Perspective

The Potential Role of the Gut Microbiota in Kidney Transplantation

Jennifer Huang,1 Thalia Salinas,1 Lars F. Westblade,2 and John R. Lee1,3

KIDNEY360 2: 890–893, 2021. doi: https://doi.org/10.34067/KID.0006912020

Introduction
Through use of high-throughput sequencing technologies, numerous studies have revealed the multifaceted role of the gut microbiota in host immunity and infection, resulting in wide-ranging implications for patients with cancer and autoimmune diseases (1). The gut microbiota’s potential to influence host immunity may be of particular importance in solid organ transplant recipients, given this population’s risk for allograft rejection and increased susceptibility to infections. In this perspective article, we present recent work on the effect of the gut microbiota in kidney transplant recipients, with a focus on infectious complications and immunosuppressive drug metabolism.

Gut Microbiota in Kidney Transplant Recipients Compared with Nontransplant Recipients
The Human Microbiome Project characterized the microbiota of 242 healthy human volunteers and found the gut microbiota was dominated by the phylum Bacteroidetes (2). This is distinctly different from kidney transplant recipients, as evidenced by several studies. Fricke et al. (3) evaluated the gut microbiota using rectal swabs in 61 kidney transplant recipients and reported a high proportion of the phylum Firmicutes rather than Bacteroidetes. Similarly, Lee et al. (4) evaluated the gut microbiota using fecal specimens in 26 kidney transplant recipients and found gut dominance by Firmicutes in this cohort. Lee et al. further noticed the gut abundance of Proteobacteria, a phylum that includes Gram-negative bacteria such as Escherichia coli, increased in the first couple of weeks after transplantation. Swarte et al. (5) studied the gut microbiota in kidney transplant recipients several years after transplantation compared with that of healthy controls and observed they had a significantly lower microbial diversity in the gut compared with healthy controls. However, none of these studies compared the kidney transplant cohort to a nontransplant, ESKD cohort, so it is unclear whether this gut microbiota signature is unique to transplant recipients, or if it is pervasive in patients with ESKD as well. Nevertheless, the studies do find an altered species composition and lower microbial diversity in the gut microbiota of kidney transplant recipients compared with that of healthy controls.

Commensal Gut Microbiota and Inhibition of Pathobionts
Recent work has shown an intricate relationship between commensal gut bacteria and pathobionts, resident microbes with pathogenic potential that are often responsible for infectious complications. Several studies have elucidated mechanisms by which commensal bacteria inhibit the growth of common pathobionts via secretion of specific metabolites. Caballero et al. (6) studied a four-bacteria consortium that included Blautia producta using an antibiotic-treated mouse model and reported that administering the consortium provided colonization resistance against vancomycin-resistant Enterococcus (VRE), an organism that commonly causes nosocomial infections in the transplant population. The group further investigated the mechanism and reported that a specific strain of Blautia producta produces a lantibiotic antimicrobial peptide that inhibits VRE growth (7). Other studies have also established a role for short-chain fatty acids (SCFAs) in inhibiting the growth of Gram-negative bacteria. Sorbara et al. observed that ampicillin-treated mice had less abundance of SCFAs than controls and were more susceptible to carbapenem-resistant Klebsiella pneumonae. They further showed that SCFAs directly inhibit K. pneumoiae and other common Gram-negative bacteria in the Enterobacteriaceae family at an acidic pH, similar to physiologic concentrations in the human gut (8). Recent studies have also established a role for secondary bile acid formation in inhibiting Clostridium difficile. Buffie et al. (9) reported that introduction of Clostridium scindens, which converts primary bile acids to secondary bile acids via 7 alpha-dehydroxylase, provides enhanced resistance to C. difficile infection in a mouse model. Taken together, these studies have elegantly established how commensal organisms may inhibit the growth of pathobionts in the gut.

