# A retrospective review of metronidazole and vancomycin in the management of *Clostridium difficile* infection in high risk patients with hematologic malignancies

Sapna Parmar, Pharm.D. • Edmund Hayes, Pharm.D., M.S. • Michael Schuster, M.D.

Stony Brook Medicine

## Abstract

**Objectives:**
To assess the incidence of *Clostridium difficile* infection (CDI) and outcomes of treatment with metronidazole or vancomycin in high risk patients with hematologic malignancies. The goal is to develop an evidence-based protocol for management of CDI in the oncology and hematopoietic stem cell transplant (HSCT) population

**Methods:**
Data collection included a retrospective review of all patients with leukemia, lymphoma, multiple myeloma, and those undergoing stem cell transplantation (SCT) with a diagnosis of CDI at Stony Brook University Hospital. The specific endpoints to be evaluated include: age, gender, underlying malignancy, type of stem cell transplant if appropriate; the concomitant antimicrobials and chemotherapeutic agents prescribed; WBC, ANC, serum creatinine, and presence of fever at presentation of CDI; outcomes of stem cell transplant and 6 month overall survival

**Results:**
77 patients with leukemia, lymphoma, multiple myeloma, and those undergoing stem cell transplantation developed CDI during the study period (incidence of 19.7%). 37.6% were stem cell transplant recipients. At time of diagnosis of CDI, 61.8% of patients presented with mild-moderate disease and 34.2% of patients presented with severe disease. The most commonly prescribed initial treatment was either PO or IV metronidazole (43.4% and 28.9%, respectively). 51.3% of patients resolved with initial treatment and 47.3% experienced treatment failure. The overall recurrence rate was 22.3%, with 25.5% in non-SCT patients and 17.2% in SCT recipients. Combination therapy was the most common treatment modality at recurrence (58.8%). The 6 month overall survival was found to be 75%, with a higher survival rate in those who did not undergo transplantation

**Conclusion:**
Development of CDI in the oncology/HSCT population continues to be a concern. Initial therapy with metronidazole may result in treatment failures and recurrences in this high risk patient population. Stronger data are necessary to assess the optimal method of managing these patients and to determine which therapy achieves the most favorable outcomes

## Introduction

- *Clostridium difficile* is the most commonly recognized cause of infectious diarrhea in healthcare settings and accounts for 20-30% of all cases of antibiotic-associated diarrhea[1]
- Major risk factors include prior/current exposure to antimicrobials, advanced age (>64 years), hospitalization, severe underlying illness, gastric acid suppression, manipulation of the gastrointestinal tract, cancer chemotherapy, and HSCT[2-4]
- The cancer/HSCT immunocompromised population possess many of the aforementioned risk factors
- Treatment of CDI in the cancer/HSCT population is similar to that in the general population and is based on currently available guidelines. Comparative efficacies of metronidazole and vancomycin have not been evaluated in cancer/HSCT patients[5]
- CDI occurs frequently and is often severe, contributing to debilitating symptoms and compromised care of underlying cancer.[2] Stronger data are necessary to assess the optimal method of managing these patients and to ascertain which therapy (metronidazole versus vancomycin) achieves the least days to resolution and most positive outcomes

## Objectives

**Primary Endpoints:**
- Assess the incidence and severity of CDI in admitted patients with hematologic malignancies based on positive PCR test result for *Clostridium difficile* toxin
- Assess the outcome of CDI after therapy with metronidazole and/or vancomycin

**Secondary Endpoints:**
- Determine the relationship between concomitant antimicrobial and chemotherapeutic agents given and development of CDI
- Identify incidence of neutropenia and determine relationship with CDI
- Evaluate use of alternative agents for refractory CDI
- Evaluate outcomes of CDI in HSCT patients
- Determine 6 month overall survival of patients who developed CDI

