90194_Auto_Edited.docx

WORD COUNT	7557	TIME SUBMITTED	28-DEC-2023 04:35PM
		PAPER ID	105787334

Update on the reciprocal interference between immunosuppressive therapy and gut microbiota after kidney transplantation

Salvadori M *et al*. Interference between immunosuppressants and the gut microbiota

Abstract

Gut microbiota is often modified after kidney transplantation. This principally happens in the first period after transplantation. Antibiotics and, most of all, immunosuppressive drugs are the main responsible. The relationship between immunosuppressive drugs and the gut microbiota is bilateral. From one side immunosuppressive drugs modify the gut microbiota, often generating dysbiosis; from the other side microbiota may interfere with the immunosuppressant pharmacokinetics, producing products more or less active with respect to the original drug. These phenomena have influence over the graft outcomes and clinical consequences as rejections, infections, diarrhea may be caused by the dysbiotic condition. Corticosteroids, calcineurin inhibitors such as tacrolimus and cyclosporine, mycophenolate mofetil and mTOR inhibitors are the immunosuppressive drugs whose effect on the gut microbiota is better known. In contrast is well known how the gut microbiota may interfere with glucocorticoids, which may be transformed into androgens. Tacrolimus may be transformed by microbiota into a product called M1 that is 15-fold less active with respect to tacrolimus. The pro-drug mycophenolate mofetil is normally transformed in mycophenolic acid that according the presence or not of microbes producing the enzyme glucuronidase, may be transformed into the inactive product.

Key Words: Immunosuppressive therapy; Kidney transplantation; Gut microbiota; Dysbiosis; Pathobionts; Graft outcomes

Salvadori M, Rosso G. Update on the reciprocal interference between immunosuppressive therapy and gut microbiota after kidney transplantation. *World J Transplant* 2023; In press

Core Tip: Gut dysbiosis frequently occurs in the first period after kidney transplantation. Among the different causes, immunosuppressive drugs play a relevant role. There is a reciprocal effect between immunosuppressive drugs and the gut microbiota. Indeed, immunosuppressive drugs may change the gut microbiota composition causing dysbiosis as related side effects as rejection and infections. In contrast, the gut microbiota may alter the pharmacokinetic of immunosuppressive drugs determining modification in their metabolism and favoring the presence of substances with lower or higher immunosuppressant effect with respect to the original compound. Physicians should pay particular attention to these possibilities and carefully control both changes in the gut microbiota and the correct level of immunosuppressive drugs.

INTRODUCTION

Among the different factors that influence the outcomes of a transplant, the gut microbiota plays a relevant role. Indeed, the relationship between the gut microbiota and the local or general immune system plays an important role in conditioning the transplant outcome. Due to this relationship, the gut microbiota may have different effects. On the one hand, the indigenous microbiota may favor the positive evolution of the graft due to, among other factors, the secretion of beneficial substances; on the other hand, the presence of pathobionts and pathogenic microbes may have deleterious effects on the graft outcomes, interfering with the metabolism of several immunosuppressant drugs.

A study from Lee *et al*[1] examined fecal specimens of five kidney transplant recipients, which provided fecal specimens prior to transplantation and 2 wk after

transplantation. *Proteobacteria* were more abundant in the posttransplantation specimens as were *Erysipelotrichales* and *Enterobacteriales*.

Other studies on the gut microbiota after kidney transplantation (KT) reported a reduction in *Faecalibacterium*[2], reduction in *Actinobacteria* and *Faecalibacterium prausnizii*[3], reduction in *Ruminococcaceae*[4], and reduction in *Clostridiales*[5].

The influences of these modifications of the gut microbiota on the posttransplant settings are reported in Table 1[6-16].

Principally in the first period after transplantation, transplant recipients need to receive both immunosuppressive drugs to avoid rejection and antibiotic therapy to avoid infections.

These drugs principally influence the changes in the gut microbiota documented in the first period after transplantation. In addition, fecal metobolomic reveals distinct profiles of kidney transplant recipients and healthy controls[17].

The aim of this study was to analyze the relevance of immunosuppressive therapy on the modification of the gut microbiota composition. In addition, this study will analyze how the gut microbiota may influence the metabolism of immunosuppressive drugs.

BENEFICIAL EFFECTS IN HEALTHY CONDITIONS

In healthy conditions, the gut microbiota is principally composed of the indigenous microbiota.

The principal functions of the gut microbiota are metabolic, structural and protective. The metabolic function is exerted by metabolizing fermentable polysaccharides to produce several compounds, and to stimulate a thick intestinal mucus layer. The production of short-chain fatty acids (SCFAs), in addition to decreasing the intestinal pH and to providing further sources of energy by binding-to G protein coupled receptors, increases energy expenditure[18], reduces food intake[19] and improves glucose metabolism. In addition, the gut microbiota can contribute to drug efficacy by enzymatically transforming drug structure and altering drug bioavailability or toxicity.

As we will describe, improved insight into the interaction between microbiota and drugs may optimize treatment efficacy[20].

Structural function is exerted by contributing to the integrity of the gut epithelium, do not allowing the cytokines present in the gut lumen to pass across the epithelium barrier.

Protective function. Several metabolites produced by the production of SCFAs contribute to the protective function of the gut microbiota. Butyrate by carbohydrate metabolism increases the intestinal barrier, and this function is due to *Clostridia* and *Faecalibacterium prausnizii*[21]. Propionate by carbohydrate metabolism suppresses colonic inflammation and decreases the innate immune response due to microbial stimulation. *Coprococcus catus* and *Roseburia*[22] favor this action. Indole by tryptophan metabolism increases the barrier function and modulates metabolism. *Lactobacillus* and *Bacteroides fragilis* favor this action[23]. Indole-3-propionic acid by tryptophan metabolism protects the intestinal barrier and increases the production of antioxidant products. *Clostridium sporogenes* provides this action[24]. Finally, the 10-hydroxy-cis-12-octadecoate by produced by *Lactobacillus* by lipid metabolism maintains the intestinal barrier function and decreases inflammation[25].

