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Perspective

Clinical Cancer Research

Can Consideration of the Microbiome Improve Antimicrobial Utilization and Treatment Outcomes in the Oncology Patient?

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Abstract

The need to provide effective and timely antimicrobial treatment to cancer patients with infections is well recognized but tempered by preliminary, but accumulating, evidence that antibiotic-induced microbiome dysbiosis affects cancer therapy response, noninfectious toxicities, and infectious complications. Given only a minority of empirically treated cancer patients are proven to have a true bacterial infection, it is important to consider the potential negative consequences of extensive broad-spectrum antimicrobial use on the commensal microbiota. Herein, we review the literature substantiating the dilemma oncologists face when treating suspected or documented infections with respect to the interaction between the host microbiome, antibiotics, and cancer-related clinical outcomes. We propose microbiome-based explorations that could assist oncologists in optimizing treatment strategies for cancer-related infections as well as the cancer itself. In addition, we discuss knowledge gaps and challenges in this nascent field that must be addressed to deliver medically relevant, translational applications. We anticipate that the emerging knowledge regarding the role of the microbiota in the health of cancer patients may cause a reappraisal of the manner in which antibiotics are used in the oncologic setting and how microorganisms are viewed by oncologists. *Clin Cancer Res; 23(13); 3263–8. ©2017 AACR.*

See related commentary by Fessler and Gajewski, p. 3229

Historical Beneficial Aspects of Antimicrobials in the Cancer Population

Antimicrobial therapy has markedly improved the outcome of cancer patients over the past 50 years. The potential dramatic impact of antimicrobials in oncology became clear when infections replaced hemorrhage and leukemia itself as the leading cause of death among acute leukemia patients in the 1960s (1). By the early 1970s, the development of methicillin for penicillin-resistant *Staphylococcus aureus* and carbenicillin for *Pseudomonas aeruginosa* (*P. aeruginosa*) meant serious infections could be effectively treated, even amid persistent neutropenia (2). As a result, neutropenic fever became an oncologic emergency demanding the rapid administration of broad-spectrum antibiotics that markedly improved the outcomes of neutropenic patients with proven infections, particularly due to *P. aeruginosa* (3, 4). Eventually, the high rates of morbidity and mortality associated with infections in patients with hematologic malignancies led to large randomized controlled trials that demonstrated that prophylactic administration of a fluoroquinolone (i.e., levofloxacin) reduced rates of neutropenic fever and confirmed infections (5). Thus, current oncology dogma primarily considers bacteria as a threat to patient health, with a low threshold for initiation of broad-spectrum antimicrobials in the preventive or therapeutic setting.

How Antibiotic-Induced Microbiome Alteration Affects the Cancer Patient

Feasible and affordable genetic means to comprehensively assay the bacteria present in a variety of sample types has paved the way for large-scale investigations such as the Human Microbiome Project (6). In addition to 16S rRNA gene sequencing, microbiome characterization methodologies have expanded to other "-omics" approaches to include whole-genome shotgun sequencing, RNA-seq, and metabolomics, which more precisely delineate bacterial community structure, gene presence/expression, and metabolic activity (7). Use of these methodologies has illuminated that the microflora have profound effects on human health, such as altering cytokine profiles, influencing inflammatory immune responses, and altering metabolites (8–11).

Although it is recognized that systemically administered antimicrobials can have a dramatic impact on the composition and function of the gastrointestinal microbiome (12), recent advances have also demonstrated that antibiotic effects on the microbiome influence the response to cancer immunotherapy. Specifically, Iida and colleagues described tumor necrosis and immune responses to be significantly reduced in antibiotic-treated colon carcinoma and melanoma tumor–bearing mice receiving immunostimulatory CpG-oligodeoxynucleotide treatment (13). Similarly, Vetizou and colleagues demonstrated that melanoma tumors in antibiotic-treated mice failed to respond to CTLA-4