Gut Microbiota and Infectious Complications in Allogeneic Hematopoietic Stem Cell Transplant Recipients
Recent investigations in allogeneic hematopoietic stem cell transplant (HSCT) recipients show the balance of commensal organisms and pathobionts in the

---

1Division of Nephrology and Hypertension, Department of Medicine, Weill Cornell Medicine, New York, New York
2Department of Pathology and Laboratory Medicine, Weill Cornell Medicine, New York, New York
3Department of Transplantation Medicine, New York Presbyterian Hospital Weill Cornell Medical Center, New York, New York

Correspondence: John R. Lee, Weill Cornell Medicine, 525 East 68th Street Box 3, New York, NY 10065. Email: jrl2002@med.cornell.edu.
gut has a significant effect on infectious outcomes. In a study of 94 patients receiving HSCT, Taur et al. (10) profiled serial stool specimens using 16S rRNA gene sequencing of the V4–V5 hypervariable region and found that a fecal abundance of >30% of Enterococcus was associated with a future risk for VRE bacteremia. A follow-up study of 696 patients receiving HSCT by this group found that a gut abundance of >30% of Gram-negative bacteria was associated with future development of Gram-negative bacteremia, and that fluoroquinolone prophylaxis decreased the risk for Gram-negative bacteremia (11). These studies suggest that intestinal domination with pathobionts in the gut can lead to the development of sepsis; however, they did not evaluate whether the bloodstream isolates came from the gut. A study by Tamburini et al. sought to evaluate this concept in 32 patients receiving HSCT. Using strain-level analysis, the group determined the strains in the gut before the development of bacteremia were most similar to the isolates from subsequent blood cultures (12). The gut microbiota may also have a role in the development of viral infections. Haak et al. (13) investigated 360 patients receiving HSCT, and noted that a gut abundance of >1% of butyrate-producing bacteria was associated with a decreased risk for the development of lower respiratory tract viral infections.

Gut Microbiota and Infectious Complications in Kidney Transplant Recipients

Similar to reports that demonstrate the gut microbiota modulate the risk of infectious complications in patients receiving HSCT, recent work suggests there may also be a relationship between commensal microbiota and infections in kidney transplant recipients. Magruder et al. investigated the role of the gut microbiota in the development of urinary tract infection (UTI), which is one of the most common infections that kidney transplant recipients encounter after transplantation. In a study of 168 kidney transplant recipients, they serially profiled fecal specimens using 16S rRNA gene sequencing and found gut abundance of Escherichia was independently associated with future development of Escherichia UTI (14). Detailed metagenomic sequencing of paired gut and urine specimens collected in patients with UTI revealed the E. coli strain in the urine was most similar to the E. coli strain in the gut in several patients, supporting gut bacteria as a source for UTIs. The group may have also identified protective gut bacteria; specifically, there was a trend toward significance for increased gut abundances of Faecalibacterium and Romboutsia to be associated with a decreased risk for Enterobacteriaceae UTI (15). Interestingly, Faecalibacterium and Romboutsia produce SCFAs, which have been shown to inhibit the growth of Enterobacteriaceae (8). Furthermore, the abundance of these bacteria was negatively correlated with the abundance of Enterobacteriaceae, supporting the concept that SCFA-producing gut bacteria may be protective of Enterobacteriaceae UTIs via inhibition of Enterobacteriaceae growth in the gut.

Further analysis of the 168 kidney transplant recipients also revealed a potential association between gut bacteria that produce butyrate, an SCFA, and protection from respiratory viral infections (16). A relative abundance >1% of butyrate-producing gut bacteria was associated with decreased development of respiratory tract viral infections in the first 2 years after transplantation, consistent with data from Haak et al. in the HSCT population.

There are now limited data, albeit mostly in the form of case reports, which suggest efficacy of gut microbiota–based therapies, such as fecal microbial transplantation (FMT), for preventing infectious complications other than C. difficile infection. In one patient study, a heart and kidney transplant recipient had recurrent C. difficile infection and recurrent Enterococcus bacteremia and UTIs (17). After undergoing FMT for recurrent C. difficile infections, the patient was free not only of C. difficile infection but also of Enterococcus bacteremia and UTIs, up to the time of publication of the case report. In a study of eight patients who were nontransplant and had recurrent UTIs and received FMT for the indication of recurrent C. difficile infections, FMT was associated with a significant decrease in UTI recurrence (18). Further studies are needed to investigate the role of gut microbiota–based therapies for preventing infectious complications in kidney transplant recipients at high risk for non-C. difficile recurrent infections.