FACTORS MODIFYING THE GUT INDIGENOUS MICROBIOTA

Several factors can modify the aforementioned gut microbiota. Among these are age, diet, genetic factors of the host, and exercise and drugs.

Many of these factors affect the intestinal microbiota after KT. These can be divided into pharmacological factors, such as anti-infectious treatments[26], immunosuppressive drugs[27] and anesthetics[28], and nonpharmacological factors, such as the normalization of renal function and its associated metabolic abnormalities[29], the modification of dietary habits[30] and the discontinuation of chronic hemodialysis[31]. All these factors are shown in Figure 1.

In the case of solid organ transplantation, a particular effect on the gut microbiota is exerted by immunosuppressive treatment.

INTERRELATIONSHIP BETWEEN IMMUNOSUPPRESSIVE THERAPY AND GUT MICROBIOTA

There is a reciprocal effect between immunosuppressive drugs and microbiota. Indeed, immunosuppressive treatment may modify the gut microbiota composition. In contrast, the gut microbiota may alter the metabolism of immunosuppressive drugs.

Several studies have documented the modification of the gut microbiota after KT. Fricke *et al*[10] documented microbiota modification in all intestinal tracts after transplantation in 60 patients. Lee *et al*[1], in the aforementioned study, documented *Bacteroidetes* reduction and *Proteobacteria* increase. Shin *et al*[32] documented the presence of *Salmonellae* and *Escherichia coli* (*E. coli*) as signs of a pro-inflammatory condition. A recent and large study from Swarte *et al*[33] analyzed 1370 fecal specimens from 415 Liver transplant and 672 kidney transplant subjects. In addition, they analyzed 1183 fecal specimens after 78 KT patients that were followed for two years. Overall, they found a reduction in indigenous microbiota, such as *Akkermansia muciniphila* and *Ruminococcus obeum*, and an increase in *Clostridium asparagiform* and *Coprobacter fastidiosus*. In addition, the authors found an increase in pathobionts, which could persist up to 20 years after transplantation.

A gut microbiota reduction in bacteria of the *Clostridiales* order is associated with rejection. The low production of SCFAs may have a role in this complication, as documented by the study of Koh *et al*[34].

Tourret *et al*[35] found that immunosuppressive treatment alters the secretion of iliac antimicrobial peptides and the gut microbiota and favors subsequent colonization by uropathogenic *E. coli*.

These gut microbiota modifications may cause several posttransplant events.

Different factors, including immunosuppression and antibiotic therapy, lifestyle and diet, may alter the microbiota and led to dysbiosis. Dysbiosis disrupts the gut epithelial barrier, causes loss of barrier integrity, and leads to overgrowth of pathogens. Leaky gut and increased permeability allow translocation of bacteria and their components

into the inner environment. In this dysbiotic condition, the proinflammatory response triggers the elimination of pathogens by intestinal epithelial cells (IL-1, IL-6, and IL-18 secretion, dendritic cells[36], and macrophages[37], which induces the development of the effector CD4+ T cells TH1 and TH17. These immune responses can preserve the activation of alloreactive T cells by cross-reacting with commensal organisms and molecular mimicry, leading to graft rejection. On the other hand, in the colon and liver, dysbiotic gut-derived uremic toxins are further metabolized to trimethylamine-N-oxide, p-cresyl sulfate (PCS) and indoxyl sulfate. The accumulation of PCS in the kidney generates reactive oxygen substances that lead to the production of inflammatory cytokines and profibrotic factors, resulting in cell injury.

On the one hand, almost all immunosuppressive drugs may determine modifications of the gut microbiota with the appearance of pathobionts and secondary dysbiosis. Their action is different according to the drugs. In contrast, the gut microbiota may modify the metabolism of immunosuppressive drugs.

GUT MICROBIOTA MODIFICATION INDUCED BY IMMUNOSUPPRESSIVE DRUGS

In a study from Gibson *et al*[38], the alteration of the gut microbiome by immunosuppressive agents used in solid organ transplantation, has been well documented.

Corticosteroids

Glucocorticoids (GCs) inhibit the expression and synthesis of Muc2, the main component of colonic mucus[39]. GCs also alter gut immunity by downregulating the ileal expression of antimicrobial C-type lectins RegIII β and Reg III γ[40] *via* the inhibition of IL-22. In addition, GCs restrict the coating of bacteria by mucosal IgA[41]. On the other hand, GCs induce a retightening of TNF-α-induced tight junction relaxation by downregulating myosin light chain kinase (MLCK) synthesis and myosin light chain 2 (MLC2) phosphorylation, which is responsible for the contraction of the perijunctional

actin-myosin filaments. Therefore, tight junction dysfunction is induced[42]. These modifications of the gut barrier may cause gut microbiome modification and facilitate a kinase back diffusion. Finally, the dysregulation of the circadian clock by exogenous GCs could also result in gut dysbiosis as documented by the study of Wu *et al*[43]. Figure 2 shows the corticosteroid action.

Tacrolimus

Tacrolimus pharmacokinetics is associated with gut microbiota diversity in kidney transplant patients as resulted from a pilot cross-sectional study by Degraeve *et al*[44].

Tacrolimus confers immunosuppressive properties to the gut microbiota both locally and systemically by increasing the population of Treg lymphocytes. Moreover, tacrolimus is responsible for local immunosuppression in the gut by inhibiting T-lymphocyte and NK cell function[45]. Tacrolimus-induced gut microbiota alterations could also result in side effects, such as high blood pressure and diabetes[46]. This fact was confirmed by the PICRUST analysis that uses marker gene data[47] and by metagenomics analysis. Tacrolimus increases gut permeability and decreases iliac RegIIIβ levels, participating in dysbiosis[40].