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Translational Relevance

Antimicrobial therapy is critical to the health of cancer patients. However, initial clinical studies in patients and laboratory-based investigations in murine models have demonstrated that disruption of the microbiome induced by antimicrobials impacts chemo- and immunotherapy response as well as treatment-related toxicities. Equally alarming is the vicious cycle of treating ever increasing multidrug-resistant infections with broad-spectrum antibiotics that further deplete the commensal microflora. Consequently, cancer clinicians face a challenging and unique dilemma when managing infections in cancer patients. It is imperative that oncologists improve their antibiotic prophylaxis and treatment strategies with consideration of microbiome research. This perspective reviews the literature substantiating the interplay of antibiotics, the microbiome, and cancer while offering possible avenues of investigation that could help physicians treat infections while maintaining the beneficial impact of the microbiota. In addition, we discuss how manipulation of the microbiome could assist in optimizing cancer treatment outcomes.

blockade immunotherapy and that the presence of *Bacteroides fragilis* was critical to the antitumor effect (14). Recently, it has also been discovered that specific microbiota shape innate and adaptive immune system influencing the PD-1–PD-L1 axis (15, 16), although no studies have specifically shown the effects of antibiotic treatment on the microbiota and anti–PD-L1 treatment response.

In addition to influencing immunotherapy response, antibiotic-treated animals also display significantly reduced tumor regression and survival in cytotoxic therapy scenarios, such as oxaliplatin-treated lymphoma-bearing mice (13). Likewise, Viaud and colleagues observed that receipt of antibiotics with activity against Gram-positive bacteria reduced Th lymphocyte and lymphoma responses in mice treated with cyclophosphamide (17). Beyond animal models, recently, it was shown that patients being treated with cyclophosphamide for chronic lymphocytic leukemia and cisplatin for relapsed lymphoma who also received anti–Gram-positive antibiotics had significantly lower overall response rate and survival (18).

Furthermore, it is becoming increasingly clear that antimicrobial-induced microbiome disruption is also a key factor in cancer treatment–related toxicities. For example, administration of antibiotics to mice undergoing hematopoietic stem cell transplantation (HSCT) significantly increased the severity of GHVD and mortality (19, 20). Consistent with murine data, investigators found receipt of antibiotics with potent anti-anaerobic activity was associated with increased GVHD risk and GVHD-related mortality following allogeneic HSCT in patients (19, 21). In addition, fluoroquinolone receipt, low microbial diversity, and Gammaproteobacteria domination of fecal microbiota were predictive of pulmonary complications among HSCT recipients (22).

Antibiotic-induced microbial dysbiosis is also a crucial aspect in the cancer patient's risk for infectious toxicities. A prime example of the "Catch-22" relationship between antimicrobial therapy and cancer care is the hematologic malignancy patient. In these patients, depletion of native commensals by antibacterial prophylaxis and empirical treatment of neutropenic fever is compounded by mucosal barrier injury from cytotoxic chemotherapy, leading to proliferation of pathogenic bacteria, translocation across disrupted intestinal epithelium, and subsequent infection (Fig. 1; ref. 23). In leukemia and HSCT patients, receipt of particular antibiotics, such as metronidazole, was associated with decreased microbial diversity and, consequently, increased intestinal domination by pathogens that commonly cause hospital-acquired and bloodstream infections (24–27). Similarly, it was also found that broad-spectrum antibiotic receipt, specifically carbapenems, was associated with loss of bacterial diversity in both the oral and stool microbiomes of patients with acute myeloid leukemia during induction chemotherapy, which was, in turn, correlated with higher subsequent infectious risk in the 90 days after neutrophil recovery (28). Moreover, a considerable body of evidence exists that clearly links high rates of *Clostridium difficile* (*C. difficile*) infections in cancer patients, particularly those undergoing HSCT, to disruption of the normal intestinal flora due to a combination of repeated use of antibiotics, immunosuppression, and cancer therapy (24).