Gut Microbiota and Metabolism of Immunosuppressive Medications

The alteration of the gut microbiota due to medications, including antibiotics, has been extensively described. There is now growing interest in how the gut microbiota affects drug metabolism. Recent work by Zimmermann et al. (19) evaluated 76 human gut bacteria and their potential ability to metabolize 271 drugs, and found considerable gut microbiota–mediated drug metabolism in vitro. Recent studies have specifically elucidated the role of the gut microbiota in influencing the metabolism of two of the most commonly used immunosuppressive medications in kidney transplant recipients: tacrolimus and mycophenolate mofetil.

In a pilot study of 19 kidney transplant recipients, Lee et al. (20) evaluated the gut microbiome using 16S rRNA gene sequencing at 1 week after transplantation and reported a correlation between higher gut abundance of Faecalibacterium prausnitzii and higher tacrolimus dosage at 1 month after transplantation. The mechanism behind this association was not initially understood. However, a follow-up study by Guo et al. (21) found in vitro evidence that F. prausnitzii and more than 20 commensal gut bacteria directly metabolize tacrolimus into a metabolite, M1, that is 15-fold less immunosuppressive than parent tacrolimus. They also found that M1 is a bacterial metabolite unique to gut bacteria, because incubation of tacrolimus with hepatic microsomes did not produce M1, and M1 production can be detected in fecal specimens obtained from kidney transplant recipients (21). The group further investigated the pharmacokinetics of M1 and parent tacrolimus after oral administration of tacrolimus in ten kidney transplant recipients (21). The group further investigated the pharmacokinetics of M1 and parent tacrolimus after oral administration of tacrolimus in ten kidney transplant recipients (21). The group further investigated the pharmacokinetics of M1 and parent tacrolimus after oral administration of tacrolimus in ten kidney transplant recipients (21). The group further investigated the pharmacokinetics of M1 and parent tacrolimus after oral administration of tacrolimus in ten kidney transplant recipients (21). The group further investigated the pharmacokinetics of M1 and parent tacrolimus after oral administration of tacrolimus in ten kidney transplant recipients (21). The group further investigated the pharmacokinetics of M1 and parent tacrolimus after oral administration of tacrolimus in ten kidney transplant recipients (21). The group further investigated the pharmacokinetics of M1 and parent tacrolimus after oral administration of tacrolimus in ten kidney transplant recipients (21). The group further investigated the pharmacokinetics of M1 and parent tacrolimus after oral administration of tacrolimus in ten kidney transplant recipients (21). The group further investigated the pharmacokinetics of M1 and parent tacrolimus after oral administration of tacrolimus in ten kidney transplant recipients (21). The group further investigated the pharmacokinetics of M1 and parent tacrolimus after oral administration of tacrolimus in ten kidney transplant recipients (21).
patients also showed an association between gut microbiota diversity and tacrolimus dosing requirements (23).

The metabolism of mycophenolate mofetil, another commonly used immunosuppressive drug in the kidney transplant population, may also be influenced by the gut microbiota. Enterohepatic recirculation of mycophenolic acid, the active form of mycophenolic mofetil, has been described (24) but the mechanism has not been explored in detail. Recent work by Taylor et al. investigated the role of bacterial beta-glucuronidase, an enzyme that can convert glucuronidated mycophenolic acid back to the active mycophenolic acid (25). The group reported that vancomycin eliminated bacteria with beta-glucuronidase activity, thereby decreasing side effects of mycophenolate mofetil, such as weight loss and colonic inflammation (26). Further studies are needed to better understand the extent of the gut microbiota’s effect on mycophenolate mofetil’s metabolism and toxicity.

