Are Antimotility Agents Safe for Use in *Clostridioides difficile* Infections? Results From an Observational Study in Malignant Hematology Patients

Carla Kuon, MD; Rae Wannier, MPH; David Sterken, MD; Margaret C. Fang, MD, MPH; Jeffrey Wolf, MD; and Priya A. Prasad, PhD, MPH

Abstract

**Objectives:** To evaluate the safety of antimotility agents (AAs) in a population of patients with hematologic malignancies and concurrent *Clostridioides difficile* infection (CDI) and to describe the outcomes of AA use in a hospital setting.

**Patients and Methods:** We used the electronic health record to identify patients who were hospitalized in the adult malignant hematology service who had 1 or more toxin-positive *C. difficile* stool assay between April 1, 2012, and September 21, 2017. We reviewed medical charts to obtain information on the use of AAs and any subsequent gastrointestinal complications.

**Results:** There were 339 patients who were stool toxin positive for CDI during the study period. Of those, 94 patients (27%) were prescribed AAs within 14 days of CDI diagnosis. All patients received CDI antimicrobial therapy within the first 24 hours. There were 2 adverse gastrointestinal events in the group that received AAs and 6 in the group that did not receive AAs. The risk of adverse events did not differ between patients who received AAs and those who did not (adjusted odds ratio, 0.36; 95% CI, 0.06 to 2.10). The mean age of the full cohort was 52.7 ± 15.5 years, and the mean length of stay was 26.7 ± 22.6 days. Early AA use (<48 hours of diagnosis) was not associated with increased adverse effects.

**Conclusion:** There was no increase in the incidence of gastrointestinal events in the arm that used AAs compared with the control arm. The evidence suggests that for patients with hematologic malignancies and CDI, the addition of AAs to appropriate antimicrobial therapy poses no additional risk.

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**Cllostridiodes difficile** infection (CDI) causes considerable morbidity in patients with cancer, and the incidence is high, ranging from 2.3% to 7% in patients receiving conventional chemotherapy to 5% to 30% after hematopoietic stem cell transplant (HSCT). The recurrence rate is as high as 50% in the population who underwent HSCT. The associated risk factors include antibiotic use, hospitalization, advanced age, and immunosuppression. Other risk factors include hypoalbuminemia, use of proton pump inhibitors, and antineoplastic therapy. Diarrhea-related complications can include dehydration, electrolyte imbalances such as hypokalemia, hypomagnesemia, and hypotension. The increased number of diarrhea days raise concern not only for increased nosocomial transmission in the inpatient setting but also for increased patient discomfort and physical deconditioning from reduced mobility. The use of antimotility agents (AAs) to reduce the number of diarrhea days and diarrhea-related complications could prove to be a useful adjunctive therapy if we can better understand their safety profile.

The use of AAs in patients with active CDI has traditionally been avoided because of fear of gastrointestinal complications. In fact, the drug loperamide is contraindicated in all cases of pseudomembranous enterocolitis as it is “thought to exacerbate toxin-mediated..."
disease and precipitate toxic mega-colon."\textsuperscript{15} The 2010 Infectious Disease Society of America (IDSA) guidelines discouraged the use of AAs because it might "obscure symptoms and cause toxic mega-colon" on the basis of low quality of evidence (grade C-III).\textsuperscript{16} The 2017 guidelines omitted this recommendation, mentioning instead that the "addition of an antimotility agent such as loperamide as an adjunct to specific antimicrobial therapy for CDI may be safe, although no prospective or randomized studies are available."\textsuperscript{17} Although some studies have suggested that there is no increase in the rate of adverse outcomes in patients with CDI who are treated with AAs,\textsuperscript{11,18} there is a paucity of data on the safety of AA use because of clinical reluctance to use these agents in CDI. In response to these concerns, we conducted a retrospective cohort study of inpatients in the malignant hematology service to describe the use and outcomes of AAs in a population of patients with hematologic malignancies and concurrent CDI.

\section*{PATIENTS AND METHODS}

\subsection*{Setting}
We conducted our retrospective observational cohort study at the University of California, San Francisco (UCSF) Medical Center, a tertiary care academic hospital with 800 beds. The study was approved with a waiver of informed consent by the UCSF Institutional Review Board. The adult malignant hematology service has 66 beds on 2 floors of the hospital. The service treats patients who are currently undergoing HSCT and those with hematologic malignancies who are undergoing chemotherapeutic treatment. The malignant hematology unit conducts more than 220 blood and marrow transplants each year.