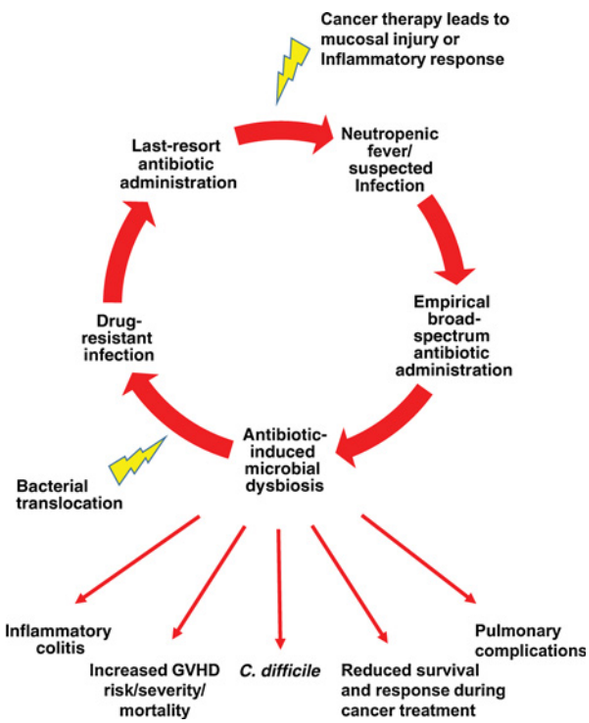

Figure 1.

The "Catch 22" relationship between antimicrobial therapy and cancer treatment in the oncology patient. This figure depicts how depletion of native commensals by antibacterial prophylaxis and empirical treatment of neutropenic fevers or suspected infections is compounded by mucosal barrier injury from cytotoxic chemotherapy, leading to proliferation of pathogenic bacteria, translocation across disrupted intestinal epithelium, and subsequent resistant infections. This leads to a vicious cycle of recurrent infectious issues and other cancer treatment–related toxicities as a result of antibiotic-induced microbial dysbiosis.

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The Microbiome as a Possible Prognostic or Diagnostic Biomarker in Oncology

The studies outlined above indicate that the ability to comprehensively assess or alter human microbiota composition may be a valuable tool in improving cancer outcomes. Indeed, from a prognostic standpoint, the composition of the microbiome prior to chemotherapy has been demonstrated to be predictive of infectious outcomes for patients with acute myelogenous leukemia and lymphoma (28, 29). Similarly, the diversity of the gastrointestinal microbiome at the time of engraftment following HSCT is associated with risk of development of and mortality from GVHD (20, 30). Finally, the abundance of the Bacteroidetes phylum was recently correlated with resistance to the development of immune-mediated colitis in patients with melanoma treated with the immune checkpoint inhibitor ipilimumab (31). Thus, these data suggest the importance of developing probability indices that risk stratify cancer patients with respect to microbiome measurements and other clinical factors, such as antimicrobial administration (32–34). Predictive risk scores that incorporate microbiome measurements would need to include factors such as diversity metrics, absence of beneficial microbes or microbial byproducts (i.e., those associated with pathogen colonization resistance, resistance against treatment complications, or antitumor effects), and domination by specific microbes related to infection. Through these types of examinations, one could envision the microbiome being incorporated as a baseline screening tool to predict which patients may respond better to cancer therapy, are at risk for treatment-related toxicity, or are at risk for infectious complications.

Microbiome composition measurements may also assist with optimizing the choice and duration of antimicrobials in the cancer patient with respect to maintaining beneficial commensal microorganisms. For instance, we advocate for trials to assess whether rapid de-escalation of broad-spectrum antimicrobials can be done safely in patients with negative cultures in the setting of asymptomatic febrile neutropenia. By merging such studies with longitudinal microbiome analyses, it could be determined whether such de-escalation helps preserve microbiome composition and whether particular microbiome characteristics are associated with a need to reinitiate antimicrobials. In addition, investigating the use of more narrow-spectrum antibiotics as well as shorter duration of therapy for infections are needed, as it has been suggested that the number of antibiotics and total antibiotic exposure is linked with recurrent infectious complications in leukemia patients (35). Moreover, pharmacokinetic studies that link concentrations of antimicrobials in the intestinal lumen to effects on the microbiome are needed. Along the same lines, it will be important to assess not only the impact of the antimicrobial itself but also its elimination (biliary vs. renal). Such data could be used to design interventions to minimize the off-target effects of systemically administered antimicrobials on the commensal microbiota.

Microbiome measurements also raise the possibility to extend antimicrobial administration in oncology patients into the arena of personalized medicine. As genomic methodologies advance in terms of decreasing price and rapid availability of results, the ability to use microbiome samples to rapidly determine the scope of pathogens and antibiotic resistance genes present within an individual is becoming a real possibility (36). By cataloging the antimicrobial resistome for each patient using metagenomic analyses, physicians could inform their therapeutic considerations for prophylaxis and infection. For example, if a particular patient were known to have intestinal domination by a pathogen resistant to standard empiric antimicrobials, oncologists could take a more individualized approach to antimicrobial initiation if that patient were to develop infectious symptoms. Moreover, using microbiome measurements, other DNA sequencing–based approaches, or biomarkers, such as procalcitonin, to separate infectious from noninfectious fevers in the oncology patient would also greatly facilitate antimicrobial targeting and microbiota preservation. In addition to differentiating infectious from noninfectious fevers, it is also crucial to understand and discern colonization versus infection. For example, the unmet need to better distinguish *C. difficile*–colonized patients from patients with *C. difficile* colitis is leading to a mass overdiagnosis and overtreatment (37). It is highly likely that knowledge of microbiome interactions with the host will play an essential role in answering these needs.