In a large study conducted in liver transplant patients, tacrolimus decreased *Bifidobacterium*, *Lactobacillus* and *Faecalibacterium prausnizii* and increased *Enterobacteriaceae* and *Enterococcus*[48]. Another relevant variable in tacrolimus -induced gut microbiota changes is the administered dose. Even if based on liver transplant in rats, an intermediate dose (0.5 mg/kg) increased beneficial indigenous bacteria such as *Bifidobacterium* and *Faecalibacterium prausnizii*, while lower or higher doses resulted in different effects with an increase in pathobionts[49]. Figure 3 shows the reciprocal interference between tacrolimus and the gut microbiota.

Cyclosporine

Fewer data are available on the effect of cyclosporine (CsA) on the gut microbiota. In addition, studies have been conducted in rats and in mouse liver transplants. CsA is a

calcineurin inhibitor similar to tacrolimus. According to these studies[50,51], CsA seems to have different effects with respect to tacrolimus increasing beneficial indigenous bacteria and decreasing pathobionts such as *Enterobacteriaceae* and *Clostridium*.

The major drawback of almost all these studies is that they are made on animals, mice overall. Recently, a study by O'Reilly *et al*[52] documented that encapsulated CsA does not change the composition of the human microbiota when assessed *ex vivo* and *in vivo* in humans. In particular, SWFCAs increased as well as butyrate and acetate in fecal samples.

In conclusion, it seems that CsA causes dysbiosis when given with other immunosuppressant drugs, but, when given alone, it preserves the indigenous bacteria.

Mycophenolate mofetil

Mycophenolate Mofetil (MMF) strips the diversity of the gut microbiota, increases the *Firmicutes*/*Bacteroidetes* ratio and favors *Clostridia*, *Bacteroides* and *Proteobacteria*, which include strains such as *Shigella* and *E. coli*. In contrast, *Akkermansia*, *Parabacteroides* and *Clostridium* are decreased[53]. This gut dysbiosis generates high fecal concentrations of lipopolysaccharides and colonic inflammation. In addition, mycophenolic acid (MPA), the active metabolite of MMF, perturbs tight junctions by upregulating MLCK and MLC2 phosphorylation. This is responsible for alteration of the gut barrier[54]. The resulting endotoxemia is responsible for a higher rate of cardiovascular events in KT recipients[55]. Finally, the abundance of *Bacteroides* correlates with a high level of activity of colonic bacterial β-glucuronidase, which converts the glucoronated form of MPA (MPAG) back to its active form. The addition of Vancomycin eliminates gut bacterial β-glucuronidase activity, decreasing *Bacteroides*. In this way, Vancomycin reduces MMF-induced gastrointestinal toxicity[56]. Figure 4 shows all the MMF activity at the gut level.

mTOR inhibitors

Few data are available on the interrelationship of mTOR inhibitors and gut microbiota. Almost all concern Rapamycin and the major limit is that all have been conducted on

animals, rats in particular. Two actions should be distinguished: Modification of microbiota and alteration of the intestinal barrier. Clinically, one important drawback of rapamycin is its action on dyslipidemia and on glucose intolerance. In rat studies[57], the action of rapamycin was characterized by the enrichment of *Proteobacteria*, depletion of *Akkermansia*, and potential functional shifts to bacteria involved in lipid metabolism. In addition, rapamycin reduced the thickness of the intestinal barrier, increasing its permeability and favoring the back diffusion of several cytokines that induce systemic inflammation. This is particularly related to the inhibition that rapamycin induces to enterocyte proliferation[58].

In conclusion, the main side effects related to rapamycin-induced dysbiosis are increased body weight, insulin resistance and altered fat metabolism[59].

INFLUENCE ON IMMUNOSUPPRESSIVE DRUG METABOLISM INDUCED BY GUT MICROBIOTA

The clinical response to classical immunosuppressant drugs is highly variable among individuals and this may be ascribed to the variety of gut microorganisms[60].

Zimmermann *et al*[61] conducted a large study on the drug metabolism modifications induced by the gut microbiota.

GCs

In particular, *Clostridium scindens* and *Propionimicrobium lymphophilum* are able to transform GCs into androgens. The consequence of this modification is a less immunosuppressive action, and it is hypothesized that a higher androgen concentration in the blood could lead to prostate cancer and mood changes[62].

Tacrolimus

Higher levels of Faecalibacterium prausnizii and Clostridiales are able to convert tacrolimus into a 15-fold less active compound called "M1"[63]. This study was confirmed by an *in vitro* study conducted by Guo *et al*[8]. This was further confirmed by

a pilot study in KT patients who detected the presence of the "M1" compound in the blood after tacrolimus administration[9]. These findings could explain in part the intrapatient variability of tacrolimus trough levels. A very recent study conducted on heart transplant patients documented a relationship between gut microbiota variability and the tacrolimus dose need[64]. Degraeve *et al*[65] documented that the gut microbiome modulates tacrolimus pharmacokinetics through the transcriptional regulation of ABCB1.

In addition, *Lactobacillus acidophilus* supplementation exerts a synergistic effect on tacrolimus efficacy by modulating Th17/Treg balance *via* the SIGNR3 pathway[66].

CsA

Fewer studies have been conducted on the influence of the gut microbiota on CsA metabolism. The enzymes CYP3A1, UGY1A1, and P-gp are relevant in the metabolism of CsA. In a recent study conducted in rats, Zhou *et al*[67] documented that the abundance of microbiota such as *Alloprevolleta* and *Oscillospiraceae* influences the expression of these enzymes and is positively related to CsA bioavailability. Studies in men and KT patients are still lacking.