\subsection*{Data Collection}
We used the electronic health record (EHR) to identify all inpatients in the malignant hematology service who screened positive for CDI during their admission and had an underlying hematologic malignancy on the basis of International Statistical Classification of Diseases, Ninth Revision (ICD-9) or International Statistical Classification of Diseases, Tenth Revision (ICD-10) codes between April 1, 2012, and September 21, 2017. Hematologic malignancy diagnoses were identified using ICD-9/10 codes for lymphoma, multiple myeloma, leukemia, and myelodysplastic syndromes as well as patients admitted for complications of chemotherapy such as neutropenic fevers. We included patients whose treatment window included chemotherapy alone as well as those whose treatment included a bone marrow transplant (allogeneic or autologous). We excluded patients diagnosed with graft vs host disease, as this cohort frequently has refractory diarrhea and a high degree of gastrointestinal complications, which could serve as a confounder in our safety and efficacy analysis. We also excluded patients diagnosed with CDI as an outpatient who were subsequently hospitalized. We excluded patients who were colonized but not infected with \textit{C difficile} and who therefore did not receive CDI antimicrobial therapy.

Data for the study were collected using UCSF’s Epic-based EHR (Epic Systems Corporation, Verona, Wisconsin) system. We obtained data from Clarity, the relational database that stores Epic’s inpatient data, including orders, medications, fluid boluses, laboratory results, ICD-9/10 diagnosis and procedure codes, progress and consultation notes, radiology results, vital signs, and patient demographic characteristics.

\subsection*{Definitions}
During our study period, patients were diagnosed with CDI if they had 1 or more stools that were positive by enzyme immunoassay for \textit{C difficile} toxin and somatic antigen, consistent with IDSA clinical practice guidelines.\textsuperscript{16,17} Stools that were negative for toxin assay but positive for antigens were sent for confirmatory toxin polymerase chain reaction testing to confirm colonization, not infection. Patients deemed colonized with \textit{C difficile} were placed on enteric precautions per IDSA guidelines, but did not receive treatment and were excluded from our study. \textit{Diarrhea} was defined as 3 or more unformed stools within a 24-hour period, and if diarrhea was documented on a given day, it was considered as a \textit{diarrhea day}. Recurrent CDI was defined as any CDI—positive test result that occurred more than 28 days after the previous positive stool toxin test result, which equates to 2
weeks after the completion of appropriate treatment with oral vancomycin or metronida-
zole. This is in adherence to the 2010 and 2017 IDSA guidelines for recurrent CDI as CDI occurring 2 to 8 weeks after the completion of therapy.16,17,19 Our study period pre-
ceded the February 2018 publication of the 2017 IDSA CDI guidelines, which recommend oral vancomycin for all cases of CDI regardless of severity. Because the 2010 IDSA guideline definition for severe CDI (white blood cell count > 15 cells x10^9 L^-1 and elevated creati-
nine) is not applicable to patients with hematologic malignancies owing to their underlying disease pathology and response to chemo-
therapy with neutropenia and frequent creati-
nine elevation, patients in our study were diagnosed with severe CDI if they required dual therapy with vancomycin and metronida-
zole. Dual therapy was a surrogate for severe illness, as clinicians evaluate patients who are severely ill and apply dual therapy in this population.

**Exposure and Covariates**
The primary exposure for our study was administration of at least 1 dose of AAs, including loperamide 2 mg, atropine/diphe-
noxylate 2.5 mg, or any dose of opium tincture, within 14 days of CDI diagnosis. Early use of AAs was defined as use of an AA within the first 48 hours of CDI diagnosis, and late use of AAs was defined if AAs were administered more than 48 hours after CDI diagnosis.

Additional covariates including demo-
graphic characteristics (sex, age, race, and ethnicity) were collected. To determine the severity of CDI, CDI treatment regimen, tem-
perature, receipt and volume of fluid boluses, intensive care unit admission, outside hospital transfers, length of stay, and the number of days of diarrhea within the first 72 hours of positive CDI test results were collected.

**Outcomes**
Outcomes were assessed from day 4 through day 14 after the positive CDI test result. This was done to avoid any overlap between the first 3 days of disease presentation being used to define disease severity to avoid duplication of data as well as in an effort to isolate the patient’s response to medication rather than initial disease severity. The primary outcome of interest for the study was the development of any adverse gastrointestinal event, including toxic megacolon, ileus, or bowel obstruction as identified using ICD-9/
10 codes (Table 1). All patients who were coded with an adverse gastrointestinal event had their charts manually reviewed to determine whether the adverse event occurred because of CDI diagnosis after AA administration and to identify adverse gastrointestinal events likely to be associated with the receipt of AAs.

