA guidelines are used to guide the treatment for all adult patients with suspected or documented C difficile infection (Table 1). However, severity of C difficile infection in patients with cancer can be difficult to assess, because neutropenia is a common adverse effect of standard chemotherapy regimens, thus compounding antibiotic selection based on clinical guidelines. It has also been suggested that vancomycin may be preferred as first-line therapy in patients with cancer because of better tolerance and fewer gastrointestinal side effects compared with metronidazole. In addition, studies have indicated growing resistance to treatment and infection recurrence with metronidazole therapy. For instance, a recent study conducted by Johnson and colleagues demonstrated that clinical success rates with metronidazole treatment for C difficile infection are significantly inferior to treatment with vancomycin (72.7% and 81.1%, respectively; P = .02). Patients were further stratified based on the severity of C difficile infection, and the rates of clinical success were again higher in patients with severe C difficile infection who received vancomycin versus metronidazole, although this difference was not significant (78.5% vs 66.3%, respectively; P = .059).

Because of the limited data available to guide C difficile infection therapy in patients with cancer, this study was designed to assess the efficacy of treatment by quantification of 90-day retreatment, and by mortality rates at MUSC to determine whether any treatment modifications are necessary in this patient population.

Methods

We conducted a retrospective cohort study to evaluate the selection and efficacy of antibiotic regimens prescribed for the treatment of C difficile infection in hospitalized patients with cancer at MUSC. Data were collected from May 1, 2011, through May 1, 2014. Patients with a positive C difficile toxin B gene detected by polymerase chain reaction were identified through an infectious disease database, and were included in the analysis if they were admitted to an inpatient oncology service at MUSC. Oncology services included in the study were inpatient malignant hematology, bone marrow transplant, solid tumor, surgical oncology, and gynecologic oncology services.

Patients with cancer who were in any intensive care unit were excluded, because their care was primarily managed by a critical care team. Patients with neurologic cancers were also excluded, because there is no designated inpatient neuro-oncology service or patient care unit, and these patients received treatment in the general neurology service, with consultation from neuro-oncology physicians.

Treatment efficacy was quantified through 90-day infection retreatment rates, collected via the infectious disease database and retrospective chart review. A 90-day window was chosen to evaluate the need for retreatment based on recommendations from the American College of Gastroenterology, as well as the use of a similar 90-day window by prospective studies measuring C difficile infection recurrence. In addition, the majority of patients included in this study were not retested for recurrent C difficile infection based on the inability to identify an active infection versus colonization, and instead received treatment based on recurrent symptoms alone. Thus, the primary outcome was defined as 90-day “retreatment” rather than “recurrence.” After performing the data collection and statistical analysis, the results were compared with the MUSC treatment guidelines and current literature regarding the treatment of C difficile infection in this patient population.

### Table 1: Recommendations4 for C difficile Infection Treatment

<table>
<thead>
<tr>
<th>Clinical definition</th>
<th>Supportive clinical data</th>
<th>Recommended treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial episode, mild or moderate</td>
<td>Leukocytosis with a WBC count ≥15,000 cells/mL or SCr &lt;1.5 times the premorbid level</td>
<td>Metronidazole, 500 mg 3 times daily, by mouth, for 10-14 days</td>
</tr>
<tr>
<td>Initial episode, severe</td>
<td>Leukocytosis with a WBC count ≥15,000 cells/mL or SCr ≥1.5 times the premorbid level</td>
<td>Vancomycin, 125 mg 4 times daily, by mouth, for 10-14 days</td>
</tr>
<tr>
<td>Initial episode, severe, complicated</td>
<td>Hypotension or shock, ileus, megacolon</td>
<td>Vancomycin, 500 mg 4 times daily, by mouth or by nasogastric tube, plus metronidazole, 500 mg every 8 hours intravenously; if complete ileus, consider adding rectal instillation of vancomycin</td>
</tr>
</tbody>
</table>

4According to the Medical University of South Carolina guidelines, which are based on the recommendations from the Society for Healthcare Epidemiology of America/Infectious Diseases Society of America. SCr indicates serum creatinine; WBC, white blood cell.

