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Antibiotics in Hematopoietic Cell Transplantation: Adversaries or Allies?

Tessa M. Andermann[1] and **Ami S. Bhatt**[2,*]

[1]Department of Infectious Diseases, Stanford University, Stanford, California

[2]Departments of Medicine (Hematology & Blood and Marrow Transplantation) and Genetics, Stanford University, Stanford, California

Rising rates of infections resulting from antibiotic-resistant bacteria (ARB) have led to a worldwide public health crisis calling for a significant improvement in antimicrobial stewardship in all healthcare settings [1]. The burden of antibiotic resistance is high for immunocompromised patients or those who have prolonged exposure to a healthcare setting; particularly vulnerable populations include those who undergo allogeneic hematopoietic stem cell transplantation (allo-HCT) [2]. Immunocompromised patients have higher rates of morbidity and mortality as a result of ARBs [3–6] and colitis resulting from *Clostridium difficile* (CDI) [7]. This finding is corroborated by the report by Bilinski et al. [8] in this issue of *Biology of Blood and Marrow Transplantation* in which intestinal colonization of allo-HCT patients with ARBs was associated with higher mortality. In their retrospective analysis, patients were screened for ARBs, including methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus* spp., and extended-spectrum beta-lactamase-producing or carbapenamase-producing *Enterobacteriaceae*, before HCT by rectal swab and culture methods. Within the cohort of 107 allo-HCT patients, gut colonization by ARBs on admission was not only associated with decreased overall survival compared with noncolonized patients (34% versus 74%, respectively, at 24 months, $P < .001$) but also with an increased incidence of systemic infection, acute graft-versus-host disease (GVHD), and nonrelapse mortality. In a multivariate analysis the only significant predictor for overall survival was gut colonization by ARBs (hazard ratio, 3.53; 95% confidence interval, 1.71 to 7.28). Positive blood cultures were observed more often in colonized patients, and these patients were also more likely to die from infection. Although details of these infectious deaths are not presented, it would be interesting to know which specific systemic infections were found and whether CDI contributed to the increase in mortality, as has been found previously [7]. Assuming that in-hospital use of broad-spectrum antibiotics is a major driver of ARB colonization, the report by Bilinksi et al. supports a growing body of evidence that promotes antimicrobial stewardship practices even—and perhaps especially—in those who are immunocompromised.

[*]Correspondence and reprint requests: Ami S. Bhatt, MD, PhD, Departments of Medicine (Hematology & Blood and Marrow Transplantation) and Genetics, Stanford University, 269 Campus Drive, Stanford, CA 94305. asbhatt@stanford.edu (A.S. Bhatt).

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Although the association between antibiotic use and ARB colonization has been well documented, it remains unclear whether antibiotic use is causally related to the increased mortality seen in ARB-colonized individuals. Indeed, ARB colonization may instead serve as a marker of poor prognosis rather than a cause of mortality. The challenge of predicting causation from a finding of association is one that exists for much of human microbiome research. For example, researchers have found that an increase in gut microbiota diversity is associated with higher overall survival and lower rates of GVHD in patients undergoing allo-HCT [9,10]. This suggests that a "healthier," more diverse microbiome may lead to improved outcomes, although confounding factors may complicate such a posited direct relationship. However, a causal relationship is certainly biologically plausible given the direct interaction found between fermentation products of commensal gut bacteria and improved host immune regulation [11].