For our secondary outcomes, we measured response to AAs by counting the number of diarrhea days, measuring markers of hydration status, and evaluating the incidence of skin breakdown. First, we defined a diarrhea day as any day with more than 3 liquid stools within a 24-hour period as charted in the EHR and counted the number of diarrhea days occurring 4 to 14 days after diagnosis. Second, we assessed hydration status by measuring the number of fluid boluses given as well as the total volume of fluid given during the same period after CDI diagnosis. Lastly, we measured the number of wound care consults during the same outcome period as a surrogate for the incidence of skin breakdown.

Statistical Analyses

Associations between demographic characteristics, markers of disease severity, and the use of AAs were assessed using the chi-square test for categorical variables and the Student t test for continuous variables. The unadjusted association between AAs and our primary outcome of adverse events was also assessed using logistic regression.

Multivariate logistic regression was used to analyze the association of adverse events with AAs after adjustment for confounding. We used a propensity score to adjust for confounding by indication and severity of illness. We included the variables sex, age, race, and ethnicity as well as markers of disease severity in our propensity score, factors that were considered confounders of the relationship between AAs and adverse gastrointestinal events. Markers of disease severity included receipt of single agent vancomycin or metronidazole during CDI vs dual agent therapy with vancomycin and metronidazole (which we categorized as severe CDI), fever measured as the highest recorded temperature during the first 72 hours, total volume of fluid boluses received in the first 72 hours, intensive care unit admission during hospital stay, outside hospital transfer, length of stay, and the number of days of diarrhea in the first 72 hours.

For our secondary analyses, we used linear regression to evaluate the association between the AA use and the continuous outcome of the total volume of fluid boluses administered. We used Poisson regression to evaluate the association of the total number of diarrhea days, number of boluses, and number of wound care consults with AAs. Poisson regression was chosen because all were low numbered count variables showing a Poisson distribution. We adjusted for covariates using the same propensity score built for the primary outcome analysis.

### TABLE 2. Patient Demographic Characteristics by AA use for the study cohort (N=339)a

| Characteristic                              | No AA (n=245) | AA (n=94) | Total | P value |
|--------------------------------------------|---------------|-----------|-------|---------|
| **Antibiotic use**                         |               |           |       |         |
| No antibiotic                              | 0 (0)         | 0 (0)     | 0 (0) | <.001   |
| Single antibiotic                          | 188 (77)      | 53 (56)   | 241 (71) |       |
| Two antibioticsb                           | 57 (23)       | 41 (44)   | 98 (29) |       |
| **Sex**                                    |               |           |       |         |
| Female                                     | 94 (38)       | 33 (35)   | 127 (37) | .667   |
| **Race**                                   |               |           |       |         |
| Asian                                      | 38 (16)       | 12 (13)   | 50 (15) | .005   |
| Black                                      | 9 (4)         | 5 (5)     | 14 (4) |       |
| White                                      | 125 (52)      | 66 (70)   | 191 (56) |       |
| Other                                      | 69 (29)       | 11 (12)   | 80 (25) |       |
| **Ethnicity**                              |               |           |       |         |
| Hispanic/Latino                            | 54 (23)       | 10 (11)   | 64 (19) | .025   |
| Intensive care unit during the stay         | 33 (13)       | 10 (11)   | 43 (13) | .604   |
| Outside hospital transfer                   | 35 (14)       | 7 (7)     | 42 (12) | .127   |
| **Language**                               |               |           |       |         |
| English                                    | 206 (84)      | 85 (90)   | 291 (86) | .825   |
| Spanish                                    | 22 (9)        | 5 (5)     | 27 (8) |       |
| Other                                      | 17 (7)        | 4 (4)     | 21 (6) |       |
| **Highest temperature (°F)**               | 99.6±1.6      | 99.9±1.8  | 99.6±1.6 | .157   |
| **Length of stay (d)**                     | 24.7±21.5     | 32.0±24.6 | 26.7±22.6 | .012   |
| **Age (y)**                                | 52.1±15.8     | 54.1±14.7 | 52.7±15.5 | .264   |
| **Time to AA use (d)**                     | —             | 1.1±2.6   | —      | —      |

aAA = antimotility agent.

bData are presented as mean ± SD or as No. (percentage). For categorical variables, P values were calculated using the χ² statistic. For continuous variables, P values were calculated using the Student t test statistic.

cTreatment with both vancomycin and metronidazole.
As part of an ad hoc analysis, we repeated the previous analyses using early vs late use AAs as our primary exposure. We defined late AA use as the onset of AA use more than 48 hours after CDI diagnosis. We looked at the effect of early AAs vs late AAs on our primary outcome adverse events as well as on all our secondary outcomes.