The Microbiome as a Possible Direct Intervention Tool

Direct manipulation of the microbiome also offers a possibility for improving cancer therapy, minimizing toxicities, and mitigating the impact of infectious diseases. For example, a recent study suggests that fecal transplantation may ameliorate steroid-resistant GVHD in HSCT recipients (38). Similarly, fecal transplantation in mice increased responses to immunotherapy, raising the possibility that optimizing the microbiome prior to immune-modulating treatment could improve response (15). However, randomized trials examining the efficacy of microbiome remediation are needed to fully evaluate therapeutic potential.

As antimicrobials are a dwindling resource, using the microbiome as a direct interventional tool could improve antimicrobial utilization by offering an alternative treatment strategy for infectious complications, alleviating antibiotic resistance and preserving drug efficacy. Such microbiome-based methods include fecal transplantation, targeted addition of a single or defined combination of bacterial species (probiotics), or prebiotics designed to stimulate the growth and retention of specific beneficial species in the form of dietary-based intervention. It is thought that autologous fecal transplant could prevent pathogen intestinal colonization, infection, and development of antibiotic resistance (39, 40). Consequently, if cancer hospitals begin to bank patient feces prior to cancer treatment, a patient's native fecal microbiota could be implanted either continuously throughout treatment or administered after broad-spectrum antimicrobial treatment to counteract the microbiome damage potentially caused by antimicrobial treatment or chemotherapy.

However, one concern with using the administration of specific bacterial cocktails or fecal transplant in the immunocompromised patient is the risk for infection, as there have been numerous reports of septicemia associated with use of probiotic therapy, such as *Lactobacillus* bacteremia or *Saccharomyces* fungemia (41, 42). Thus, prebiotic administration or dietary intervention may be more desirable toxicity mitigation strategies. Recent examinations have suggested the beneficial impact of fiber on the microbiome, as it relates to inflammation and mucosal barrier injury, particularly in that specific fibers increase the number of butyrate-producing bacteria (43, 44). The short-chain fatty acid butyrate is importantly involved in adaptive immune responses,

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such as colonic T-cell differentiation (45–47). These data indicate that bypassing the microbiota and providing bacterial metabolites, such as short-chain fatty acids, is an alternative possibility. In addition, these studies suggest the importance of performing microbiome examination in tandem with metabolic and immunology research to improve intervention strategies that specifically target the host microbiota.

Critical Cancer–Microbiome Knowledge Gaps

It is important to remember the era of cancer–microbiome research is relatively nascent and, thus, fundamental questions remain unanswered. For example, how useful are single-microbiome measurements given the microbiome inter- and intrapatient variability, particularly when ill? Although the majority of oncology patients lose microbial diversity during chemotherapy, interpatient changes are highly variable, with some patients maintaining a relatively preserved microbiota, whereas others exhibit microbiome domination by one or two pathogens (25, 28). Gaining knowledge regarding the factors that drive such drastically different microbiota trajectories is essential to designing and targeting microbiota preservation strategies. In addition to differences among individuals, more information is needed regarding variance in local microbiota composition at the intestinal mucosa versus what is present in stool samples.

Moreover, the integration of more advanced approaches, such as whole-genome sequencing and metabolomics, is needed to potentially uncover mechanisms by which the microbiome can impact clinical outcomes. For example, significant progress is being made toward culturing the entire intestinal bacterial microbiome using methods such as "culturomics,"not only to improve upon the identification of viable species within the gut but also to capture the functional biodiversity (48). Moreover, elucidating the role that the mycobiome and virome play in immune responses, cancer therapy response, cancer treatment toxicities, and infectious complications will also need to be incorporated in future research, as these areas remain mostly unexplored. This effort, however, will need to include improving sequencing methods and databases for fungi and viruses.