Determining causality is important for many reasons. Apart from the fundamental importance of describing pathobiologic mechanisms in detail, one primary reason to investigate causality is to better understand the potential role of therapeutics that restore the taxonomic diversity of the intestinal flora. It is well recognized that the use of antibiotics results in a loss of commensal organisms and decreased diversity, leaving an ecologic niche that allows for the proliferation of pathogens [12]. The loss of microbiota diversity can contribute to intestinal domination by potentially less evolutionarily fit, antibiotic-resistant pathogens and a higher risk of bacteremia resulting from these enterodominant pathogens [13]. Having a greater proportion of commensal intestinal organisms can overcome resistant pathogens through both direct competition for nutrients or antagonism and indirect pathways that impact host immunity [14]. Thus, re-establishing a varied and resilient intestinal microbiota through probiotics or microbiota transfer and reducing ARB colonization burden through both direct and indirect means may be expected to improve rates of infection, GVHD, and overall survival. This is certainly the hope and is in fact the case with refractory CDI, which is cured in up to 90% of patients after fecal microbiota transfer [15]. In addition, evidence suggests that the addition of an organism that metabolizes bile salts, for instance, *Clostridium scindens*, confers bile acid–dependent resistance to CDI in an animal model of the disease, an example of precision microbiota reconstitution [16]. Other potential applications for microbiota-based therapeutics, apart from treatment of infection, include using donor stool from the stem cell donor for concurrent fecal microbiota transplantation with allo-HCT. This may provide greater immunologic tolerance toward gut microbiota and potentially reduce rates of intestinal GVHD.

If we are to understand more about causality, we must also learn much more about what it means to restore a microbial community from a state of dysbiosis to one of homeostasis. Apart from lacking abundant antibiotic-resistant pathogens, a healthy microbiota requires a multidimensional definition. This definition is complicated by the uniqueness of microbiota structure and composition for every individual. Variability in the intestinal microbial milieu is the result of complex factors such as geography, diet, and age [17]. In contrast to the variability found in microbiota taxonomic composition within and across populations, the presence of genes involved in metabolic pathways important for microbiota function has been found to be potentially more stable and consistent across diverse human populations [18]. Predicting the "function" of a complex microbial community based on the consortium

of metabolically important genes identified by next-generation metagenomic sequencing may thus serve as a more consistent and informative indicator of the biologic activity of a given community, in comparison with taxonomic classifiers. Functional classification may therefore overcome challenges associated with interindividual and geographic microbial variability. Analysis of microbiota “function” would include the demonstration of important biochemical pathways that contribute to the health of the microbiome and the host. Pertinent to the article by Bilinski et al. [8], looking at genes encoding antibiotic resistance may be much more informative than evaluating taxonomic composition alone. Classification of the resistome by identifying antibiotic resistance genes within microbial reservoirs of organisms that are difficult to culture would be a potentially sensitive approach to understand the genetic and biologic effects of antibiotic exposure. A “healthy” microbiome may therefore have a multitude of properties including (1) overall lower numbers of antibiotic-resistance genes, (2) a more complete consortium of important biochemical pathways that support immunologic regulation, (3) enough stability to resist pathogen colonization or domination, particularly when disturbed by exogenous factors, and (4) resilience to perturbances, defined as the ability of a microbiome to returning to its prior state after an insult. Furthermore, a well-functioning microbiota might, in the face of pathogen colonization, resist the development of disease [18].

In the setting of increasing antibiotic resistance, a shift in our approach to the treatment of infectious diseases may be required. This paradigm shift necessitates an increased focus on vital host–microbiota interactions that when restored to homeostasis can be used to prevent and treat infections. In addition, the ability to restore the normal function and composition of the microbiota may have wider reaching effects beyond providing resistance to the colonization of antibiotic-resistant pathogens. Therapies that beneficially impact microbiota function, colonization resistance, and diversity have already been proven effective in CDI and may be able to significantly improve outcomes in dysbiosis-associated diseases such as GVHD. What is needed now more than ever is research that pushes the limits of metagenomic sequencing and big data to better understand the complexities of host–microbiota interactions and to elucidate causality and states of homeostasis. Defining these has implications not only for the fields of stem cell transplantation and infectious diseases but for a growing multitude of other important disease states as well.

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REFERENCES

1. Roca I, Akova M, Baquero F, et al. The global threat of antimicrobial resistance: science for intervention. New Microbes New Infect. 2015; 6:22–29. [PubMed: 26029375]
2. Macesic N, Morrissey CO, Cheng AC, et al. Changing microbial epidemiology in hematopoietic stem cell transplant recipients: increasing resistance over a 9-year period. Transplant Infect Dis. 2014; 16:887–896.

