Letter to the Editor

Gut Colonization by Multidrug-Resistant Gram-Negative Bacteria Is an Independent Risk Factor for Development of Intestinal Acute Graft-versus-Host Disease

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To the Editor:

We read with great interest the paper by Patriarca et al. [1] analyzing risk factors and outcomes of infections by multidrug-resistant (MDR) gram-negative (GN) bacteria in patients undergoing hematopoietic stem cell transplantation (HSCT). In this study, the rates and severity of acute graft-versus-host disease (GVHD) in 122 patients after allogeneic HSCT were similar in patients with and without colonization or infection by MDR GN bacteria. We would like to comment on this issue, based on our results, which may suggest different conclusions.

We analyzed 145 adult patients who consecutively underwent allogeneic HSCT in our institution between 2011 and 2014 and were screened weekly by cultivating stool specimens for gut colonization by MDR bacteria. Eighty-eight male and 57 female patients at a median age of 46 years (range, 18 to 64) underwent allogeneic HSCT, mostly for myeloid malignancies (70%). The donors were unrelated in 74 patients, related in 67 patients, and haploidentical in 4 patients. Most of the patients (70%) received peripheral blood stem cells after a reduced-intensity conditioning regimen (56%). All patients received standard gut decontamination with ciprofloxacin from day 0. At the time of HSCT, 28% patients were colonized with MDR GN bacteria, whereas another 22% patients became colonized in the early post-transplantation period. Among colonized patients, 58% were colonized by MDR Pseudomonas aeruginosa, 43% by extended-spectrum β-lactamase–producing Enterobacteriaceae, 27% by carbapenem-resistant Enterobacteriaceae, and 9% by MDR Acinetobacter baumannii. Overall survival at 36 months was comparable in MDR GN colonized patients to that of noncolonized patients (49%; 95% confidence interval [CI], 38% to 62% versus 53%; 95% CI, 4% to 63%). However, the cumulative incidence of severe (grade III or IV) acute GVHD was significantly higher in patients colonized with MDR GN bacteria (27%, 95% CI, 19% to 39%) than in noncolonized patients (14%, 95% CI, 7% to 23%) (P = .04). Moreover, patients colonized with MDR GN bacteria had significantly more gastrointestinal (GI) GVHD than noncolonized patients (cumulative incidence, 28%; 95% CI, 20% to 41% versus 14%; 95% CI, 7% to 23%; P = .02) (Figure 1) and more acute GVHD-related mortality (cumulative incidence, 16%; 95% CI, 9% to 26% versus 7%; 95% CI, 3% to 15%; P = .10). A substantial and independent role of gut colonization with MDR GN bacteria on the development of GI GVHD was confirmed by multivariate analysis using time-dependent covariate functions for high-risk disease, myeloablative conditioning, peripheral blood stem cells, unrelated donor (hazard ratio [HR], 2.14; 95% CI, .99 to 4.68; P = .05), older age (HR, 2.15; 95% CI, 1.00 to 4.59; P = .04) and MDR GN bacteria gut colonization (HR, 2.26; 95% CI, 1.05 to 4.83; P = .03). In summary, our results show that MDR GN bacteria have a significant role in the development of severe acute GVHD. These results are consistent with a similar study previously reported by our group on another study population, where gut colonization with MDR bacteria predisposed to more severe and more frequent GI GVHD [2]. Moreover, we now...
showed that gut colonization with MDR GN bacteria represents an independent risk factor for GI GVHD, together with previously known risk factors of older age of patients and HSCT from an unrelated donor.

Possible reasons for discrepancies between the study done by Patriarca et al. and our study could lie in differences between our peritransplantation screening strategies. In the Italian study, screening of gut colonization was done by rectal swabs only at the time of admission and, only if clinically indicated, later. Our patients were screened on a weekly basis during hospitalization and as many as 22% of our patients became colonized in the early post-transplantation period after gut decontamination/or systemic antibiotics were started. By taking serial stool specimens, we were able to detect all GN bacteria before and after they became MDR. Furthermore, the epidemiology of gut colonization in our study was quite different, with the majority of our patients colonized with MDR Pseudomonas aeruginosa, a common opportunistic pathogen in immunocompromised patients.

We, as many others, use standard gut decontamination strategy based on the early studies that indicated that eradication of intestinal bacteria could prevent the development of acute GVHD [3]. However, gut decontamination seems to lead to the loss of natural microbiota diversity and the overgrowth of opportunistic pathogens with emerging multidrug resistance. According to our results, these MDR pathogens have an important role in the development of acute GVHD. Furthermore, recent studies have demonstrated that commensal bacteria are critical for maintaining immune homeostasis in the intestine and prevention of GVHD [4-6]. In light of these new findings, the common practice of gut decontamination should be re-examined [7]. We support the position of our Italian colleagues and other experts who do not consider gut colonization with MDR GN bacteria as contraindication for allogeneic HSCT. However, we feel that screening patients for gut colonization with MDR GN bacteria is justified to identify patients who are at risk of developing severe acute GVHD. With the lack of efficient antibiotics, new decolonization strategies, such as fecal microbiota transplantation, represent a novel and attractive approach for restoration of healthy gut flora [8,9]. Whether it could also play a role in the prevention of GI GVHD remains to be seen.

REFERENCES