Mycophenolate mofetil

MMF is associated with gastrointestinal side effects such as pain and diarrhea. An intact gut microbiota favors MMF-induced gastrointestinal toxicity. An explanation is that the abundance of Bacteroides, *Escherichia* and *Shigella*[53] favors the expansion of pathobionts. This correlates with a high level of activity of colonic bacterial β-glucuronidase, an enzyme that converts the MPAG back into its active form. Modulation of the gut microbiota with antibiotics[56] reduces β-glucuronidase activity, decreases colonic MPA levels, and ameliorates the digestive side effects of MMF. In a follow-up study in kidney transplant patients, Zhang *et al*[15] found a correlation between high levels of *Coprococcus* and *Subdoligranulum* and fecal β-glucuronidase activity in fecal samples. In addition, this correlated with long duration of diarrhea.

Finally, in a recent study from Khan *et al*[68] fecal β-glucuronidase activity was different between KT patients and hematopoietic cell transplant patients. This fact could explain the different dose requirements of MMF between KT patients.

CLINICAL IMPLICATIONS OF DYSBIOSIS IN SOLID ORGAN TRANSPLANTATIONS

Intestinal dysbiosis-associated with immunosuppressive therapy is a key factor in the pathogenesis of several post-transplant disease[69].

The principal clinical manifestations of dysbiosis in SOT are as follows: (1) Gut microbiota modification induced by immunosuppressive drugs; (2) influence on immunosuppressive drug metabolism induced by gut microbiota; (3) rejection; (4) infections; and (5) diarrhea.

The first two points have already been discussed. They, as aforementioned "per se", may induce dysbiosis whose principal consequences are as follows.

Rejection

Studies on animals have documented that *Proteobacteria* induce graft rejection *via* a proinflammatory state, while *Bifidobacterium pseudolongum* decreases pro-inflammatory cytokines such as IL-6 and TNF-α and increases IL-10[70]. However, clinical studies in men are few. Pilot studies found an increase in the *Proteobacteria/Firmicutes* ratio during rejection episodes[71,72]. The pilot study of Lee *et al*[1] found a decrease in Bacteroidetes in kidney transplant rejection, but this finding was not confirmed by the study of Fricke *et al*[10].

In the aforementioned study of Wang *et al*[7], careful attention was given to identify the microbiota involved in kidney acute rejection in 53 patients. Significantly, higher levels with respect to controls were found for *Clostridiales* and *Lactobacillaceae,* while lower levels were found for *Clostridia* and *Faecalibacterium*. In the study of Fricke *et al*[10], a decreased relative abundance that correlated with future development of rejection events was found for *Anaerotruncus, Coprobacillus*, and *Coprococcus*.

The role of antibiotics in protecting or favoring acute rejection is still debated. The majority of these studies have been conducted on animals[73,74]. This is not surprising considering that some bacteria are protective and others are not protective.

Infections

A healthy microbiota protects against the development of infections. This protection is principally related to three factors: (1) The production of antimicrobial factors[75]; and (2) the induction of IgA production[76] and the reinforcement of the epithelial barrier[77]. In conditions of dysbiosis, some of these factors are lacking, and this fact may induce the colonization of pathobionts and generate infections in different organs, such as the urinary tract (UTI). Several studies have documented how the gut microbiota may favor infections. The study of Lee *et al*[1] documented that the increased abundance of *Enterococcus* is associated with the development of Enterococcus in UTIs. The study of Fricke *et al*[10] documented that the reduction of *Clostridiales*, *Peptoniphilus*, *Mogibacterium*, and *Coriobacterineae* is associated with the development of infections after six months posttransplantation. The study of Magruder *et al*[11] documented that the increased abundance in the gut of *E. coli* and *Enterococcus* is associated with bacteriuria of the same bacteria. Another study by Lee *et al*[13] documented that a relative abundance higher than 1% of butyrate-producing bacteria was associated with a lower risk of respiratory viral infection and CMV viremia. Finally, the dangerous emergence of multidrug resistant bacteria is related to dysbiosis, as documented by the study of Annavajhala *et al*[78].

Diarrhea

Diarrhea is another posttransplant complication that is often related to altered gut microbiota. Apart from the cases in which pathogens such as *Clostridium difficile* (*C. difficile*) are involved, diarrhea is often related to modifications in the gut microbiota and to the presence of pathobionts. Several studies that analyzed the gut microbiota comparing patients with or without posttransplant diarrhea confirmed that its

modification is a frequent cause of posttransplant diarrhea. Lee *et al*[1] documented in a small group of kidney transplant recipients that a decreased abundance of bacteria such as *Bacteroides, Ruminococcus, Coprococcus*, and *Dorea* is associated with the development of posttransplant diarrhea. Nevertheless, Lee *et al*[14] in a further study, analyzed fecal specimens at three months post-transplantation in 64 KT recipients. Eighteen patients had diarrhea and 46 patients did not have diarrhea. In this study, they found that several bacteria with changes in relative abundance were associated with the development of diarrhea. These bacteria were *Eubacterium, Anaerostipes, Coprococcus, Romboutsia, Ruminococcus, Dorea, Faecalibacterium Oscillibacter, Ruminiclostridium, Blautia, Bifidobacterium*, *Fusicatenibacter,* and *Bacteroides*. With respect to the previous study, they found more bacteria responsible. This fact could be ascribed either to the higher number of patients studied or to the use of a more predictive technique. Indeed, in this study, they profiled the gut microbiota using 16S rRNA gene V4-V5 deep sequencing. In a different study, Zhang *et al*[15] analyzed the gut microbiota profiles and fecal beta-glucuronidase activity in kidney transplant recipients with and without posttransplant diarrhea. Bacteria, whose decreased relative abundance was associated with the development of non-infectious diarrhea, were similar to those found by the study of Lee *et al*[1]. In addition, in this study, the authors evaluated the microbiota whose relative abundance was associated with β-glucuronidase activity, which in turn is associated with prolonged diarrhea. These bacteria were *Subdoligranulum, Coprococcus, Tyzzerella*, and E*rysipelotrichaceae*. Clearly, this finding is related to the active form of MPA as a cause of diarrhea.