The primary end point was 90-day C difficile infection retreatment rates, defined as any retreatment for C difficile infection in the presence of recurrent symptoms within 90 days of treatment. Secondary end points included the need for escalation of therapy after initial C difficile infection treatment, inpatient deaths, 90-day all-cause mortality, and 90-day hospice discharge rate. Data collected included patient demographics, cancer history, and treatment information; known previous occurrences of C difficile infection; prophylactic or systemic antibiotics used at the time of C difficile infection treatment; documented concomitant infections; laboratory data at baseline and at initiation of C difficile infection treatment; documentation of signs suggesting severe, complicated C difficile infection, including hypotension, shock, ileus, or megacolon; treatment for C difficile infection; and patient outcome data.

Patients were assigned a severity score of mild-to-moderate C difficile infection, severe, or severe and complicated based on MUSC’s C difficile infection diagnosis and treatment guidelines (Table 1). To further classify patients as having a severe, complicated infection, information regarding the presence of hypotension, shock, ileus, or megacolon was collected from the patients’ medical charts. Hypotension was defined as ≥2 episodes of a systolic blood pressure <90 mm Hg or a diastolic blood pressure <60 mm Hg within 24 hours of C difficile infection diagnosis.

For data analysis, descriptive statistics were performed using Microsoft Excel. Median and interquartile ratio

### Table 2: Patient Demographic and Baseline Characteristics (N = 79)

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Results</th>
<th>Patient characteristics</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yrs (IQR)</td>
<td>62 (51-68)</td>
<td>Patients receiving active chemotherapy regimens, n (%)</td>
<td>43 (54.4)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>43 (54.4)</td>
<td>Median time from most recent chemotherapy administration, a days (IQR)</td>
<td>10 (5-17.5)</td>
</tr>
<tr>
<td>Cancer type, n (%)</td>
<td></td>
<td>Patients receiving active radiation therapy, n (%)</td>
<td>5 (6.3)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>16 (20.3)</td>
<td>Mean time from most recent radiation therapy, b days (IQR)</td>
<td>11 (3-22.5)</td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>15 (19.0)</td>
<td>History of autologous HSCT, n (%)</td>
<td>10 (12.7)</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>8 (10.1)</td>
<td>History of allogeneic HSCT, n (%)</td>
<td>11 (13.9)</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>6 (7.6)</td>
<td>Patients receiving systemic antibiotics at time of specimen, n (%)</td>
<td>39 (49.4)</td>
</tr>
<tr>
<td>Ovarian</td>
<td>5 (6.3)</td>
<td>Median time of continuous antibiotics before specimen, days (IQR)</td>
<td>3 (1-5)</td>
</tr>
<tr>
<td>Acute lymphoblastic leukemia</td>
<td>3 (3.8)</td>
<td>Patients receiving fluoroquinolone prophylaxis at time of specimen, n (%)</td>
<td>15 (19.0)</td>
</tr>
<tr>
<td>Gastric</td>
<td>3 (3.8)</td>
<td>Laboratory data</td>
<td></td>
</tr>
<tr>
<td>Lung cancer</td>
<td>3 (3.8)</td>
<td>Breast</td>
<td>3 (3.8)</td>
</tr>
<tr>
<td>Cervical</td>
<td>3 (3.8)</td>
<td>Median WBC count at time of diagnosis, cells/mm³ (IQR)</td>
<td>2810 (610-9600)</td>
</tr>
<tr>
<td>Endometrial</td>
<td>2 (2.5)</td>
<td>Kidney</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Kidney</td>
<td>1 (1.3)</td>
<td>Median ANC at time of diagnosis, cells/mm³ (IQR)</td>
<td>1320 (300-7200)</td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>1 (1.3)</td>
<td>Colorectal</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>1 (1.3)</td>
<td>Median premorbid SCr, mg/dL (IQR)</td>
<td>0.9 (0.7-1.1)</td>
</tr>
<tr>
<td>Head/neck</td>
<td>1 (1.3)</td>
<td>Head/neck</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Chronic myeloid leukemia</td>
<td>1 (1.3)</td>
<td>Median change in premorbid and SCr at time of specimen (IQR)</td>
<td>0.9 (0.8-1.1)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (10.1)</td>
<td>Patients with neutropenia (ANC &lt;500 cells/µL), n (%)</td>
<td>26 (32.9)</td>
</tr>
</tbody>
</table>

a43 patients.
b5 patients.