## Methods

- Upon IRB approval, a retrospective review of 390 patients with diagnosis of CDI from January 2009 - January 2012 was conducted
- Adults with primary diagnosis of leukemia, lymphoma, multiple myeloma, and those undergoing stem cell transplantation were included in the primary analysis
- Pregnant woman, children (< 18 years), and patients with diagnosis of recurrent CDI were excluded
- Outcomes defined as:
  - Resolution: therapy with either/both agents for a total of 10-14 days
  - Initial treatment failure:
    - Therapy with either/both agents for > 14 days and/or
    - Use of second line therapy
  - Recurrence: need for re-treatment for CDI within 6 weeks post-initial therapy
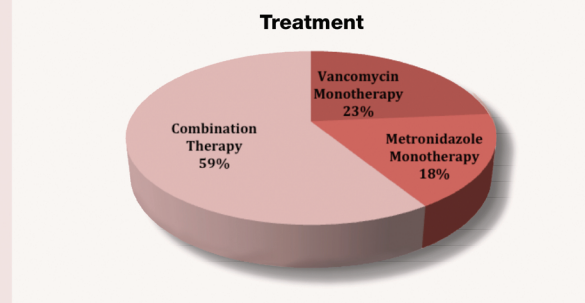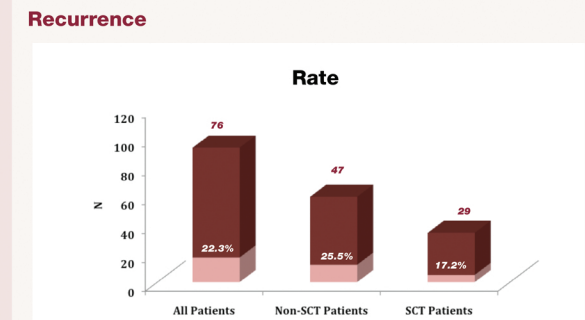
## Results

**Incidence**
N (%)



| | Overall Incidence 77 (19.7) | |
|---|---|---|
| Non-SCT 47 (13) | | SCT only 25 (20.5) |
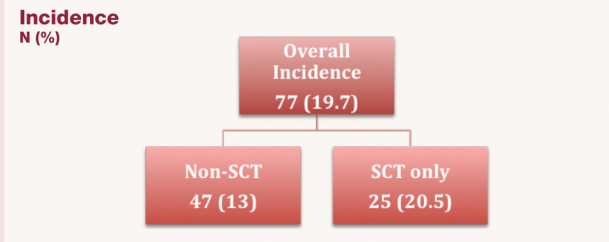
### Baseline Characteristics

| | N = 77 (%) |
|---|---|
| Median age (years) | 60 ± 15 (26-85) |
| **Gender** | |
| Male | 44 (57.1) |
| Female | 33 (42.8) |
| **Underlying malignancy** | |
| AML | 26 (33.7) |
| B-cell lymphoma | 17 (22) |
| Multiple myeloma | 15 (19.5) |
| ALL | 8 (10.3) |
| Other | 6 (7.8) |
| Chronic leukemia | 5 (6.5) |
| **Stem cell transplantation** | 29 (37.6) |
| Autologous | 18 (62.1) |
| Allogeneic | 11 (37.9) |
| **Concomitant antimicrobials** | |
| Cefepime | 47 (61) |
| Vancomycin | 41 (53.2) |
| Fluoroquinolones | 28 (36.7) |
| Sulfamethoxazole/TMP | 24 (31.2) |
| Carbapenems | 23 (29.8) |
| Linezolid | 17 (22.1) |
| Piperacillin/tazobactam | 10 (12.9) |
| Aztreonam | 8 (10.4) |
| Other | 20 (25.9) |
| **Concomitant chemotherapy** | |
| Cytarabine | 20 (25.9) |
| Etoposide | 13 (16.9) |
| Cyclophosphamide | 12 (15.6) |
| Melphalan | 12 (15.6) |
| Methotrexate | 11 (14.3) |
| Vincristine | 10 (12.9) |
| Other | 23 (29.8) |