Conclusions

The gut microbiota is increasingly recognized as influencing a variety of complications associated with kidney transplant recipients. Its role in post-transplant infections has been recently suggested, but further studies are needed to better understand how commensal organisms function as a community to combat infectious complications. Further characterization of these microbial consortia may allow the development of defined microbiota-based treatments for the prevention of infections. In addition, some bacterial subsets have protective properties from an infection standpoint and may also directly metabolize immunosuppressive medications essential for preserving graft function in kidney transplant recipients. Further research on the dynamics between the gut microbiota and immunosuppressive drug metabolism has the potential to personalize immunosuppressive therapies for kidney transplant recipients, and thereby reduce the post-transplant complications of infection and graft loss.

Disclosures

J.R. Lee holds US-2020-0048713-A1 patent titled “Methods of Detecting Cell-Free DNA in Biological Samples;” reports receiving research support under an investigator-initiated research grant from BioFire Diagnostics, LLC; reports being an Academic Editor, PLOS ONE; and reports other interests/relationships with the American Society of Nephrology Career Advancement Committee. L. Westblade reports receiving research support from Accelerate Diagnostics, Inc., Affinity Biosensors, LLC, BioFire Diagnostics, LLC, Hardy Diagnostics, and Roche Molecular Systems, Inc., and reports receiving consulting fees from Roche Molecular Systems, Inc., Shionogi, Inc, and Talis Biomedical. All remaining authors have nothing to disclose.

Funding

This work was supported by the National Institute of Allergy and Infectious Diseases K23 AI 124464 grant (to J.R. Lee).

Acknowledgments

The content of this article reflects the personal experience and views of the author(s) and should not be considered medical advice or recommendations. The content does not reflect the views or opinions of the American Society of Nephrology (ASN) or Kidney360. Responsibility for the information and views expressed herein lies entirely with the author(s).

Author Contributions

J. Huang and J.R. Lee wrote the original draft; and all authors conceptualized the study and reviewed and edited the manuscript.