We also performed a sensitivity analysis extending the outcome assessment period to days 0 to 14 instead of the outcome assessment period of 4 to 14 days, which was used in our primary analysis. This was done to investigate the dependence of our results on the presentation of disease severity at the onset as there was significant variability in time to AA use.

**RESULTS**

We identified 339 patients with CDI in our cohort. Patient characteristics including age, sex, race, malignancy type, and length of stay are presented in Table 2. The mean age was 52.7 years. Of the 339 patients who were diagnosed with CDI, 7 patients (2%) had a recurrent infection. The mean length of stay was 26.7 days. Antimotility agents were used in 27% of cases (n = 94).

**Primary Outcome**

There were 2 diagnoses of adverse gastrointestinal events in the cohort that received AAs, which occurred 10 and 12 days after CDI diagnosis, vs 6 cases of adverse gastrointestinal events in the cohort that did not receive AAs. None of the patients in the AA cohort developed toxic megacolon, required surgery, or suffered a CDI-related death. The risk of adverse events did not differ between patients who received AAs and those who did not (2.1% vs 2.4%; adjusted odds ratio, 0.36; 95% CI, 0.06 to 2.10) (Table 3).

**Secondary Outcomes**

Overall, patients who received AAs had more number of days of diarrhea (4.85 vs 2.24; P<.001) (Table 3), though this was not significant in the adjusted analysis (relative risk [RR], 1.06; 95% CI, 0.78 to 1.43; P<.111). Early use of AAs was associated with a 0.49 RR in the number of days of diarrhea in the unadjusted analysis and a 0.61 RR in the adjusted analysis (P<.001) (Table 4). There

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**Table 3. Unadjusted and Adjusted Multivariate Analyses for Primary and Secondary Outcomes by AA Use**

| Outcome          | No AAs (n=245) | 6 (2.4) | 2.24±3.15 | 0.79±0.97 | Number of fluid boluses administered (dL) |
|------------------|---------------|---------|-----------|-----------|-----------------------------------------|
| Adverse events   | 384           | <0.01   | 4.85±3.44 | 0.78±0.12 | 0.11±0.03 | Total volume fluid boluses administered (dL) |
| Number of fluid boluses | 2 (1.2) | <0.01   | 2.10±0.73 | 0.80±0.36 | 0.10±0.05 | Total volume fluid boluses administered (dL) |
| Number of wound care consults | 9.53 | 0.49 | 5.48±5.53 | 0.50±0.15 | 0.50±0.25 | Total volume fluid boluses administered (dL) |

AA = antimotility agent; OR = odds ratio; RD = risk difference; RR = risk ratio.

Data are presented as mean ± SD or as No. (percentage) unless stated otherwise. The primary outcome of adverse events was analyzed using logistic regression. The number of days of diarrhea, number of fluid boluses, and number of wound care consults were analyzed using Poisson regression. The total volume of fluid boluses administered was analyzed using linear regression. The adjusted analyses incorporated a propensity score to control for confounders.
were no significant differences in the number of fluid boluses given, the total volume of intravenous fluid given, or the number of wound care consults in adjusted or unadjusted analyses.

**Subgroup Analysis of Those Who Received AAs**

Of the 94 who received AAs, 33 (35.1%) were administered in the first 48 hours, with no adverse effects. There were 40 patients (42.6%) who received AAs during days 2 to 7, 13 patients (13.8%) received AAs on days 8 to 10, and 8 patients (8.5%) received AAs on days 11 to 14 (Figure). In a linear regression of time delay to AA use and length of stay, every additional day of delay in AA use was associated with an increase in length of stay of 1.35 days (standard error, 0.6956; \( P = 0.0563 \)), though the results were not statistically significant (Table 4).