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Table 3  Infection and Treatment Characteristics (N = 79)

<table>
<thead>
<tr>
<th>Infection and treatment characteristics</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>C difficile infection severity classification, n (%)</td>
<td></td>
</tr>
<tr>
<td>Mild to moderate</td>
<td>65 (82.3)</td>
</tr>
<tr>
<td>Severe</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Severe and complicated</td>
<td>13 (16.4)</td>
</tr>
<tr>
<td>Initial treatment, oral metronidazole monotherapy, n (%)</td>
<td></td>
</tr>
<tr>
<td>500 mg every 8 hours, n</td>
<td>44</td>
</tr>
<tr>
<td>500 mg every 12 hours, n</td>
<td>1</td>
</tr>
<tr>
<td>Initial treatment, oral vancomycin monotherapy, n (%)</td>
<td></td>
</tr>
<tr>
<td>125 mg every 6 hours, n</td>
<td>15</td>
</tr>
<tr>
<td>250 mg every 6 hours, n</td>
<td>4</td>
</tr>
<tr>
<td>500 mg every 6 hours, n</td>
<td>2</td>
</tr>
<tr>
<td>Initial treatment, IV metronidazole monotherapy, n (%)</td>
<td></td>
</tr>
<tr>
<td>500 mg every 8 hours, n</td>
<td>8</td>
</tr>
<tr>
<td>Initial treatment, combination regimens, n (%)</td>
<td></td>
</tr>
<tr>
<td>Oral vancomycin + IV metronidazole, n</td>
<td>4</td>
</tr>
<tr>
<td>Oral vancomycin + rectal vancomycin + IV metronidazole, n</td>
<td>1</td>
</tr>
<tr>
<td>Median number of days of C difficile infection treatment (IQR)</td>
<td>14 (14-14)</td>
</tr>
<tr>
<td>Median length of hospitalization, days (IQR)</td>
<td>6 (3-17)</td>
</tr>
</tbody>
</table>

IQR indicates interquartile ratio; IV, intravenous.

Table 4  Initial Treatment Regimens for C difficile Infection

<table>
<thead>
<tr>
<th>Initial treatment regimen</th>
<th>Patients, n (%) (N = 79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral metronidazole monotherapy</td>
<td>45 (57.0)</td>
</tr>
<tr>
<td>500 mg every 8 hrs</td>
<td>44 (55.6)</td>
</tr>
<tr>
<td>500 mg every 12 hrs</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Oral vancomycin monotherapy</td>
<td>21 (26.6)</td>
</tr>
<tr>
<td>125 mg every 6 hrs</td>
<td>15 (19.0)</td>
</tr>
<tr>
<td>250 mg every 6 hrs</td>
<td>4 (5.1)</td>
</tr>
<tr>
<td>500 mg every 6 hrs</td>
<td>2 (2.5)</td>
</tr>
<tr>
<td>IV metronidazole monotherapy</td>
<td>8 (10.1)</td>
</tr>
<tr>
<td>500 mg every 8 hrs</td>
<td>8 (10.1)</td>
</tr>
<tr>
<td>500 mg every 12 hrs</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Combination regimens</td>
<td>5 (6.3)</td>
</tr>
<tr>
<td>Oral vancomycin + IV metronidazole</td>
<td>4 (5.1)</td>
</tr>
<tr>
<td>Oral vancomycin + rectal vancomycin + IV metronidazole</td>
<td>1 (1.3)</td>
</tr>
</tbody>
</table>

IV indicates intravenous.

calculations were used for quantitative analysis of non-normally distributed variables. Further data analysis was conducted through SPSS Statistics Software (Version 22.0; IBM, Armonk, NY). Pearson's chi-square test and Fisher's exact test were used for comparison of categorical data, and Kaplan-Meier survival analyses were used to compare recurrence and mortality rates.

Results

A total of 79 adult patients in an oncology service at our institution were treated for an initial episode of C difficile infection between May 1, 2011, and May 1, 2014, and were included in the analysis. Rates of C difficile infection were similar for the 3 years included in the analysis, with 26 to 27 infections treated annually.

Table 2 presents demographic and clinical characteristics of patients included in this analysis. Most (82%) infections were classified as mild to moderate based on WBC count and serum creatinine (Table 3).