References

1. Lazar V, Ditu LM, Pircalabioiu GG, Gheorghe I, Curutiu C, Holban AM, Picu A, Petcu L, Chiliriu MC: Aspects of Gut Microbiota and Immune System Interactions in Infectious Diseases, Immunopathology, and Cancer. Front Immunol 9: 1830, 2018 https://doi.org/10.3389/fimmu.2018.01830
2. Human Microbiome Project Consortium: Structure, function and diversity of the healthy human microbiome. Nature 486: 207–214, 2012 https://doi.org/10.1038/nature11234
3. Fricke WF, Maddox C, Song Y, Bromberg JS: Human microbiota characterization in the course of renal transplantation. Am J Transplant 14: 416–427, 2014 https://doi.org/10.1111/ajt.12588
4. Lee JR, Muthukumar T, Dadhania D, Toussaint NC, Ling L, Pamer E, Suthanthiran M: Gut microbial community structure and complications after kidney transplantation: a pilot study. Transplantation 98: 697–705, 2014 https://doi.org/10.1097/TP.00000000000003370
5. Swarte JC, Douwes RM, Hu S, Vich Vila A, Eisenga MF, van Londen M, Gomes-Neto AW, Weersma RK, Harmsen HJM, Bakker SjL: Characteristics and Dysbiosis of the Gut Microbiome in Renal Transplant Recipients. J Clin Med 9: 386, 2020 https://doi.org/10.3390/jcm9020386
6. Caballero S, Kim S, Carter RA, Leiner IM, Sussa B, Miller L, Kim GJ, Ling L, Pamer EG: Cooperating Commensals Restore Colonization Resistance to Vancomycin-Resistant Enterococcus faecium. Cell Host Microbe 21: 592–602.e4, 2017 https://doi.org/10.1016/j.chom.2017.04.002
7. Kim SG, Becattini S, Moody TU, Shihia PV, Littmann ER, Seok R, Gjonbalaj M, Eaton V, Fontana E, Amoretti L, Wright R, Caballero S, Wang ZX, Jung HJ, Morjaria SM, Leiner IM, Qin W, Ramos RJF, Cross JR, Narushima S, Honda K, Peled JU, Hendrickson RC, Taur Y, van den Brink MR, Pamer EG: Microbiota-derived lantibiotic restores resistance against vancomycin-resistant Enterococcus. Nature 572: 665–669, 2019 https://doi.org/10.1038/s41586-019-1501-z
8. Sorbara MT, Dubin K, Littmann ER, Moody TU, Fontana E, Seok R, Leiner IM, Taur Y, Peled JU, van den Brink MR, Litvak Y, Baumler AJ, Chabard P, Pickard AJ, Cross JR, Pamer EG: Inhibiting antibiotic-resistant Enterobacteriaceae by microbiota-mediated intracellular acidification. J Exp Med 216: 84–98, 2019 https://doi.org/10.1084/jem.20181639
9. Bullie CG, Bucci V, Stein RR, Mc Kenney PT, Ling L, Gobourne A, No D, Liu H, Kinnebrew M, Viale A, Littmann E, van den Brink MR, Jerk RR, Taur Y, Sander C, Cross JR, Toussaint NC, Xavier JB, Pamer EG: Precision microbiome reconstitution restores bile acid mediated resistance to Clostridium difficile. Nature 517: 205–208, 2015 https://doi.org/10.1038/nature13828
10. Taur Y, Xavier JB, Lipuma L, Ubeda C, Goldberg J, Gobourne A, Lee YJ, Dubin KA, Sacci ND, Viale A, Perales MA, Jerk RR, van den Brink MR, Pamer EG: Intestinal dominance and the role of bacteremia in patients undergoing allogeneic hematopoietic stem cell transplantation. Clin Infect Dis 55: 905–914, 2012 https://doi.org/10.1093/cid/cis580
11. Stoma I, Littmann ER, Peled JU, Giralt S, van den Brink MR, Pamer EG, Taur Y: Compositional flux within the intestinal microbiota and risk for bloodstream infection with gram-negative bacteria [published online ahead of print January 24, 2020]. Clin Infect Dis https://doi.org/10.1093/cid/ciaa068
12. Tamburini FB, Andermann TM, Tkachenko E, Sencych F, Banaei N, Bhatt AS: Precision identification of diverse bloodstream pathogens in the gut microbiome. Nat Med 24: 1809–1814, 2018 https://doi.org/10.1038/s41591-018-0202-8
13. Haak BW, Littmann ER, Chaudhur JI, Pickard AJ, Fontana E, Adhi F, Gyaltsen Y, Ling L, Morjaria SM, Peled JU, van den Brink MR,
Geyer AI, Cross JR, Pamer EG, Taur Y: Impact of gut colonization with butyrate-producing microbiota on respiratory viral infection following allo-HCT. *Blood* 131: 2978–2986, 2018 https://doi.org/10.1182/blood-2018-01-828996

14. Magruder M, Sholi AN, Gong C, Zhang L, Edusei E, Huang J, Albakry S, Satlin MJ, Westblade LF, Crawford C, Dadhania DM, Lubetzky M, Taur Y, Litman T, Ling L, Burnham P, De Vlaminck I, Pamer E, Suthanthiran M, Lee JR: Gut uropathogen abundance is a risk factor for development of bacteriuria and urinary tract infection. *Nat Commun* 10: 5521, 2019 https://doi.org/10.1038/s41467-019-13467-w

15. Magruder M, Edusei E, Zhang L, Albakry S, Satlin MJ, Westblade LF, Malha L, Sze C, Lubetzky M, Dadhania DM, Lee JR: Gut commensal microbiota and decreased risk for Enterobacteriaceae bacteriuria and urinary tract infection. *Gut Microbes* 12: 1805281, 2020 https://doi.org/10.1080/19490976.2020.1805281