It is also crucial to improve our statistical methodologies so that the complex nature of microbiome data, particularly with regard to longitudinal sampling, can be incorporated into clinical models. Statistical challenges include developing strategies to look for associations in high-dimensional data, a problem that is also being addressed by other types of big data (i.e., exome, proteomics, transcriptomics, etc.). Some challenges are unique to the microbiome, which features the additional layer of evolutionary relationships and potential interactions between bacteria, fungi, and viruses. The further development of biostatistical methods that can identify statistically meaningful relationships among networks integrating high-dimensional microbiome data with complex variables, such as gene function, metabolites, antibiotic administration, diet, and patient outcomes, is key to conceiving dependable interventions.

Conclusions

The dramatic impact of the commensal microbiota on the health of the cancer patient is increasing in appreciation. As profound effects of antibiotics on the human microbiome have been demonstrated, it is imperative that antibiotic administration and stewardship strategies in patients with malignancy be considered within the context of the microbiome. Many possible future avenues of investigation exist that could potentially aid physicians in treating cancer-related infections while limiting collateral damage to the microbiota (Table 1). As more exploratory work is done to understand the microbiome's role in cancer and cancer treatment–related toxicities, carefully designed animal models and interventional trials will be critical to moving beyond basic association or biomarker studies to determine the mechanisms by which the microbiome modulates patient outcomes. The integration of microbiome-based approaches into the clinical arena offers a tremendous new opportunity to improve outcomes across the cancer care continuum.

Table 1. Translational microbiome–based research strategies and interventions to support the management of infectious diseases and antimicrobial administration among high-risk cancer patients

Infectious disease management objective	Microbiome research strategy
Risk stratification of patients for infection or colonization with antibiotic-resistant pathogens prior to cancer treatment	• Develop baseline microbiome disruption indices that take into consideration diversity metrics, absence of beneficial microbial products, domination by microbes related with infection, and other clinical factors, i.e., comorbidities, other medications, previous cancer treatments, etc. • Develop models evaluating the effects of antimicrobial administration on microbiota composition, function, and antimicrobial resistance acquisition during cancer therapy
Personalization of antimicrobial administration and infection control decisions for optimal patient outcomes	• Intensive trials understanding the short- and long-term effects on the microbiome and patient infectious outcomes when using de-escalation of therapy, switching from intravenous to oral therapy, and discontinuation of antimicrobial therapy when cultures are negative • Using microbiome measurements or sequencing-based approaches to separate infectious from noninfectious fever • Improving methods to be able to catalog an individual's resistome in real time to aid physicians in their therapeutic considerations for prophylaxis and treatment
Infection prevention or microbiome synergism with antimicrobial therapy during cancer treatment	• Research determining specific probiotic candidates to be used during cancer treatment for desired outcomes • Trials understanding the benefits of autologous fecal reimplantation during cancer therapies to prevent infection and development of antibiotic resistance • Research defining precise prebiotic candidates or diet manipulation approaches to be used during cancer therapy for preferred outcomes

Disclosure of Potential Conflicts of Interest

R.R. Jenq holds ownership interest (including patents) in Seres Therapeutics, and is a consultant/advisory board member for Evelo Biosciences, Seres Therapeutics, and Ziopharm Oncology. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: J.R. Galloway-Peña, S.A. Shelburne
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References