Of the 2 individuals who received AAs with an adverse gastrointestinal event, neither of them were given more than 1 type of AA, both were given loperamide, with an average number of 3.5 doses, an average dose size of 2 mg per dose, and an average length of dosing of 2.75 days. This is in contrast to the average number of doses of AAs given to the patients in the study without adverse gastrointestinal events, who had a far higher number of doses given (8.13±8.94), with an average dose size of 2.5±0.8 mg per dose for patients who received loperamide and a length of medication receipt of 3.01±2.38 days (Table 5). Thus, we did not observe a correlation between the increased number of doses and adverse gastrointestinal events.

**Sensitivity Analysis of the Outcome Assessment Window**

The sensitivity analysis extending the outcome assessment period to days 0 to 14 did not change any of the effect estimates meaningfully, nor did it change any of the inferences for the outcomes (Table 6).

**DISCUSSION**

Our study contributes to the literature evaluating the safety of AAs as adjunct therapy in the treatment of CDI in the population of patients with hematologic malignancies. We found that the use of AAs in the malignant

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**TABLE 4.** Unadjusted and Adjusted Analyses for Primary and Secondary Outcomes by Early (n=33) vs Late (n=61) Use in Antimotility Agent Users

| Outcome                          | Unadjusted analysis                     | Adjusted analysis                        |
|---------------------------------|-----------------------------------------|------------------------------------------|
|                                 | OR (95% CI)                             | P value                                  |
| Adverse events                  | *                                       | *                                        |
|                                 | RR (95% CI)                             | P value                                  |
| Number of days of diarrhea      | 0.49 (0.39 to 0.62)                     | <.001                                    |
|                                 | 0.61 (0.48 to 0.79)                     | <.001                                    |
| Length of stay (d)              | -7.83 (−18.40 to 2.74)                  | .15                                      |
|                                 | -4.88 (−14.74 to 4.99)                  | .336                                     |

*OR, odds ratio; RD, risk difference; RR, risk ratio; *, no value.

Late exposure to antimotility agent use was defined as >48 h of diagnosis to the initiation of treatment after the diagnosis of *Clostridioides difficile* infection diagnosis. The number of days of diarrhea was analyzed using Poisson regression. The length of stay was analyzed using linear regression. There were only 2 adverse events in this population, making it inappropriate to conduct a logistic regression analysis.
hematology service was not associated with an increased risk of gastrointestinal complications. In addition, the early use of AAs (within 48 hours) did not increase the risk of gastrointestinal complications despite being used in more than a quarter (27.1%) of the cohort treated with AAs.

In 2009, Koo and colleagues18 reviewed the literature and described a patient cohort with CDI who suffered from complications due to AA use. Tellingly, in this series of 55 patients, those who suffered from complications were given AAs alone before proper antibiotic therapy for CDI and the 23 patients who received metronidazole or vancomycin along with AAs suffered from no complications. In 2013, Krishna et al11 studied the use of AAs in patients with CDI and multiple myeloma and found that the use of AAs and prophylactic CDI antibiotic therapy in patients with diarrhea was associated with excellent outcomes.

Although there was no significant difference in the number of days of diarrhea between patients who received AAs and those who did not, among those who received AAs, early use of AAs was associated with a reduction in the number of diarrhea days as compared with late use AAs. The difference should be interpreted with caution, given the smaller cohort and the potential for bias related to the timing of AA administration. In addition, the lack of overall decrease in the number of diarrhea days with total AA use may reflect confounding by indication. The outcome of ongoing diarrhea that is used retrospectively to make the treatment decision to add AAs later in therapy is likely to select for patients who have already developed refractory diarrhea and have accumulated more number of diarrhea days, which will lead to a bias in the estimate for the association of AA use with diarrhea days away from a protective effect. Likewise, there could be a bias in

| Antimotility agent | Dose (mg) | Length of dosing (d) | Patients receiving alone (%) | Number of doses |
|--------------------|-----------|---------------------|-----------------------------|----------------|
| Loperamide         | 2.5±0.84  | 3.0±2.4             | 71 (75.5)                   | 5.8±5.3        |
| Diphenoxylate/atropine | 3.4±1.2  | 2.9±2.5             | 0 (0.0)                     | 8.9±10.0       |
| Opium              | 2.3±2.2   | 3.1±2.8             | 0 (0.0)                     | 7.9±9.4        |

*aData are presented as mean ± SD or as No. (percentage).
*bMany patients received multiple agents over the course of their stay.

