pregnant women. Poor adherence to serial phlebotomies has been reported, as well as decreasing fetal HB (Hb F) values with iron restriction. An increased platelet count is a well-known accompanying feature of iron-deficient states, and its pathophysiology is now better understood. Recently, the increased platelet count of iron deficiency anemia has been associated with increased thrombotic risk in a large retrospective survey.[10] This potential complication should be carefully considered, given the prothrombotic, procoagulant state of SCD. However, the convergence of multiple case reports, small case series, and the report of Parrow et al in a validated murine model of the disease all seem to indicate that iron restriction should now be seriously considered for both SCA and Hb SC disease, either as repeated phlebotomies or novel therapies, or both.

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TRANSPLANTATION

Comment on Greco et al, page 1556

Acute GVHD: do we trust our gut?

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In this issue of *Blood*, Greco and colleagues analyzed fecal microbiome diversity by 16S next-generation-sequencing techniques at 3 early time points in 100 consecutive hematopoietic stem cell transplantation (HSCT) recipients at a single center, suggesting that changes in microbiome diversity during the peri-HSCT period can identify recipients at higher risk of developing acute graft-versus-host disease (GVHD).[1] In recent years, there have been multiple analyses suggesting associations between restricted intestinal microbiome diversity (dysbiosis) and adverse outcomes after HSCT. As more data accumulate, those of us who treat patients are left wondering if any of these associations have any practical clinical value.

A 65-year-old man with complex karyotype acute myeloid leukemia in first complete remission is referred for evaluation for allogeneic HSCT. He was initially treated with conventional induction chemotherapy. His course was complicated by extended-spectrum β-lactamase–resistant *Escherichia coli* and vancomycin-resistant enterococcus bacteremia followed by *Clostridium difficile* colitis. A fully matched unrelated donor was identified. Normally, given the patient's age, disease, and donor, my recommendation would be a reduced-intensity conditioning HSCT employing standard tacrolimus/methotrexate GVHD prophylaxis. However, the recent infectious complications would indicate that this patient likely has significant dysbiosis. Should this alter my approach to GVHD prevention, perhaps adding anti-thymocyte globulin or employing a posttransplant cyclophosphamide-based approach? Should I defer HSCT after 1 to 2 cycles of consolidation chemotherapy in hopes that his microbiome can recover? Should I add measures designed to reconstitute microbiome diversity before, during, or after HSCT?

The multiple analyses suggesting the association of dysbiosis with outcomes such as acute GVHD, relapse, and mortality have been well summarized in a recent review in *Blood*.[2] In a landmark international study from 4 large centers involving 1362 patients, Peled and colleagues observed a pattern of loss of microbiome diversity through the HSCT process with domination by single taxa. Greater microbiome diversity during HSCT was associated with improved overall survival with subset analyses, suggesting this was driven by acute GVHD-related mortality.[3] Greco et al have built on this observation with samples collected at baseline, during nadir, and at engraftment, even finding that certain single-taxa predominance of *Enterococcus* or *Staphylococcus* species appeared to be associated with specific organ manifestations of acute GVHD. The limitations of this study reside in the relatively small sample size, homogenous conditioning/GVHD prophylaxis regimens, and lack of presented data on any association with nonrelapse mortality or survival.[1] Larger and more comprehensive analyses are needed to prove if such single-center analyses suggesting specific taxa associations with specific outcomes, as has been shown by other centers for GVHD[4] and relapse,[5] are valid, as these associations likely also reflect significant influences of local practices, antibiotic choices, hospital flora, and diet. Importantly, the BMT CTN 1801 collaboration is an ongoing prospective multicenter observational trial investigating if fecal microbiome diversity around the time of engraftment predicts 1-year nonrelapse mortality after reduced-intensity conditioning HSCT

performed as part of the larger phase 3 BMT CTN 1703 trial (#NCT03959241). Other important analyses will help to further define the relationship between microbiome diversity and HSCT outcomes with the samples and data collected serving as an invaluable biorepository for future studies.

The actual mechanisms through which dysbiosis mediates acute GVHD remain unclear. Proposed pathways have included innate recognition of pathogen-associated molecular patterns, effects of local microbiome produced metabolites, such as butyrate or indole, and activation of T helper 17 cells. Recently, a murine study suggested that microbiome composition exerts an effect on acute GVHD through regulation of major histocompatibility complex II expression on intestinal epithelial cells via an interleukin-12/interferon-γ axis.[6] Further research into elucidating the biological basis behind the clinical observations is ongoing.

The practical role of the microbiome in HSCT can be envisioned in 2 somewhat overlapping ways: (1) a biomarker for the identification of patients at higher risk for acute GVHD or other complications after HSCT, and (2) a target for intervention aimed at changing microbiome diversity to impact clinical outcomes. Formal analysis of the value of microbiome diversity added to other currently investigated preemptive GVHD biomarkers[7] would be of interest, although perhaps the microbiome best offers an added assessment of risk at baseline prior to HSCT. Multiple ongoing trials are attempting to preserve or improve the diversity of the intestinal microbiome for HSCT recipients. These include approaches using prebiotics, selection of empiric antibiotics during hematological nadir, and artificial cocktails of various probiotic formulations. Fecal microbiota transplantation (FMT) derived from both autologous[8] and allogeneic[9] sources has been used after HSCT to accelerate the recovery of microbiome diversity, whereas allogeneic FMT has also been used to successfully treat steroid-refractory acute intestinal GVHD.[10]

With rapidly improving technology to analyze the constituents of the microbiome (including viruses and fungi) and innovation of novel interventions, it is difficult to know how to best proceed. However, at some point, we as a community will have to agree on prospective clinical trials to test if improving microbiome diversity can impact clinical outcomes. The primary clinical end point of such a trial is not straightforward, but acute GVHD would appear to be the primary driver of any effect with possibly infection, relapse, and survival included as part of a composite primary end point. Selecting a high-risk population through fecal microbiome analysis either before or during the HSCT period would seem ideal in order to be able to show an effect, and the findings by Greco et al lend additional credence to that suggestion. How and when to select these patients and what intervention to test remain unclear. Although we have made significant progress since the first evidence showing the associations between microbiome diversity and outcomes after HSCT, it may be time to test if we can truly trust our gut microbiome to improve outcomes.

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