### CDI Characteristics

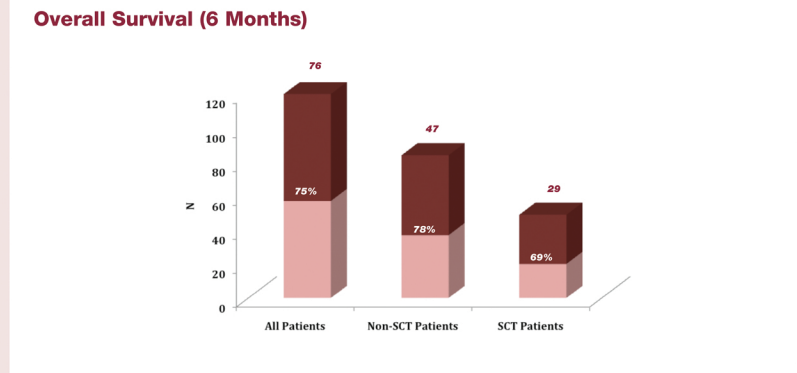| Severity | N (%) |
|---|---|
| Mild-moderate | 47 (61.8) |
| Severe | 29 (34.2) |
| **Laboratory parameters** | |
| Fever > 38.0° C at diagnosis | 21 (27.6) |
| WBC count (k/mcL) | 1.1 ± 10 (0.1-67.5) |
| Absolute neutrophil count (k/mcL) | 0.35 ± 6.5 (0-49.9) |
| Serum creatinine baseline (mg/dL) | 0.79 ± 1.78 (0.4-12.2) |
| Serum creatinine at diagnosis (mg/dL) | 0.7 ± 0.97 (0.27-7.27) |

**Initial Treatment**



N = 76
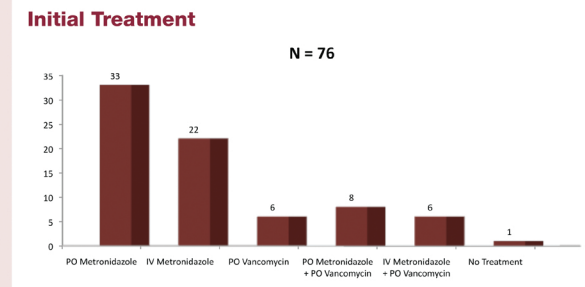
### Treatment Outcomes

| | All patients N = 76 (%) | Non-SCT patients N = 47 (%) | SCT patients only N = 29 (%) |
|---|---|---|---|
| Resolution | 39 (51.3) | 24 (51.1) | 15 (51.7) |
| 1° treatment failure | 17 (22.3) | 11 (23.4) | 6 (20.7) |
| 1° failure; 2° resolution | 12 (15.8) | 5 (10.6) | 7 (24.1) |
| Treatment failure | 7 (9.2) | 6 (12.8) | 1 (3.4) |
| Not treated | 1 (1.3) | 1 (2.1) | 0 (0) |

### Recurrence



**Rate**



**Treatment**

- Vancomycin Monotherapy 23%
- Metronidazole Monotherapy 18%
- Combination Therapy 59%

## Results

**Overall Survival (6 Months)**



## Discussion

- Of the 390 patients screened retrospectively from January 2009 – January 2012, 77 developed CDI (19.7%) with an incidence of 13% in non-SCT patients and 20.5% in SCT recipients
- Use of broad-spectrum antimicrobials was common during the study period with cefepime and vancomycin being employed most often (61% and 53.2%, respectively)
- Seventy two percent of patients received metronidazole as initial therapy which resulted in a 51% overall resolution of CDI
- Primary treatment failures were seen in 22% of patients and second-line treatment resulted in a 15.8% resolution rate
- Overall failure rate with initial therapy was 9.2% with a slightly higher incidence in non-SCT patients (12.8%)
- Approximately one-fourth of patients recurred and were most commonly managed with combination therapy (58.8%)
- The overall survival rate was 75% and was found to be similar in non-SCT patients and SCT recipients (78.7% and 68.9%, respectively)

## Conclusion

Development of CDI in the oncology/HSCT population continues to be a concern. Initial therapy with metronidazole may result in treatment failures and recurrences in this high risk patient population. Stronger data are necessary to assess the optimal method of managing these patients and to determine which therapy achieves the most favorable outcomes

## References

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## Disclosures

Authors of this presentation do not have anything to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation