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EDITORIAL COMMENTARY

Oral Vancomycin to Prevent *Clostridioides difficile* in Stem Cell Transplant Recipients: The Last Frontier in Antimicrobial Prophylaxis

Carolyn D. Alonso[1,2]

[1]Division of Infectious Diseases, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA, and [2]Harvard Medical School, Boston, Massachusetts, USA

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Despite major advances in cancer therapies over the last decade, infection still represents an Achilles' heel in the management of patients following stem cell transplantation. While we have refined prophylactic strategies against enteric gram-negative bacteria, honed in on appropriate approaches to prevent viral pathogens such a cytomegalovirus, and further improved antifungal prophylaxis in this setting, prevention of *Clostridioides difficile* infection (CDI) continues to be an area where the data are not clear. CDI affects an estimated 460 000 patients per year, resulting in symptomatic diarrheal disease [1], lengthening of hospitalizations [2], and downstream consequences in the stem cell transplant population, including a possible association with graft-vs-host disease [3]. Rates of CDI in the cancer population are more than double that of the general hospital population, independent of testing methods [4]. Multiple strategies to combat this problem have been explored, including enhanced infection control [5] and diagnostic and antimicrobial stewardship interventions [6, 7]. Unfortunately, despite best efforts, these strategies have fallen short of eliminating CDI in many major cancer centers. Logically, the traditional approach to prevent CDI, using prophylactic oral antimicrobials, has been utilized by some clinicians, including use of agents such as metronidazole, oral vancomycin, and fidaxomicin to prevent primary and recurrent CDI [8].

In this issue of *Open Forum Infectious Diseases*, Williams and colleagues retrospectively evaluated the effect of oral vancomycin prophylaxis (OVP) on a cohort of 254 autologous hematopoietic stem cell transplant (HCT) recipients from January 2012 through December 2021 at a single academic medical center [9]. Groups were separated into patients treated with OVP and those who did not receive OVP, following an institutional shift to OVP in 2017. Between 2012 and 2016 (106 patients), OVP was not used. From 2017 to 2021, oral vancomycin at 125 mg twice a day was given to all patients undergoing autologous HCT (148 patients), from the start of conditioning through discharge. Patients were followed for development of CDI during the HCT hospitalization and in the 180 days following discharge. The primary outcome was CDI during the index HCT hospitalization. Secondary outcomes included CDI in the 180 days after follow-up and differences in admission length of stay.

Overall, CDI rates were consistent with the published literature [10], with 10% of the cohort (26 patients) developing CDI during the study period. Most cases (69%) occurred during the index hospitalization. CDI occurred in 4% of patients receiving OVP and in 11% of patients who were not receiving OVP ($P = .03$). At any given point during the index hospitalization, OVP was associated with a 63.7% reduction in risk of CDI (hazard ratio, 0.363; 95% CI, .122–.995; $P = .049$). There were no statistically significant differences in the secondary outcomes of CDI in the 180 days postdischarge (2% in the no-OVP group vs 4% in the OVP group, $P = .47$) or in the composite outcome of CDI during HCT and in the 180-day follow-up period (13.2% in the no-OVP group vs 8.1% in the OVP group, $P = .19$).

The study had several limitations. Notably, there were changes to the diagnostic testing for CDI during the study period, and consequently the definition of CDI changed over time. CDI testing was triggered by a nursing-driven algorithm that encouraged *C difficile* testing in a patient with new-onset diarrhea. From 2012 to 2018, the institution used an Xpert *C difficile* test based on polymerase chain reaction (PCR). A positive PCR

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Correspondence: Carolyn D. Alonso, MD, Division of Infectious Diseases, Beth Israel Deaconess Medical Center, 330 Brookline Ave, Boston, MA 02215 (calonso@bidmc.harvard.edu).

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result was interpreted as CDI. After 2018, the institution switched to PCR screening, followed by reflex testing with an enzyme immunoassay for the detection of *C difficile* glutamate dehydrogenase antigen and toxins A and B. During this time, a positive enzyme immunoassay result indicated CDI. As acknowledged by the authors, the looser criteria for CDI in the earlier period raise the possibility that *C difficile* carriers may have been included. More stringent CDI testing in this population is necessary [11].

Considering that real-world data may be heterogenous, the study may have benefited from exploration of other potential causes of diarrhea (ie, medications, cytomegalovirus, laxatives, mucositis) to further adjudicate the cases [12]. Study groups were unbalanced by underlying malignancy and conditioning regimen. Notably, more than double the number of participants in the no-OVP group (53% vs 25%) received conditioning with BEAM (carmustine, etoposide, cytarabine, and melphalan). Gastrointestinal toxicity has been reported with melphalan-based therapy, when given in high doses or when given as part of the BEAM regimen [13], making it challenging to know whether the study findings may have been influenced by clinical covariates such as the conditioning regimen. Finally, while the authors found no difference in CDI rates in patients by OVP exposure at 180 days, antibiotic exposure was not measured beyond the index hospitalization. So much can happen in the vulnerable period beyond the initial hospitalization, including rehabilitation or nursing facility stays, readmissions for complications, and additional infections needing antimicrobial therapy.

Notwithstanding these limitations, if the study's finding of a clinical benefit of OVP is verified, this would add to several other relevant studies that have suggested a potential benefit to this approach [8], and it would be the first to address the problem in the autologous HCT population. The authors should be commended for tackling a longer follow-up period, which has been a major shortcoming of prior research. The work also underscores the recognition that OVP does not prevent risk for CDI entirely. Many unanswered questions remain. What is the optimal dosing and duration of OVP? Which key populations should we target for OVP? What are the effects on the intestinal microbiome? Are there potential negative sequalae to this approach? It will behoove future studies to evaluate the effects of OVP on measurable outcomes, such as rates of multidrug-resistant organisms and bacteremic episodes. Moving the needle forward in the field may require an alternative approach to our traditional methods of antimicrobial prophylaxis. Novel approaches to restore the gut microbiome with oral regenerative bacteriotherapy are currently in development for patients undergoing stem cell transplant [14]. Early findings provide promise that some gastrointestinal complications may be preventable post-HCT [15]. Perhaps our future prophylactic strategies will contain a cocktail of targeted antimicrobials with restorative microbes to squeeze out the niche that antibiotics have created for *C difficile*. Williams et al open the conversation on how best to approach this last frontier in antimicrobial prophylaxis in the stem cell transplant population.

Note

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