The majority of patients (n = 45; 57.0%) initially received monotherapy consisting of oral metronidazole, followed by oral vancomycin (n = 21, 26.6%) and intravenous (IV) metronidazole (n = 8, 10.1%). In addition, 4 patients received combination regimens consisting of oral vancomycin and IV metronidazole, and 1 patient received a 3-drug regimen containing oral vancomycin, rectal vancomycin, and IV metronidazole (Table 4). No patients received initial therapy with rifaximin, fidaxomycin, tigecycline, or IV immunoglobulin, and the majority of patients received 14 days of therapy regardless of antibiotics utilized (Table 3).

Figure 1 depicts initial treatments according to C difficile infection severity.
difficult infection severity, demonstrating that the majority of patients were initially treated with metronidazole monotherapy regardless of difficult infection severity. Of note, these initial treatment regimens may not reflect the total therapy that the patient received throughout the entire course of difficult infection treatment, because regimens might have been adjusted or escalated as a result of persistent infection. Table 5 outlines the escalation of difficult infection treatment.

### Table 5: Escalation of C difficile Infection Treatment

<table>
<thead>
<tr>
<th>Treatment characteristics</th>
<th>Patients (N = 79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients requiring ≥1 escalations of therapy, n (%)</td>
<td>25 (31.6)</td>
</tr>
<tr>
<td>Switch from oral or IV metronidazole to oral vancomycin, n (%)</td>
<td>7 (8.9)</td>
</tr>
<tr>
<td>Addition of oral vancomycin, n (%)</td>
<td>7 (8.9)</td>
</tr>
<tr>
<td>Addition of IV metronidazole, n (%)</td>
<td>4 (5.1)</td>
</tr>
<tr>
<td>Switch from oral metronidazole to IV metronidazole, n (%)</td>
<td>3 (3.8)</td>
</tr>
<tr>
<td>Increase oral vancomycin dose, n (%)</td>
<td>2 (2.5)</td>
</tr>
<tr>
<td>Addition of oral metronidazole, n (%)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Median days to first treatment escalation from treatment initiation, n (IQR)</td>
<td>3 (2-5)</td>
</tr>
<tr>
<td>Patients requiring ≥2 escalations of therapy, n (%)</td>
<td>6 (7.8)</td>
</tr>
<tr>
<td>Switch from oral metronidazole to IV metronidazole, n (%)</td>
<td>3 (3.8)</td>
</tr>
<tr>
<td>Switch from oral or IV metronidazole to oral vancomycin, n (%)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Addition of IV metronidazole, n (%)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Addition of oral vancomycin, n (%)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Median days to second treatment escalation from treatment initiation, n (IQR)</td>
<td>3 (2-5)</td>
</tr>
<tr>
<td>Patients requiring 3 escalations of therapy, n (%)</td>
<td>2 (2.5)</td>
</tr>
<tr>
<td>Increase oral vancomycin dose, n (%)</td>
<td>2 (2.5)</td>
</tr>
<tr>
<td>Median time to third treatment escalation from treatment initiation, days (IQR)</td>
<td>8.5 (7-10)</td>
</tr>
<tr>
<td>Patients requiring 4 escalations of therapy, n (%)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Switch to fidaxomicin, n (%)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Time to fourth treatment escalation from treatment initiation, days (IQR)</td>
<td>13 (13-13)</td>
</tr>
</tbody>
</table>

IQR indicates interquartile ratio; IV, intravenous.

Among patients who required escalation of therapy (ie, change in drug, dose, and/or route) for persistent diarrhea, 25 (31.6%) patients required ≥1 escalations of therapy, 6 patients required ≥2 treatment escalations, 2 patients required 3 treatment escalations, and 1 patient required 4 treatment escalations. Various methods of treatment escalation were used based on the patient’s initial therapy, including switching from metronidazole to vancomycin, the addition of vancomycin, the addition of metronidazole, and/or increasing the vancomycin dose (Table 5).

The first treatment escalations were documented at a median of 3 days after initiation of difficult infection therapy. Notably, requirements for escalation of therapy were similar between groups, regardless of initial treatment, including 7 (33%) patients who received vancomycin monotherapy, 17 (32%) patients who received metronidazole monotherapy, and 1 (20%) patient who received combination therapy (P = .841).