16. Lee JR, Huang J, Magruder M, Zhang LT, Gong C, Sholi AN, Albakry S, Edusei E, Muthukumar T, Lubetzky M, Dadhania DM, Taur Y, Pamer EG, Suthanthiran M: Butyrate-producing gut bacteria and viral infections in kidney transplant recipients: A pilot study. *Transpl Infect Dis* 21: e13180, 2019 https://doi.org/10.1111/tid.13180

17. Stripling J, Kumar R, Baddley JW, Nellore A, Dixon P, Howard D, Pateck T, Letkowitz EJ, Tallaj JA, Benjamin WH Jr, Morrow CD, Rodriguez JM: Loss of Vancomycin-Resistant Enterococcal Fecal Dominance in an Organ Transplant Patient With Clostridium difficile Colitis After Fecal Microbiota Transplant. *Open Forum Infect Dis* 2: ofv078, 2015 https://doi.org/10.1093/ofid/ofv078

18. Tariq R, Pardi DS, Tosh PK, Walker KC, Razonable RR, Khanna S: Fecal Microbiota Transplantation for Recurrent Clostridium difficile Infection Reduces Recurrent Urinary Tract Infection Frequency. *Clin Infect Dis* 65: 1745–1747, 2017 https://doi.org/10.1093/cid/cix618

19. Zimmermann M, Zimmermann-Kogadeeva M, Wegmann R, Goodman AL: Mapping human microbiome drug metabolism by gut bacteria and their genes. *Nature* 570: 462–467, 2019 https://doi.org/10.1038/s41586-019-1291-3

20. Lee JR, Muthukumar T, Dadhania D, Taur Y, Jenq RR, Toussaint NC, Litman T, Pamer E, Suthanthiran M: Gut microbiota and tacrolimus dosing in kidney transplantation. *PLoS One* 10: e0122399, 2015 https://doi.org/10.1371/journal.pone.0122399

21. Guo Y, Crnkovic CM, Won KJ, Yang X, Lee JR, Orjala J, Lee H, Jeong H: Commensal Gut Bacteria Converst the Immunosuppressant Tacrolimus to Less Potent Metabolites. *Drug Metab Dispos* 47: 194–202, 2019 https://doi.org/10.1124/dmd.118.084772

22. Guo Y, Lee H, Edusei E, Albakry S, Jeong H, Lee JR: Blood Profiles of Gut Bacterial Tacrolimus Metabolites in Kidney Transplant Recipients. *Transplant Direct* 6: e001, 2020 https://doi.org/10.1097/TXD.0000000000001052

23. Jennings DL, Bohn B, Zuver A, Onat D, Gaine M, Royzman E, Hupf J, Brunjes D, Latif F, Restaino S, Garan AR, Topkara VK, Takayama H, Takeda K, Naka Y, Farr M, Nandakumar R, Uholemann AC, Colombo PC, Demmer RT, Yuzepolskaya M: Gut microbial diversity, inflammation, and oxidative stress are associated with tacrolimus dosing requirements early after heart transplantation. *PLoS One* 15: e0233646, 2020 https://doi.org/10.1371/journal.pone.0233646

24. Jeong H, Kaplan B: Therapeutic monitoring of mycophenolate mofetil. *Clin J Am Soc Nephrol* 2: 184–191, 2007 https://doi.org/10.2215/CJN.02860806

25. Pellock SJ, Redinbo MR: Glucuronides in the gut: Sugar-driven symbioses between microbe and host. *J Biol Chem* 292: 8569–8576, 2017 https://doi.org/10.1074/jbc.R116.767434

26. Taylor MR, Flannigan KL, Rahim H, Mohamud A, Lewis IA, Hirota SA, Greenway SC: Vancomycin relieves mycophenolate mofetil-induced gastrointestinal toxicity by eliminating gut bacterial β-glucuronidase activity. *Sci Adv* 5: eaax2358, 2019 https://doi.org/10.1126/sciadv.aax2358

Received: November 30, 2020 Accepted: March 5, 2021