Determining the Optimal Use of Antibiotics in Hematopoietic Stem Cell Transplant Recipients

Miranda So, PharmD, MPH

This study by Rashidi and colleagues sought to characterize the association of antibiotic exposure and timing of the exposure relative to allogeneic hematopoietic stem cell transplantation (allo-HCT) with the hazard of developing acute graft-vs-host disease (aGVHD), which is one of the most common complications of allo-HCT. Rashidi et al applied 3 orthogonal methods (conventional Cox proportional-hazards regression, marginal structural models, and machine learning) to analyze data collected from 2023 patients who underwent their first T-replete allo-HCT at a single center between 2010 and 2021. Each of the included analytical methods has its own strengths and weaknesses, but together they provided a comprehensive perspective. Rashidi et al reported that weeks 1 and 2 after allo-HCT were the highest-risk intervals, with several antibiotic exposures associated with higher risk of subsequent aGVHD. Of note, carbapenem exposure weeks 1 and 2 after allo-HCT was associated with a minimum hazard ratio (HR) of 2.75 (95% CI, 1.77-4.28), whereas week 1 after allo-HCT exposure to penicillins with β-lactamase inhibitors was associated with a minimum HR of 6.55 (95% CI, 2.35-18.20). Across all 3 methods, the data from the study by Rashidi et al also suggest that pre-allo-HCT exposure to penicillins with β-lactamase inhibitors was associated with a lower risk of aGVHD.

These findings have implications on patient care, as penicillins with β-lactamase inhibitor (eg, piperacillin-tazobactam) and carbapenems (eg, meropenem) are broad-spectrum antibiotics with antipseudomonal activity commonly administered during pre-engraftment, when the patient is most at risk of infections due to profound and prolonged neutropenia. Although there was some variability in the results among the 3 analytical methods, taken together, they suggest that a thoughtful and judicious approach to antibiotic prescribing during the critical periods during and immediately after allo-HCT is warranted to mitigate against aGVHD. In addition to the significant morbidity affecting the skin, gastrointestinal tract, and liver, treatment for aGVHD commonly involves escalating the dose of immunosuppression plus systemic corticosteroids. In turn, these interventions create additional risks for infections and perpetuate the cycle for more antimicrobials.

Determining the optimal use of antibiotics is a topic of interest to both allo-HCT clinicians and the antimicrobial stewardship team. In the past decade, cancer therapy underwent dramatic advances through the discovery of targeted small-molecule therapies, novel application of stem cell transplant techniques, and the emerging use of cellular therapy, such as chimeric antigen receptor T-cell therapy. However, infectious complications and antimicrobial resistance continue to pose significant threats to clinical success. Compared with cancer treatment, the antimicrobial pipeline has made modest progress in the availability of new classes of antibiotics, although not nearly as prolific. Thus, preserving the effectiveness of antibiotics and mitigating against antibiotic resistance remain integral to supporting patients throughout their cancer treatment. Antimicrobial stewardship interventions for the prevention and management of neutropenic fever in patients receiving treatment for hematological malignant neoplasms is gaining momentum. For patients undergoing allo-HCT, the role of antibiotics, regimen selection, and timing of antibiotic administration during the peritransplant periods (ie, pretransplant conditioning regimen and pre-engraftment after HCT) is less well understood. Furthermore, there is a lack of consensus framework to assess the likelihood of benefit vs the potential harms from antibiotic exposure in the immediate, medium, and long term after allo-HCT, making implementation of antimicrobial stewardship more challenging.
may be perceived as protective for the patient by the prescriber, especially during the pre-engraftment phase when the patient is profoundly neutropenic with severe mucositis and is susceptible to health care–associated infections. However, emerging data are pointing toward the potential harms. While not specific to the hematology-oncology population, a study by Curran et al. found that each day of antibiotic therapy was associated with 4% increased odds of experiencing an adverse drug event (odds ratio [OR], 1.04; 95% CI, 1.02–1.07). In particular, each additional day of antibiotics was associated with 13% increased odds of dermatological adverse events (OR per additional day, 1.13; 95% CI, 1.05–1.21). Specific to the HCT population, a study by Peled et al. profiled 8767 fecal samples from 1362 patients who underwent allo-HCT at 4 cancer centers across 3 continents. Peled et al. observed patterns of microbiota disruption characterized by loss of diversity and domination by single taxa. Importantly, higher diversity of intestinal microbiota was associated with a lower risk of death. Furthermore, subgroup analyses found an association between lower intestinal diversity and higher risks of transplantation-related death and death attributable to GVHD. While the observational nature of the study by Peled et al. introduces risk of biases—patients who were more severely ill may have had more cancer therapy, more health care, and more antibiotic exposure and thus were at higher risk of worse outcome, including mortality after allo-HCT—these findings were consistent with prior studies and the current understanding of the pathogenesis of microbiome injury.

The results from the study by Rashidi et al. improve our understanding of the deleterious association of gut microbiota disruption with the development of aGVHD and contribute to risk vs benefit assessments in antibiotic prescribing. These findings pave the way for designing and evaluating future antimicrobial stewardship interventions aimed at tailoring antibiotic regimens to minimize potential harms and maximize likelihood of benefits in patients undergoing allo-HCT. Prescribers and antimicrobial stewardship clinicians share a common goal in allo-HCT: to ensure the patient undergoes successful transplantation with minimal risk of infections or aGVHD. Therefore, optimizing antibiotic use is the optimal opportunity for collaboration between the antimicrobial stewardship and allo-HCT teams.

ARTICLE INFORMATION
Published: June 7, 2023. doi:10.1001/jamanetworkopen.2023.17101
Open Access: This is an open access article distributed under the terms of the CC-BY License. © 2023 So M. JAMA Network Open.

Corresponding Author: Miranda So, PharmD, MPH, PMB-800, 9th Floor, Munk Building, Toronto General Hospital, University Health Network, 585 University Ave, Toronto ON M5G 2N2, Canada (miranda.so@uhn.ca).

Author Affiliations: SH-UHN Antimicrobial Stewardship Program, University Health Network, Toronto, Canada; Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Canada; Toronto General Hospital Research Institute, Toronto, Canada.

Conflict of Interest Disclosures: None reported.

REFERENCES