With regard to the primary end point of difficult infection retreatment rates, 16 (20.3%) patients from the total sample required retreatment for a recurrent episode of difficult infection within 90 days of the initial treatment (Table 6). However, 22 (27.8%) patients died or were discharged to hospice and were presumed deceased within 6 months. When censoring for death or discharge...
to hospice within 90 days, a similar proportion of patients (11 of the remaining 57, 19.3%) required retreatment.

Retreatment rates were similar, regardless of systemic antibiotic administration, fluoroquinolone prophylaxis, or neutropenia, and were similar between patients with hematologic versus nonhematologic malignancies (56% vs 44% of the total retreatments, respectively). However, active chemotherapy was associated with an increased rate of retreatment, with 13 of the 16 (81%) patients requiring retreatment while receiving active chemotherapy treatments (P = .016).

With regard to the 90-day retreatment rates, we observed a 26.4% retreatment rate in patients who initially received metronidazole therapy (14/53 patients) compared with a 20% retreatment rate for patients who initiated combination therapy (1/5 patients) and a 4.8% retreatment rate for patients who initiated oral vancomycin (1/21 patients) for *C difficile* infection (P = .113; Figure 2). The difference in retreatment rates between vancomycin and metronidazole trends toward significance (P = .053) when excluding patients who received combination therapy, because of the very low number (5) of patients in that group, which potentially skews the retreatment comparisons.

The 90-day retreatment rates were also calculated for patients receiving vancomycin at any point during their therapy (42/79, 53%), including patients who received up-front combination therapy with vancomycin or those who received vancomycin because of escalation of therapy, versus those who did not receive vancomycin at any point during their treatment (37/79, 47%). Five of the 42 (11.9%) patients who received any vancomycin required retreatment at 90 days compared with 11 of the 37 (29.7%) patients who had never received vancomycin who required retreatment at 90 days (P = .057).

Retreatment rates also varied widely according to *C difficile* infection severity, with 25% (16/65) of patients classified as having mild-to-moderate infection requiring retreatment, no (0/1) patients classified as having severe infection requiring retreatment, and 15% (2/13) of patients classified as having a severe, complicated infection requiring retreatment (P = .90).

These results suggest that *C difficile* infection severity ratings do not accurately predict recurrence rates, because a higher percentage of patients with mild-to-moderate infections required retreatment compared with those with more severe infection. In addition, retreatment rates did not vary based on length of retreatment, because both groups (ie, patients requiring retreatment vs those who did not) were treated for a median of 14 days regardless of *C difficile* infection therapy. Of the 79 patients, 76 (96.2%) received the recommended antibiotic duration (ie, 10-14 days) or more), as clinically indicated.

There were 5 (6.3%) inpatient deaths during the initial admission for *C difficile* infection treatment, with a median of 20 days until inpatient death (Table 6). Two of the 5 inpatient deaths were identified as possibly related to *C difficile* infection, although the cause of death could not be directly attributed to the infection. Four (80%) of these inpatient deaths were in patients who initially received metronidazole monotherapy for *C difficile* infection, including 2 deaths that were possibly related to the infection (P = .209). Overall, 14 (17.7%) deaths were documented in the total sample of 79 patients within 90 days of initial *C difficile* infection treat-
ment, with a median time to death of 45 days (Table 6).

When classifying these deaths according to initial treatment, 21% (11/53) of patients who started with metronidazole monotherapy died within 90 days compared with 20% (1/5) of patients who started with combination therapy and 10% (2/21) of patients who started with oral vancomycin therapy for C difficile infection ($P = .517$; Figure 3). However, this difference becomes even less apparent when looking at patients’ total C difficile infection therapy, with 7 deaths occurring among the 42 patients who received vancomycin therapy at any point and 7 deaths among the 37 patients who did not receive any vancomycin therapy ($P = 1.000$).

**Discussion**

This study included patients with a wide range of malignancy types, clinical characteristics, and varying severity of C difficile infection. Although our study was not designed to assess the accuracy of current C difficile infection severity classifications in patients with cancer, our findings support other researchers’ hypotheses that common severity assessment criteria, such as those used in the SHEA/IDSA guidelines, may not adequately capture the severity of infection in patients with laboratory abnormalities related to hematologic malignancies and the associated treatments.