Treatment of severe dysbiosis

The principal interventions for the treatment of gut dysbiosis are diet, fecal microbiota transplantation (FMT), prebiotics, probiotics, postbiotics and phages. Few studies have been conducted in SOT. The effect of diet is rather nonspecific, and the most serious phase II trials have been conducted in patients with hematopoietic stem cell transplantation[79].

FMT is the transfer of fecal material from a healthy subject to a patient affected by severe dysbiosis. The most frequent circumstance occurs for patients affected by recurrent *C. difficile* infections. The most important report of FMT in transplant patients is a multicenter study conducted on 94 SOT[80]. In addition, it is well documented that FMT mitigates intestinal barrier injury and gut dysbiosis induced by antibiotics and cyclophosphamide[81].

The use of probiotics and prebiotics is still the object of preclinical studies in the field of SOT, and preliminary data are available in the case of hematopoietic stem cell transplantation together with the use of microbiota-accessible carbohydrates[79].

Considering that, the argument of this review is the reciprocal interactions between the gut microbiota and the immunosuppressive drugs, the best treatment and prophylactic measure is the careful monitoring of the immunosuppressive drugs principally when a dysbiotic condition is suspected. This is principally recommended in the case of clinical manifestations often related to dysbiosis such as rejection, infection and diarrhea. Nevertheless, the use of the therapeutic measures aforementioned has the highlighted limitations.

In conclusion to date the gut microbiota in KT represents a target for a personalized therapy as documented by the studies of García-Martínez *et al*[82] and Nobakht *et al*[83].

CONCLUSION

REFERENCES

1 **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* 2014; **98**: 697-705 [PMID: 25289916 DOI: 10.1097/TP.0000000000000370]

2 **Guirong YE**, Minjie Z, Lixin YU, Junsheng YE, Lin Y, Lisha S. [Gut microbiota in renal transplant recipients, patients with chronic kidney disease and healthy subjects]. *Nan*

Fang Yi Ke Da Xue Xue Bao 2018; **38**: 1401-1408 [PMID: 30613005 DOI: 10.12122/j.issn.1673-4254.2018.12.01]

3 **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* 2020; **9** [PMID: 32024079 DOI: 10.3390/jcm9020386]

4 **Souai N**, Zidi O, Mosbah A, Kosai I, Manaa JE, Mokhtar NB, Asimakis E, Stathopoulou P, Cherif A, Tsiamis G, Kouidhi S. Impact of the Post-Transplant Period and Lifestyle Diseases on Human Gut Microbiota in Kidney Graft Recipients. *Microorganisms* 2020; **8** [PMID: 33158078 DOI: 10.3390/microorganisms8111724]

5 **Yu DH**, Ying N, Lian ZH, Fa YQ. The Alteration human of gut microbiota and metabolites before and after renal transplantation. *Microb Pathog* 2021; **160**: 105191 [PMID: 34571151 DOI: 10.1016/j.micpath.2021.105191]

6 **Kidney Disease Improving Global Outcomes**. Transplant Recipient-KDIGO. [cited 5 October 2023]. Available from: https://kdigo.org/guidelines/transplant-recipient/

7 **Wang J**, Li X, Wu X, Wang Z, Zhang C, Cao G, Liu S, Yan T. Gut microbiota alterations associated with antibody-mediated rejection after kidney transplantation. *Appl Microbiol Biotechnol* 2021; **105**: 2473-2484 [PMID: 33625548 DOI: 10.1007/s00253-020-11069-x]

8 **Guo Y**, Crnkovic CM, Won KJ, Yang X, Lee JR, Orjala J, Lee H, Jeong H. Commensal Gut Bacteria Convert the Immunosuppressant Tacrolimus to Less Potent Metabolites. *Drug Metab Dispos* 2019; **47**: 194-202 [PMID: 30598508 DOI: 10.1124/dmd.118.084772]

9 **Guo Y**, Lee H, Edusei E, Albakry S, Jeong H, Lee JR. Blood Profiles of Gut Bacterial Tacrolimus Metabolite in Kidney Transplant Recipients. *Transplant Direct* 2020; **6**: e601 [PMID: 33134481 DOI: 10.1097/TXD.0000000000001052]

10 **Fricke WF**, Maddox C, Song Y, Bromberg JS. Human microbiota characterization in the course of renal transplantation. *Am J Transplant* 2014; **14**: 416-427 [PMID: 24373208 DOI: 10.1111/ajt.12588]

11 **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, Littman E, 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* 2019; **10**: 5521 [PMID: 31797927 DOI: 10.1038/s41467-019-13467-w]

12 **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* 2020; **12**: 1805281 [PMID: 32865119 DOI: 10.1080/19490976.2020.1805281]

13 **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* 2019; **21**: e13180 [PMID: 31544324 DOI: 10.1111/tid.13180]

14 **Lee JR**, Magruder M, Zhang L, Westblade LF, Satlin MJ, Robertson A, Edusei E, Crawford C, Ling L, Taur Y, Schluter J, Lubetzky M, Dadhania D, Pamer E, Suthanthiran M. Gut microbiota dysbiosis and diarrhea in kidney transplant recipients. *Am J Transplant* 2019; **19**: 488-500 [PMID: 29920927 DOI: 10.1111/ajt.14974]