3. Girmenia C, Rossolini GM, Piciocchi A, et al. Infections by carbapenem-resistant *Klebsiella pneumoniae* in SCT recipients: a nationwide retrospective survey from Italy. Bone Marrow Transplant. 2015; 50:282–288. [PubMed: 25310302]
4. Haeusler GM, Mechinaud F, Daley AJ, et al. Antibiotic-resistant gram-negative bacteremia in pediatric oncology patients—risk factors and outcomes. Pediatr Infect Dis J. 2013; 32:723–726. [PubMed: 23838774]
5. Moghnieh R, Estaitieh N, Mugharbil A, et al. Third generation cephalosporin resistant *Enterobacteriaceae* and multidrug resistant gram-negative bacteria causing bacteremia in febrile neutropenia adult cancer patients in Lebanon, broad spectrum antibiotics use as a major risk factor, and correlation with poor prognosis. Front Cell Infect Microbiol. 2015; 5:11. [PubMed: 25729741]
6. Wang L, Wang Y, Fan X, et al. Prevalence of resistant gram-negative bacilli in bloodstream infection in febrile neutropenia patients undergoing hematopoietic stem cell transplantation: a single center retrospective cohort study. Medicine (Baltimore). 2015; 94:e1931. [PubMed: 26559260]
7. Alonso CD, Kamboj M. *Clostridium difficile* infection (CDI) in solid organ and hematopoietic stem cell transplant recipients. Curr Infect Dis Rep. 2014; 16:1–10.
8. Bilinski J, Robak K, Peric Z, et al. Impact of Gut Colonization by Antibiotic-Resistant Bacteria on the Outcomes of Allogeneic Hematopoietic Stem Cell Transplantation: A Retrospective, Single-Center Study. Biol Blood Marrow Transplant. 2016; 22:1087–1093. [PubMed: 26900084]
9. Holler E, Butzhammer P, Schmid K, et al. Metagenomic analysis of the stool microbiome in patients receiving allogeneic stem cell transplantation: loss of diversity is associated with use of systemic antibiotics and more pronounced in gastrointestinal graft-versus-host disease. Biol Blood Marrow Transplant. 2014; 20:640–645. [PubMed: 24492144]
10. Taur Y, Jenq RR, Perales M-A, et al. The effects of intestinal tract bacterial diversity on mortality following allogeneic hematopoietic stem cell transplantation. Blood. 2014; 124:1174–1182. [PubMed: 24939656]
11. Smith PM, Howitt MR, Panikov N, et al. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. Science. 2013; 341:569–573. [PubMed: 23828891]
12. Buffie CG, Jarchum I, Equinda M, et al. Profound alterations of intestinal microbiota following a single dose of clindamycin results in sustained susceptibility to *Clostridium difficile*-induced colitis. Infect Immun. 2012; 80:62–73. [PubMed: 22006564]
13. Taur Y, Xavier JB, Lipuma L, et al. Intestinal domination and the risk of bacteremia in patients undergoing allogeneic hematopoietic stem cell transplantation. Clin Infect Dis. 2012; 55:905–914. [PubMed: 22718773]
14. Buffie CG, Pamer EG. Microbiota-mediated colonization resistance against intestinal pathogens. Nat Rev Immunol. 2013; 13:790–801. [PubMed: 24096337]
15. Youngster I, Russell GH, Pindar C, et al. Oral, capsulized, frozen fecal microbiota transplantation for relapsing clostridium difficile infection. JAMA. 2014; 312:1772–1778. [PubMed: 25322359]
16. Buffie CG, Bucci V, Stein RR, et al. Precision microbiome reconstitution restores bile acid mediated resistance to *Clostridium difficile*. Nature. 2015; 517:205–208. [PubMed: 25337874]
17. Bäckhed F, Fraser CM, Ringel Y, et al. Defining a healthy human gut microbiome: current concepts, future directions, and clinical applications. Cell Host Microbe. 2012; 12:611–622. [PubMed: 23159051]
18. Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. Nature. 2012; 486:207–214. [PubMed: 22699609]