With regard to C difficile infection retreatment, our study indicates a comparable 90-day C difficile infection retreatment rate (20.3%) compared with other studies in patients with cancer. These retreatment rates are also similar to those presented in the literature for nononcology patient populations, which range from 6% to 25%. However, our study also suggests the need for more aggressive treatment of C difficile infection in patients with cancer based on the numerically higher retreatment rates observed in patients receiving initial metronidazole monotherapy versus initial vancomycin monotherapy (26.4% vs 4.8%, respectively).

In addition, we observed a higher retreatment rate in patients who did not receive any vancomycin therapy versus those who received vancomycin at any point (29.7% vs 11.9%, respectively). Although these differences were not significant in our study, our results point toward a better response in patients who received vancomycin therapy, initially or through therapy escalation. The relatively small patient population might have limited the ability to observe any significant differences between the treatment groups, and, therefore, we believe that this limitation, in combination with our findings, supports the use of vancomycin therapy preferentially over metronidazole in patients with cancer and C difficile infection to reduce the need for retreatment.

Although not assessed in our study, it is also important to consider the increasing role of metronidazole resistance when choosing an appropriate C difficile infection treatment regimen. Historically, the preferred initial treatment for C difficile infection has been oral metronidazole 500 mg every 8 hours. However, Musher and colleagues saw a cure rate of only 50% with oral metronidazole therapy in patients without cancer. Of the 50% of patients who were not cured, 22% continued to have symptoms of colitis despite a full course of metronidazole therapy, and 28% had an initial response but had infection recurrence within 90 days.

These data suggest that C difficile infections are becoming increasingly harder to treat with oral metronidazole, and the potential for resistance and recurrence must be considered in oncology and nononcology patient populations. Although we did not find any cases of possible resistance in our study, we observed that patients at our institution who received vancomycin therapy, initially or through escalation, were less likely to require retreatment than those who received metronidazole monotherapy.

We also attempted to measure any correlation between C difficile infection therapy and death within 90 days; however, an accurate cause of death is typically not available for patients who pass away outside of the hospital, and thus the assessment of C difficile infection–related deaths was limited. In addition, several treatment escalations were observed in our analysis, with 25 (31.6%) patients requiring a treatment escalation for persistent symptoms. Similar rates of treatment escalation were observed, regardless of initial treatment regimen.

However, further analysis demonstrated no relationship between treatment escalation and the need for C difficile infection retreatment, with only 3 (12%) of the 25 patients requiring treatment escalation also requiring C difficile infection retreatment within 90 days. This suggests that the need for C difficile infection treatment escalation because of persistent symptoms does not necessarily correlate with risk for C difficile infection recurrence.

It is important to note that the median time to first treatment escalation observed in this study was 3 days (interquartile ratio, 2-5 days). National guidelines currently recommend waiting 5 to 7 days before changing therapy for a presumed inadequate response; however, this recommendation is based on studies in nononcology patient populations that do not have many of the additional risk factors and clinical issues related to patients with cancer. Therefore, a shorter window before therapy escalation is appropriate in patients with cancer.  

**Limitations**

Several limitations need to be taken into consider-
ation when interpreting the results of this study. The sample size is relatively small, although it is comparable to existing studies on the topic.\textsuperscript{10} This, combined with high overall mortality and loss to follow-up, could affect the ability to detect true \textit{C difficile} infection retreatment rates for this population. In addition, a significant proportion (14\%) of patients were discharged to hospice care during follow-up, with a presumed prognosis of \textless{}6 months of life, also limiting the ability to adequately detect outcomes in this subset of patients. Nonetheless, when the data were censored for death and discharge to hospice, the retreatment rate was similar to our overall retreatment rate.

Furthermore, a single-center, retrospective chart review may have unknown confounders. Although the study design attempted to minimize confounding, the data were limited to the information available in the electronic medical record; recurrences and/or deaths outside of our institution were not necessarily documented and thus not captured in the data. In addition, possible confounders, such as \textit{C difficile} infection risk factors, were not controlled for in this limited analysis; however, statistical analyses did not identify any correlations between 90-day retreatment and current treatment with systemic antibiotics (\(P = .565\)) or use of fluoroquinolone prophylaxis (\(P = .644\)).