15 **Zhang LT**, Westblade LF, Iqbal F, Taylor MR, Chung A, Satlin MJ, Magruder M, Edusei E, Albakry S, Botticelli B, Robertson A, Alston T, Dadhania DM, Lubetzky M, Hirota SA, Greenway SC, Lee JR. Gut microbiota profiles and fecal beta-glucuronidase activity in kidney transplant recipients with and without post-transplant diarrhea. *Clin Transplant* 2021; **35**: e14260 [PMID: 33605497 DOI: 10.1111/ctr.14260]

16 **Lecronier M**, Tashk P, Tamzali Y, Tenaillon O, Denamur E, Barrou B, Aron-Wisnewsky J, Tourret J. Gut microbiota composition alterations are associated with the onset of diabetes in kidney transplant recipients. *PLoS One* 2020; **15**: e0227373 [PMID: 31910227 DOI: 10.1371/journal.pone.0227373]

17 **Kouidhi S**, Zidi O, Alhujaily M, Souai N, Mosbah A, Belali TM, Ghedira K, El Kossai I, El Manaa J, Mnif W, Cherif A. Fecal Metabolomics Reveals Distinct Profiles of Kidney

Transplant Recipients and Healthy Controls. *Diagnostics (Basel)* 2021; **11** [PMID: 33946812 DOI: 10.3390/diagnostics11050807]

18 **Flint A**, Raben A, Blundell JE, Astrup A. Reproducibility, power and validity of visual analogue scales in assessment of appetite sensations in single test meal studies. *Int J Obes Relat Metab Disord* 2000; **24**: 38-48 [PMID: 10702749 DOI: 10.1038/sj.ijo.0801126]

19 **Batterham RL**, Cowley MA, Small CJ, Herzog H, Cohen MA, Dakin CL, Wren AM, Brynes AE, Low MJ, Ghatei MA, Cone RD, Bloom SR. Gut hormone PYY(3-36) physiologically inhibits food intake. *Nature* 2002; **418**: 650-654 [PMID: 12167864 DOI: 10.1038/nature00887]

20 **Weersma RK**, Zhernakova A, Fu J. Interaction between drugs and the gut microbiome. *Gut* 2020; **69**: 1510-1519 [PMID: 32409589 DOI: 10.1136/gutjnl-2019-320204]

21 **Kelly CJ**, Zheng L, Campbell EL, Saeedi B, Scholz CC, Bayless AJ, Wilson KE, Glover LE, Kominsky DJ, Magnuson A, Weir TL, Ehrentraut SF, Pickel C, Kuhn KA, Lanis JM, Nguyen V, Taylor CT, Colgan SP. Crosstalk between Microbiota-Derived Short-Chain Fatty Acids and Intestinal Epithelial HIF Augments Tissue Barrier Function. *Cell Host Microbe* 2015; **17**: 662-671 [PMID: 25865369 DOI: 10.1016/j.chom.2015.03.005]

22 **Tong LC**, Wang Y, Wang ZB, Liu WY, Sun S, Li L, Su DF, Zhang LC. Propionate Ameliorates Dextran Sodium Sulfate-Induced Colitis by Improving Intestinal Barrier Function and Reducing Inflammation and Oxidative Stress. *Front Pharmacol* 2016; **7**: 253 [PMID: 27574508 DOI: 10.3389/fphar.2016.00253]

23 **Bansal T**, Alaniz RC, Wood TK, Jayaraman A. The bacterial signal indole increases epithelial-cell tight-junction resistance and attenuates indicators of inflammation. *Proc Natl Acad Sci U S A* 2010; **107**: 228-233 [PMID: 19966295 DOI: 10.1073/pnas.0906112107]

24 **Hwang IK**, Yoo KY, Li H, Park OK, Lee CH, Choi JH, Jeong YG, Lee YL, Kim YM, Kwon YG, Won MH. Indole-3-propionic acid attenuates neuronal damage and oxidative stress in the ischemic hippocampus. *J Neurosci Res* 2009; **87**: 2126-2137 [PMID: 19235887 DOI: 10.1002/jnr.22030]

25 **Miyamoto J**, Mizukure T, Park SB, Kishino S, Kimura I, Hirano K, Bergamo P, Rossi M, Suzuki T, Arita M, Ogawa J, Tanabe S. A gut microbial metabolite of linoleic acid, 10-hydroxy-cis-12-octadecenoic acid, ameliorates intestinal epithelial barrier impairment partially *via* GPR40-MEK-ERK pathway. *J Biol Chem* 2015; **290**: 2902-2918 [PMID: 25505251 DOI: 10.1074/jbc.M114.610733]

26 **Modi SR**, Collins JJ, Relman DA. Antibiotics and the gut microbiota. *J Clin Invest* 2014; **124**: 4212-4218 [PMID: 25271726 DOI: 10.1172/JCI72333]

27 **Gabarre P**, Loens C, Tamzali Y, Barrou B, Jaisser F, Tourret J. Immunosuppressive therapy after solid organ transplantation and the gut microbiota: Bidirectional interactions with clinical consequences. *Am J Transplant* 2022; **22**: 1014-1030 [PMID: 34510717 DOI: 10.1111/ajt.16836]

28 **Serbanescu MA**, Mathena RP, Xu J, Santiago-Rodriguez T, Hartsell TL, Cano RJ, Mintz CD. General Anesthesia Alters the Diversity and Composition of the Intestinal Microbiota in Mice. *Anesth Analg* 2019; **129**: e126-e129 [PMID: 30489316 DOI: 10.1213/ANE.0000000000003938]