table 5. Summary of Dosing of Antimotility Agents Separately Reported for Loperamide, Diphenoxylate/Atropine, and Opium

| Outcome                  | Adjusted analysis | Unadjusted analysis |
|--------------------------|-------------------|---------------------|
|                          | OR (95% CI)       | P value             | OR (95% CI)       | P value             |
| Adverse events           | 0.36 (0.06 to 2.10) | .255               | 0.87 (0.17 to 4.37) | .384               |
| Number of days of diarrhea | 1.04 (0.83 to 1.30) | .031               | 1.80 (1.62 to 1.99) | <.001               |
| Number of fluid boluses  | 0.68 (0.34 to 1.37) | .726               | 0.96 (0.79 to 1.18) | .724               |
| Number of wound care consults | 1.09 (−3.27 to 5.45) | .28               | 1.00 (0.53 to 1.89) | .994               |
| Total volume of fluid    | 1.09 (−3.27 to 5.45) | .625               | 0.23 (−3.73 to 4.19) | .909               |

*aOR = odds ratio; RD = risk difference; RR = risk ratio.
*bThe primary outcome of adverse events was analyzed using logistic regression. The number of days of diarrhea, number of fluid boluses, and number of wound care consults were analyzed using Poisson regression. The total volume of fluid boluses administered was analyzed using linear regression. The adjusted analyses incorporated a propensity score to control for confounders.

Table 6. Adjusted and Unadjusted Multivariate Analyses for Primary and Secondary Outcomes by Antimotility Agent Use During Days 0 to 14 After CDI Diagnosis
the estimate for the association of early AA use vs late AA use in a protective direction. We found no significant difference in our secondary outcomes of the number of fluid boluses given, the total volume of intravenous fluid given, or the number of wound care consults in adjusted or unadjusted analyses.

The favorable outcomes and lack of adverse effects after AA use most likely reflects the aggressive screening for CDI in the population of patients with hematologic malignancies and prompt initiation of antimicrobial treatment in the case of a confirmed infection in the inpatient setting. The malignant hematology protocol of UCSF mandates CDI testing after each third loose stool and prompt initiation of antimicrobial treatment within 4 hours of a confirmed infection. This finding appears to support the findings from the study by Koo and colleagues, in which adverse outcomes in the use of AAs appeared to be related to delays in antimicrobial treatment rather than AA use as adjunct therapy.

There are limitations to this study. First, our model includes several covariates even though there were only 8 outcomes. However, the rule of thumb that 10 events are needed per variable in a multivariate model has been found to be too conservative in epidemiological analysis. Second, for our secondary outcomes, the number of wound care consults is a sensitive but not a specific surrogate for the incidence of skin breakdown due to CDI; therefore, true incidence may be lower, as skin breakdown may occur because of prolonged bed rest from chemotherapy-related fatigue or other variables inherent to chemotherapy treatment. Third, the unpredictable nature of AA use depending on physician style likely reflects some inherent random element to the data, which is relevant to our choice of study. Fourth, our study relied on the use of ICD-9/10 codes to identify adverse gastrointestinal events, though the adverse events included are major complications that would include billable procedures that would have been identified using coding. Finally, our study is retrospective and observational. The strengths of this study include its larger cohort size relative to previous studies and use of the EHR to capture any in-hospital complications. Given the concerns regarding AA safety in CDI, it would be difficult to conduct a randomized controlled trial without further evidence that can come from observational studies like ours. With the results of this study, an argument can be made that there is evidence to justify a randomized controlled trial as a next step.

CONCLUSION

Our study suggests that the use of AAs for malignant hematology in patients who are being appropriately treated for CDI with antimicrobial therapy does not appear to increase the risk of gastrointestinal complications. Additionally, early use of AAs in the first 48 hours of diagnosis and antibiotic therapy was not associated with any increase in adverse outcomes and appeared to decrease the number of diarrhea days. Reassessment of current guidelines for CDI therapy and future prospective studies should be considered.

Abbreviations and Acronyms: AA = antimotility agent; CDI = *Clostridium difficile* infection; EHR = electronic health record; HSCT = hematopoietic stem cell transplant; ICD-9 = International Classification of Diseases, Ninth Revision; ICD-10 = International Statistical Classification of Diseases, Tenth Revision; IDSA = Infectious Disease Society of America; RR = relative risk; UCSF = University of California, San Francisco

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Correspondence: Address to Carla Kuon, MD, Division of Hospital Medicine, University of California, San Francisco, 1545 Divisadero St, 4th Floor San Francisco, CA 94143.

ORCID
Carla Kuon: https://orcid.org/0000-0003-0723-3803

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