However, our analysis identified treatment with active chemotherapy as an additional risk for \textit{C difficile} infection recurrence, with 13 of the 16 patients requiring retreatment receiving active chemotherapy, which could have also affected the retreatment rates (\(P = .016\)). In addition, multiple potential causes of diarrhea in the study population may have contributed to the retreatment rates observed in this study (eg, prolonged broad-spectrum antibiotic exposure, chemotherapy, concurrent medications, and graft-versus-host disease). Another possible confounding factor is the inability to clinically distinguish a true recurrent \textit{C difficile} infection from a new primary infection, potentially skewing the retreatment rates.

Another notable limitation that could have significantly affected our findings is that final treatment decisions are at the discretion of the medical team and are largely based on patients’ clinical status and clinician preference; therefore, prescribing patterns of individual providers could have influenced our findings. For example, the use of IV metronidazole monotherapy falls outside of current institutional and national guidelines, because it is known to have lower fecal concentrations compared with oral metronidazole. Nonetheless, we found that 8 patients were prescribed IV metronidazole monotherapy for initial \textit{C difficile} infection management. Because of the retrospective nature of our analysis, we were unable to identify the clinical reasoning behind the choice to prescribe IV metronidazole monotherapy, but acknowledge that it was an inappropriate choice for initial \textit{C difficile} infection treatment.

In addition, our analysis is primarily based on initial treatment; although we attempted to capture the entirety of \textit{C difficile} infection treatment, this presented a challenge because patients’ medications and/or doses were often changed based on symptoms with no standardized approach to treatment escalation. Thus, most of the outcomes reported in this study are correlated to the patients’ initial \textit{C difficile} infection treatment or whether the patient received any vancomycin versus no vancomycin. Treatment escalations were reported as a separate outcome to help quantify the changes that were made throughout \textit{C difficile} infection treatments.

Finally, because of the advanced age and immunosuppressed status of many patients with cancer, severity classifications based on WBC count and serum creatinine elevations underestimate \textit{C difficile} infection severity in these patients and may be unreliable in this population.\textsuperscript{3} When considering the laboratory parameters for our oncology patient population, the median WBC count (2810 cells/mm\(^3\)) and serum creatinine level (0.9 mg/dL) were much lower than expected in a typical sample of patients with \textit{C difficile} infection. Thus, it is important to note that the increased retreatment rates seen in the metronidazole group could be related to underclassification of infection severity in these patients, leading to inadequate treatment of patients who may have required more aggressive \textit{C difficile} infection therapy.

More recent practice guidelines for \textit{C difficile} infection management from the \textit{American Journal of Gastroenterology} broaden the criteria for severe and complicated disease (eg, mental status changes, WBC count <2000 cells/mm\(^3\), end organ failure), which may more accurately stage severity in this population, and offers a precedent for new treatment protocol.\textsuperscript{11} The inability to accurately and consistently stratify patients for treatment is an inherent limitation; however, this further illustrates the need for evidence-based guidance for \textit{C difficile} infection management specific to the adult oncology patient population.

Conclusions

The results of this study suggest that \textit{C difficile} infection treatment with vancomycin, initially or through treatment escalation, reduces the need for retreatment in the inpatient setting in patients with cancer. In addition, the severity of \textit{C difficile} infection is difficult to assess in this patient population, because of various laboratory abnormalities, and may lead to undertreatment based on conventional treatment recommendations, such as those...
from SHEA/IDSA.

Based on the results of this study, our institution has implemented an oncology-specific treatment guideline recommending all patients with cancer receive up-front oral vancomycin therapy rather than metronidazole for initial episodes of mild-to-moderate \textit{C difficile} infection. Patients with severe or severe and complicated \textit{C difficile} infection will continue to be treated according to SHEA/IDSA guidelines. This guideline implementation will be followed by an analysis that will again assess 90-day retreatment and mortality rates, as well as changes in the acquisition of multidrug-resistant organisms (eg, vancomycin-resistant \textit{Enterococcus}, methicillin-resistant \textit{Staphylococcus aureus}) within 90 days. Future prospective, randomized trials are necessary to further clarify the role of these drugs in treating \textit{C difficile} infection in oncology and nononcology patient populations.

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Author Disclosure Statement

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