29 **Sampaio-Maia B**, Simões-Silva L, Pestana M, Araujo R, Soares-Silva IJ. The Role of the Gut Microbiome on Chronic Kidney Disease. *Adv Appl Microbiol* 2016; **96**: 65-94 [PMID: 27565581 DOI: 10.1016/bs.aambs.2016.06.002]

30 **Conlon MA**, Bird AR. The impact of diet and lifestyle on gut microbiota and human health. *Nutrients* 2014; **7**: 17-44 [PMID: 25545101 DOI: 10.3390/nu7010017]

31 **Jazani NH**, Savoj J, Lustgarten M, Lau WL, Vaziri ND. Impact of Gut Dysbiosis on Neurohormonal Pathways in Chronic Kidney Disease. *Diseases* 2019; **7** [PMID: 30781823 DOI: 10.3390/diseases7010021]

32 **Shin NR**, Whon TW, Bae JW. Proteobacteria: microbial signature of dysbiosis in gut microbiota. *Trends Biotechnol* 2015; **33**: 496-503 [PMID: 26210164 DOI: 10.1016/j.tibtech.2015.06.011]

33 **Swarte JC**, Li Y, Hu S, Björk JR, Gacesa R, Vich Vila A, Douwes RM, Collij V, Kurilshikov A, Post A, Klaassen MAY, Eisenga MF, Gomes-Neto AW, Kremer D, Jansen BH, Knobbe TJ, Berger SP, Sanders JF, Heiner-Fokkema MR, Porte RJ, Cuperus FJC, de

Meijer VE, Wijmenga C, Festen EAM, Zhernakova A, Fu J, Harmsen HJM, Blokzijl H, Bakker SJL, Weersma RK. Gut microbiome dysbiosis is associated with increased mortality after solid organ transplantation. *Sci Transl Med* 2022; **14**: eabn7566 [PMID: 36044594 DOI: 10.1126/scitranslmed.abn7566]

34 **Koh A**, De Vadder F, Kovatcheva-Datchary P, Bäckhed F. From Dietary Fiber to Host Physiology: Short-Chain Fatty Acids as Key Bacterial Metabolites. *Cell* 2016; **165**: 1332-1345 [PMID: 27259147 DOI: 10.1016/j.cell.2016.05.041]

35 **Tourret J**, Willing BP, Dion S, MacPherson J, Denamur E, Finlay BB. Immunosuppressive Treatment Alters Secretion of Ileal Antimicrobial Peptides and Gut Microbiota, and Favors Subsequent Colonization by Uropathogenic Escherichia coli. *Transplantation* 2017; **101**: 74-82 [PMID: 27681266 DOI: 10.1097/TP.0000000000001492]

36 **Zununi Vahed S**, Ardalan M, Samadi N, Omidi Y. Pharmacogenetics and drug-induced nephrotoxicity in renal transplant recipients. *Bioimpacts* 2015; **5**: 45-54 [PMID: 25901296 DOI: 10.15171/bi.2015.12]

37 **Zununi Vahed S**, Samadi N, Mostafidi E, Ardalan MR, Omidi Y. Genetics and Epigenetics of Chronic Allograft Dysfunction in Kidney Transplants. *Iran J Kidney Dis* 2016; **10**: 1-9 [PMID: 26837673]

38 **Gibson CM**, Childs-Kean LM, Naziruddin Z, Howell CK. The alteration of the gut microbiome by immunosuppressive agents used in solid organ transplantation. *Transpl Infect Dis* 2021; **23**: e13397 [PMID: 32609940 DOI: 10.1111/tid.13397]

39 **Silen W**, Machen TE, Forte JG. Acid-base balance in amphibian gastric mucosa. *Am J Physiol* 1975; **229**: 721-730 [PMID: 2015 DOI: 10.1097/MIB.0000000000000332]

40 **Muniz LR**, Knosp C, Yeretssian G. Intestinal antimicrobial peptides during homeostasis, infection, and disease. *Front Immunol* 2012; **3**: 310 [PMID: 23087688 DOI: 10.3389/fimmu.2012.00310]

41 **Alverdy J**, Aoys E. The effect of glucocorticoid administration on bacterial translocation. Evidence for an acquired mucosal immunodeficient state. *Ann Surg* 1991; **214**: 719-723 [PMID: 1741652 DOI: 10.1097/00000658-199112000-00012]

42 **Boivin MA**, Ye D, Kennedy JC, Al-Sadi R, Shepela C, Ma TY. Mechanism of glucocorticoid regulation of the intestinal tight junction barrier. *Am J Physiol Gastrointest Liver Physiol* 2007; **292**: G590-G598 [PMID: 17068119 DOI: 10.1152/ajpgi.00252.2006]

43 **Wu T**, Yang L, Jiang J, Ni Y, Zhu J, Zheng X, Wang Q, Lu X, Fu Z. Chronic glucocorticoid treatment induced circadian clock disorder leads to lipid metabolism and gut microbiota alterations in rats. *Life Sci* 2018; **192**: 173-182 [PMID: 29196049 DOI: 10.1016/j.lfs.2017.11.049]

44 **Degraeve AL**, Bindels LB, Haufroid V, Moudio S, Boland L, Delongie KA, Dewulf JP, Eddour DC, Mourad M, Elens L. Tacrolimus Pharmacokinetics is Associated with Gut Microbiota Diversity in Kidney Transplant Patients: Results from a Pilot Cross-Sectional Study. *Clin Pharmacol Ther* 2024; **115**: 104-115 [PMID: 37846607 DOI: 10.1002/cpt.3077]

45 **van Dieren JM**, Lambers ME, Kuipers EJ, Samsom JN, van der Woude CJ, Nieuwenhuis EE. Local immune regulation of mucosal inflammation by tacrolimus. *Dig Dis Sci* 2010; **55**: 2514-2519 [PMID: 19949865 DOI: 10.1007/s10620-009-1047-2]