1. Hersh EM, Bodey GP, Nies BA, Freireich EJ. Causes of death in acute leukemia: a ten-year study of 414 patients from 1954–1963. JAMA 1965;193:105–9.
2. Bodey GP. The changing face of febrile neutropenia-from monotherapy to moulds to mucositis. Fever and neutropenia: the early years. J Antimicrob Chemother 2009;63Suppl 1:i3–13.
3. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 2011;52:e56–93.
4. Schimpff S, Satterlee W, Young VM, Serpick A. Empiric therapy with carbenicillin and gentamicin for febrile patients with cancer and granulocytopenia. N Engl J Med 1971;284:1061–5.
5. Bucaneve G, Micozzi A, Menichetti F, Martino P, Dionisi MS, Martinelli G, et al. Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. N Engl J Med 2005;353:977–87.
6. Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. Nature 2012;486:207–14.
7. Noecker C, McNally CP, Eng A, Borenstein E. High-resolution characterization of the human microbiome. Transl Res 2017;179:7–23.
8. McDermott AJ, Huffnagle GB. The microbiome and regulation of mucosal immunity. Immunology 2014;142:24–31.
9. Nishio J, Honda K. Immunoregulation by the gut microbiota. Cell Mol Life Sci 2012;69:3635–50.
10. Thaiss CA, Zmora N, Levy M, Elinav E. The microbiome and innate immunity. Nature 2016;535:65–74.
11. Blottiere HM, de Vos WM, Ehrlich SD, Dore J. Human intestinal metagenomics: state of the art and future. Curr Opin Microbiol 2013;16:232–9.
12. Modi SR, Collins JJ, Relman DA. Antibiotics and the gut microbiota. J Clin Invest 2014;124:4212–8.
13. Iida N, Dzutsev A, Stewart CA, Smith L, Bouladoux N, Weingarten RA, et al. Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment. Science 2013;342:967–70.
14. Vetizou M, Pitt JM, Daillere R, Lepage P, Waldschmitt N, Flament C, et al. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. Science 2015;350:1079–84.
15. Sivan A, Corrales L, Hubert N, Williams JB, Aquino-Michaels K, Earley ZM, et al. Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti-PD-L1 efficacy. Science 2015;350:1084–9.
16. Rabe H, Nordstrom I, Andersson K, Lundell AC, Rudin A. *Staphylococcus aureus* convert neonatal conventional CD4(+) T cells into FOXP3(+) CD25(+) CD127(low) T cells via the PD-1/PD-L1 axis. Immunology 2014;141:467–81.
17. Viaud S, Saccheri F, Mignot G, Yamazaki T, Daillere R, Hannani D, et al. The intestinal microbiota modulates the anticancer immune effects of cyclophosphamide. Science 2013;342:971–6.
18. Pflug N, Kluth S, Vehreschild JJ, Bahlo J, Tacke D, Biehl L, et al. Efficacy of antineoplastic treatment is associated with the use of antibiotics that modulate intestinal microbiota. Oncoimmunology 2016;5:e1150399.
19. Shono Y, Docampo MD, Peled JU, Perobelli SM, Velardi E, Tsai JJ, et al. Increased GVHD-related mortality with broad-spectrum antibiotic use after allogeneic hematopoietic stem cell transplantation in human patients and mice. Sci Trans Med 2016;8:339ra371.
20. Jenq RR, Ubeda C, Taur Y, Menezes CC, Khanin R, Dudakov JA, et al. Regulation of intestinal inflammation by microbiota following allogeneic bone marrow transplantation. J Exp Med 2012;209:903–11.
21. Holler E, Butzhammer P, Schmid K, Hundsrucker C, Koestler J, Peter 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;20:640–5.
22. Harris B, Morjaria SM, Littmann ER, Geyer AI, Stover DE, Barker JN, et al. Gut microbiota predict pulmonary infiltrates after allogeneic hematopoietic cell transplantation. Am J Respir Crit Care Med 2016;194:450–63.
23. Taur Y, Pamer EG. Microbiome mediation of infections in the cancer setting. Genome Med 2016;8:40.
24. Taur Y, Pamer EG. The intestinal microbiota and susceptibility to infection in immunocompromised patients. Curr Opin Infect Dis 2013;26:332–7.
25. Taur Y, Xavier JB, Lipuma L, Ubeda C, Goldberg J, Gobourne A, et al. Intestinal domination and the risk of bacteremia in patients undergoing allogeneic hematopoietic stem cell transplantation. Clin Infect Dis 2012;55:905–14.
26. Ubeda C, Taur Y, Jenq RR, Equinda MJ, Son T, Samstein M, et al. Vancomycin-resistant *Enterococcus* domination of intestinal microbiota is enabled by antibiotic treatment in mice and precedes bloodstream invasion in humans. J Clin Invest 2010;120:4332–41.
27. van Vliet MJ, Tissing WJ, Dun CA, Meessen NE, Kamps WA, de Bont ES, et al. Chemotherapy treatment in pediatric patients with acute myeloid leukemia receiving antimicrobial prophylaxis leads to a relative increase of colonization with potentially pathogenic bacteria in the gut. Clin Infect Dis 2009;49:262–70.
28. Galloway-Pena JR, Smith DP, Sahasrabhojane P, Ajami NJ, Wadsworth WD, Daver NG, et al. The role of the gastrointestinal microbiome in infectious complications during induction chemotherapy for acute myeloid leukemia. Cancer 2016;122:2186–96.
29. Montassier E, Al-Ghalith GA, Ward T, Corvec S, Gastinne T, Potel G, et al. Pretreatment gut microbiome predicts chemotherapy-related bloodstream infection. Genome Med 2016;8:49.
30. Taur Y, Jenq RR, Perales MA, Littmann ER, Morjaria S, Ling L, et al. The effects of intestinal tract bacterial diversity on mortality following allogeneic hematopoietic stem cell transplantation. Blood 2014;124:1174–82.
31. Dubin K, Callahan MK, Ren B, Khanin R, Viale A, Ling L, et al. Intestinal microbiome analyses identify melanoma patients at risk for checkpoint-blockade-induced colitis. Nat Commun 2016;7:10391.
32. Tosh PK, McDonald LC. Infection control in the multidrug-resistant era: tending the human microbiome. Clin Infect Dis 2012;54:707–13.
33. Halpin AL, McDonald LC. Editorial Commentary: the dawning of microbiome remediation for addressing antibiotic resistance. Clin Infect Dis 2016;62:1487–8.
34. Halpin AL, de Man TJ, Kraft CS, Perry KA, Chan AW, Lieu S, et al. Intestinal microbiome disruption in patients in a long-term acute care hospital: a case for development of microbiome disruption indices to improve infection prevention. Am J Infect Control 2016;44:830–6.
35. Galloway-Peña JR, Smith DP, Sahasrabhojane P, Wadsworth WD, Fellman BM, Ajami NJ, et al. Characterization of oral and gut microbiome

