Biol Blood Marrow Transplant 25 (2019) e250–e251

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Intestinal Acute Graft-versus-Host Disease: A Bug Highway to the Bloodstream

Mitchell E. Horwitz*

Duke University School of Medicine, Division of Hematologic Malignancies and Cellular Therapy, Durham, NC, USA

Article history:
Received 7 June 2019
Accepted 12 June 2019

Intestinal acute graft-versus-host disease (aGVHD) remains one of the most vexing and dangerous complications of allogeneic stem cell transplantation. Not only do patient with intestinal aGVHD experience profound metabolic and nutritional derangements, but they also face the constant threat of infectious complications. While infectious risk plagues all patients with GVHD, the profound disruption of the intestinal epithelium that characterizes intestinal aGVHD raises the stakes to another level. The study by Petersen et al [1] in this issue of BBMT focuses on the association between the emergence of intestinal aGVHD and bacterial bloodstream infections (BSIs). BSIs are among the most serious of infectious complications. They lead to extended hospital stays, broad-spectrum antibiotic use, and thus further disruption of the intestinal microbiome. BSI has been shown to be an independent predictor of transplantation-related mortality and is most commonly associated with indwelling venous catheters [2]. However, translocation of bacteria from an inflamed intestinal lumen into the bloodstream of a highly immunocompromised host is another important portal of entry. This is a single-center retrospective study of 229 adult patients who experienced intestinal aGVHD over an 8-year time period. Of note, many of these patients had aGVHD involving other organs as well. Fungal BSIs were not included in the analysis.

In this study, the overall incidence of 1 or more BSIs in patients affected by intestinal aGVHD was 17%. Multivariate analysis identified treatment with etanercept or a previous BSI as independent risk factors for a BSI.

Looking closer at the data, one can derive 3 important take-home messages from the study. First, more than two-thirds of the observed BSIs occurred in patients with grade IV intestinal aGVHD. Nearly one-half of the 54 patients with grade IV intestinal aGVHD developed a BSI, a statistically significantly different rate compared with those with grade III intestinal GVHD ($p = .0002$). Second, gram-negative organisms were the most common isolate. This is not surprising, given the prominence of gram-negative organisms within the intestinal flora. This finding was previously reported in a pediatric cohort as well [3].

Third, and most important, the authors report that 36% of the BSIs were classified as "breakthrough" infection, having occurred despite ongoing antibiotic therapy. Ten of the 16 breakthrough infections were observed during fluroquinolone therapy used at this and many other centers as bacterial prophylaxis. This third point merits a bit more discussion, given its implications for therapeutic strategies to reduce the risk of BSI. At first blush, one could argue that the frequency of antibiotic resistant BSIs among patients with grade IV intestinal GVHD justifies a proposal to broaden the spectrum of antibiotic prophylaxis used in this population. However, the negative impact on both the intestinal microbiome and, in turn, the likelihood of GVHD resolution calls this practice into question. Might it be better to withhold antibiotic prophylaxis completely in favor of a rigorous preemptive strategy for BSIs, thereby preserving some semblance of microbiome diversity for as long as possible? The answers to this and other such questions lie in the conduct of much-needed prospective clinical trials. The relatively low incidence of BSI among patients with less severe intestinal GVHD, as reported by the authors, certainly supports a more conservative stance toward antibiotic prophylaxis in this population.

The detection and treatment of acute GVHD has been heavily researched over the years. We are now seeing the fruits of this research making its way to clinical practice. Powerful biomarker assays for both the detection and prognostication of acute GVHD are now commercially available [4]. Ruxolitinib recently became the first Food and Drug Administration-approved medication for the treatment of steroid-refractory acute GVHD. However, until we can eliminate the risk of GVHD following allogeneic stem cell transplantation, guidelines that will allow for standardization of the supportive care for those afflicted by this complication need to be established. By clarifying the incidence and the characteristics of BSIs in patients with intestinal GVHD, Petersen et al make an important contribution toward crafting a framework for such guidelines.

Financial disclosure: See Acknowledgments on page e251

* Correspondence and reprint requests: Mitchell E. Horwitz, Duke University School of Medicine, Division of Hematologic Malignancies and Cellular Therapy, 2400 Pratt Street, Box 3961, Durham, NC 27710, USA.
E-mail address: mitchell.horwitz@duke.edu

https://doi.org/10.1016/j.bbmt.2019.06.011

ACKNOWLEDGMENTS

Financial disclosure: The author has received clinical trial support from Gamida Cell, CSL Behring, and Incyte.

Conflict of interest statement: There are no conflicts of interest to report.

REFERENCES

1. Petersen J, Lindner C, Hakki M. Incidence and outcomes of bacterial bloodstream infections during acute graft-versus-host disease involving the gastrointestinal tract after hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2019;25:1648–1653.
2. Poutsiaka DD, Price LL, Ucuzian A, et al. Blood stream infection after hematopoietic stem cell transplantation is associated with increased mortality. *Bone Marrow Transplant*. 2007;40:63–70.
3. Levinson A, Pinkney K, Jin Z, et al. Acute gastrointestinal graft-vs-host disease is associated with increased enteric bacterial bloodstream infection density in pediatric allogeneic hematopoietic cell transplant recipients. *Clin Infect Dis*. 2015;61:350–357.
4. Hartwell MJ, Ozbeck U, Holler E, et al. An early-biomarker algorithm predicts lethal graft-versus-host disease and survival. *JCI Insight*. 2018;3:e89798.