Clinical Infectious Diseases Advance Access published May 9, 2015

EDITORIAL COMMENTARY

The Gut Microbiota Strikes Again

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Keywords. graft vs host disease; blood stream infection; probiotics; microbiota.

Hematopoietic stem cell transplantation (HSCT) is a lifesaving intervention in malignant and nonmalignant disease. However, as is the case with many good things, there is a dark side. For allogeneic HSCT, these include infection and graft vs host disease (GVHD), common complications associated with substantial morbidity and mortality although these have decreased in recent years [1, 2]. A number of strategies aimed at preventing each of these complications have been studied and some adopted into clinical practice. Preventive strategies for infection that have been studied include gut decontamination, administration of hematopoietic colony stimulating factors and prophylactic antibiotics, most specifically fluoroquinolones (reviewed in [3]). Current and potential strategies to reduce the incidence of acute GVHD (aGVHD) have been recently reviewed [4].

Levinson et al postulate in their study published in the current issue of *CID* that acute gut GVHD (aG-GVHD) increases the risk of blood stream infection with enteric organisms (EB-BSI) [5]. From a pathophysiological perspective, this hypothesis makes sense: damage resulting from attack of the stem cell graft on the host's gut epithelium provides a portal of entry for enteric organisms. In this retrospective study of pediatric allogeneic HSCT recipients, EB-BSI developed in almost half of all patients. The strongest predictor of EB-BSI was time to neutrophil engraftment. Additionally, there was a trend to aG-GVHD as a predictor. EB-BSI was more common after the onset of aG-GVHD than before in the group that developed aG-GVHD. It was also more common in those with aG-GVHD than in patients who did not develop any aGVHD, when the first 30 days after HSCT were excluded to account for the confounding variable of neutrophil engraftment. The development of EB-BSI was significantly associated with mortality in the entire cohort but not in those who developed aG-GVHD, likely due to the small numbers involved as pointed out by the authors. In their discussion, the authors noted the relationship between antibiotic usage and reduced gut microbial diversity observed by others, the latter of which is associated with mortality after HSCT [6]. They acknowledge that a limitation of their study was the lack of antibiotic data because such information might have had an impact on their analysis of mortality. Based on these data, the authors highlight the seriousness of EB-BSI in HSCT patients and the need for preventive measures. The potential strategy proposed by them was the use of probiotics, presumably by stabilizing or restoring the gut microbiota after HSCT.

The gut microbiota performs important homeostatic functions systemically and locally, including supporting intestinal epithelial health, host nutritional status, colonization resistance, and immune system functioning [7]. These considerations tie in directly with the Levinson study because maintenance of intact intestinal epithelium and colonization resistance by a healthy gut microbiota would presumably guard against systemic invasion by enteric bacteria. Therefore, is it a good idea to disrupt these homeostatic functions with prophylactic antibiotics used in HSCT? Recent data suggest that it is not. The disarray in the gastrointestinal (GI) microbiota that occurs during HSCT contributes to aGVHD in mice and humans [8]. Microbial diversity, a marker of a healthy microbiota, diminishes during HSCT, in large part due to frequent antibiotic usage, and is associated with increased mortality after HSCT [6]. Presumably through the loss of colonization resistance provided by a diverse microbiota, there is overgrowth of potential pathogens such as Enterococcus species and Gram negative bacilli during HSCT [9–12]. Eventually, blood stream infections with these pathogens ensue, as shown by Levinson and others [5, 11, 12].

Another consideration is the role of the gut microbiota in the genesis of GVHD (reviewed in [13]). This occurs through

Received 1 April 2015; accepted 5 April 2015.

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Clinical Infectious Diseases®

DOI: 10.1093/cid/civ292

the damage inflicted by irradiation and chemotherapy during the conditioning period prior to HSCT, allowing bacteria and microbial products to leak through the intestinal epithelium and provoke an inflammatory response. This response appears to be mediated through the innate immune system, with involvement of pattern-recognition receptors (PRR) such as Toll-like receptors to which bind microbial constituents termed pathogen-associated molecular patterns. Activation of PRR in this way results in the production of an inflammatory cascade creating an environment favoring the emergence of allo-reactive T cells derived from the graft. The end result is tissue damage to the host inflicted by the graft's immune effectors. The role of the gut microbiota in the development of GVHD is supported by observations that ridding the gut of its bacterial burden using antibiotics reduces acute GVHD. This is a strategy that has been employed by some transplant centers.

Returning to the proposal by Levinson et al regarding using probiotics to improve outcomes after HSCT, what is the evidence that probiotics are effective in preventing infection and/or GVHD? A number of studies have examined the effects of probiotics on infection prevention in patient populations other than those undergoing HSCT. The most consistent and convincing evidence demonstrates that probiotics can prevent intestinal and upper respiratory tract infections (reviewed in [14]), most notably *Clostridium difficile* colitis [15]. In addition, there is evidence that the use of probiotics reduces nosocomial infections [16–20]. However, such findings are not universal [21–23]. Probiotics as infection prevention have not been studied in HSCT patients.

There is classic and emerging experimental evidence to support the idea that the use of probiotics and/or modulating the GI microbiota prevents GVHD. Over 40 years ago, during the infancy of HSCT, van Bekkum et al demonstrated that modulating the GI microbiota attenuated complications of experimental transplantation including GVHD and mortality [24]. A decade ago, a study by Gerbitz et al showed in a mouse model of acute GVHD that supplementing mice with probiotics was associated with reduced bacterial translocation from the GI tract, less systemic inflammation and a reduction in acute GVHD while improving survival [25]. More recently, in a different mouse model of acute GVHD, similar results were observed when using a probiotic as a tolerogenic adjuvant [26]. Strategies other than probiotics to enhance the health and stability of the GI microbiota during HSCT have been proposed [6].

There are several issues to be considered when designing studies of probiotics in the prevention of infection or GVHD in patients undergoing HSCT. The heterogeneity of studies examining effects of probiotics in infection prevention make it difficult to construct a cohesive picture of their utility. The probiotic regimens, study populations, study designs and outcomes employed varied greatly. Additionally, many of these studies are limited by small size, thereby increasing the risk of being underpowered and not generalizable. Another important issue is safety. In general, probiotics are well tolerated, but infections with probiotic strains, notably blood stream infections, have been observed (reviewed in [27, 28]). Other potential adverse consequences of probiotic administration, such as unanticipated effects on the immune system and transfer of drug resistance from exogenously administered probiotic strains to native strains of microorganisms, have been suggested [29]. In addition, patients with severe underlying disease, including immunosuppression and malignancy, might be at higher risk for adverse effects from probiotics [27].

Levinson et al have contributed to the knowledge of the interplay between noninfectious and infectious outcomes after HSCT. The complexities in caring for and studying this patient population illuminate substantial and exciting research gaps. For instance, do skin GVHD and/or the skin microbiota contribute to infection after HSCT? Does infection influence the likelihood or severity of subsequent GVHD? How is the maintenance or restoration of the gut microbiota during HSCT best accomplished? How effective and safe are probiotics or other means of microbiota manipulation as a tool to prevent complications from HSCT? Larger, well-designed studies are needed to more fully elucidate these relationships in order to devise strategies to improve infectious and noninfectious outcomes after HSCT.

Notes

Acknowledgments. The author thanks Drs Jose Caro, Susan Hadley, and Alysse Wurcel for their helpful comments.

Potential conflict of interest. Author certifies no potential conflicts of interest.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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