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temporal variability in hospitalized cancer patients. Genome Med 2017;9:21.
36. Sommer MO, Dantas G, Church GM. Functional characterization of the antibiotic resistance reservoir in the human microflora. Science 2009;325:1128–31.
37. Kamboj M, Sheahan A, Sun J, Taur Y, Robilotti E, Babady E, et al. Transmission of *Clostridiumdifficile* during hospitalization for allogeneic stem cell transplant. Infect Control Hosp Epidemiol 2016;37:8–15.
38. Kakihana K, Fujioka Y, Suda W, Najima Y, Kuwata G, Sasajima S, et al. Fecal microbiota transplantation for patients with steroid-resistant/dependent acute graft-versus-host disease of the gut. Blood 2016;128:2083–8.
39. Khanna S, Tosh PK. A clinician's primer on the role of the microbiome in human health and disease. Mayo Clin Proc 2014;89:107–14.
40. Crum-Cianflone NF, Sullivan E, Ballon-Landa G. Fecal microbiota transplantation and successful resolution of multidrug-resistant-organism colonization. J Clin Microbiol 2015;53:1986–9.
41. Cesaro S, Chinello P, Rossi L, Zanesco L. *Saccharomycescerevisiae* fungemia in a neutropenic patient treated with Saccharomyces boulardii. Support Care Cancer 2000;8:504–5.
42. Land MH, Rouster-Stevens K, Woods CR, Cannon ML, Cnota J, Shetty AK. *Lactobacillus* sepsis associated with probiotic therapy. Pediatrics 2005;115:178–81.
43. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature 2014;505:559–63.
44. Turnbaugh PJ, Ridaura VK, Faith JJ, Rey FE, Knight R, Gordon JI. The effect of diet on the human gut microbiome: a metagenomic analysis in humanized gnotobiotic mice. Sci Transl Med 2009;1:6ra14.
45. Arpaia N, Campbell C, Fan X, Dikiy S, van der Veeken J, deRoos P, et al. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. Nature 2013;504:451–5.
46. Furusawa Y, Obata Y, Fukuda S, Endo TA, Nakato G, Takahashi D, et al. et al: Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. Nature 2013;504:446–50.
47. Smith PM, Howitt MR, Panikov N, Michaud M, Gallini CA, Bohlooly YM, et al. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. Science 2013;341:569–73.
48. Lagier JC, Khelaifia S, Alou MT, Ndongo S, Dione N, Hugon P, et al. Culture of previously uncultured members of the human gut microbiota by culturomics. Nat Microbiol 2016;1:16203.

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