46 **Zhang Z**, Liu L, Tang H, Jiao W, Zeng S, Xu Y, Zhang Q, Sun Z, Mukherjee A, Zhang X, Hu X. Immunosuppressive effect of the gut microbiome altered by high-dose tacrolimus in mice. *Am J Transplant* 2018; **18**: 1646-1656 [PMID: 29316256 DOI: 10.1111/ajt.14661]

47 **Langille MG**, Zaneveld J, Caporaso JG, McDonald D, Knights D, Reyes JA, Clemente JC, Burkepile DE, Vega Thurber RL, Knight R, Beiko RG, Huttenhower C. Predictive functional profiling of microbial communities using 16S rRNA marker gene sequences. *Nat Biotechnol* 2013; **31**: 814-821 [PMID: 23975157 DOI: 10.1038/nbt.2676]

48 **Wu ZW**, Ling ZX, Lu HF, Zuo J, Sheng JF, Zheng SS, Li LJ. Changes of gut bacteria and immune parameters in liver transplant recipients. *Hepatobiliary Pancreat Dis Int* 2012; **11**: 40-50 [PMID: 22251469 DOI: 10.1016/s1499-3872(11)60124-0]

49 **Jiang JW**, Ren ZG, Lu HF, Zhang H, Li A, Cui GY, Jia JJ, Xie HY, Chen XH, He Y, Jiang L, Li LJ. Optimal immunosuppressor induces stable gut microbiota after liver transplantation. *World J Gastroenterol* 2018; **24**: 3871-3883 [PMID: 30228781 DOI: 10.3748/wjg.v24.i34.3871]

50 **Freeman DJ**. Pharmacology and pharmacokinetics of cyclosporine. *Clin Biochem* 1991; **24**: 9-14 [PMID: 2060139 DOI: 10.1016/0009-9120(91)90084-r]

51 **Jia J**, Tian X, Jiang J, Ren Z, Lu H, He N, Xie H, Zhou L, Zheng S. Structural shifts in the intestinal microbiota of rats treated with cyclosporine A after orthotropic liver transplantation. *Front Med* 2019; **13**: 451-460 [PMID: 31020543 DOI: 10.1007/s11684-018-0675-3]

52 **O'Reilly C**, O'Sullivan Ó, Cotter PD, O'Connor PM, Shanahan F, Cullen A, Rea MC, Hill C, Coulter I, Ross RP. Encapsulated cyclosporine does not change the composition of the human microbiota when assessed *ex vivo* and in vivo. *J Med Microbiol* 2020; **69**: 854-863 [PMID: 31958048 DOI: 10.1099/jmm.0.001130]

53 **Flannigan KL**, Taylor MR, Pereira SK, Rodriguez-Arguello J, Moffat AW, Alston L, Wang X, Poon KK, Beck PL, Rioux KP, Jonnalagadda M, Chelikani PK, Galipeau HJ, Lewis IA, Workentine ML, Greenway SC, Hirota SA. An intact microbiota is required for the gastrointestinal toxicity of the immunosuppressant mycophenolate mofetil. *J Heart Lung Transplant* 2018; **37**: 1047-1059 [PMID: 30173823 DOI: 10.1016/j.healun.2018.05.002]

54 **Qasim M**, Rahman H, Ahmed R, Oellerich M, Asif AR. Mycophenolic acid mediated disruption of the intestinal epithelial tight junctions. *Exp Cell Res* 2014; **322**: 277-289 [PMID: 24509232 DOI: 10.1016/j.yexcr.2014.01.021]

55 **Chan W**, Chin SH, Whittaker AC, Jones D, Kaur O, Bosch JA, Borrows R. The Associations of Muscle Strength, Muscle Mass, and Adiposity With Clinical Outcomes and Quality of Life in Prevalent Kidney Transplant Recipients. *J Ren Nutr* 2019; **29**: 536-547 [PMID: 31416679 DOI: 10.1053/j.jrn.2019.06.009]

56 **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* 2019; **5**: eaax2358 [PMID: 31457102 DOI: 10.1126/sciadv.aax2358]

57 **Bhat M**, Pasini E, Copeland J, Angeli M, Husain S, Kumar D, Renner E, Teterina A, Allard J, Guttman DS, Humar A. Impact of Immunosuppression on the Metagenomic

Composition of the Intestinal Microbiome: a Systems Biology Approach to Post-Transplant Diabetes. *Sci Rep* 2017; **7**: 10277 [PMID: 28860611 DOI: 10.1038/s41598-017-10471-2]

58 **Faller WJ**, Jackson TJ, Knight JR, Ridgway RA, Jamieson T, Karim SA, Jones C, Radulescu S, Huels DJ, Myant KB, Dudek KM, Casey HA, Scopelliti A, Cordero JB, Vidal M, Pende M, Ryazanov AG, Sonenberg N, Meyuhas O, Hall MN, Bushell M, Willis AE, Sansom OJ. mTORC1-mediated translational elongation limits intestinal tumour initiation and growth. *Nature* 2015; **517**: 497-500 [PMID: 25383520 DOI: 10.1038/nature13896]

59 **Jung MJ**, Lee J, Shin NR, Kim MS, Hyun DW, Yun JH, Kim PS, Whon TW, Bae JW. Chronic Repression of mTOR Complex 2 Induces Changes in the Gut Microbiota of Diet-induced Obese Mice. *Sci Rep* 2016; **6**: 30887 [PMID: 27471110 DOI: 10.1038/srep30887]

60 **Manes A**, Di Renzo T, Dodani L, Reale A, Gautiero C, Di Lauro M, Nasti G, Manco F, Muscariello E, Guida B, Tarantino G, Cataldi M. Pharmacomicrobiomics of Classical Immunosuppressant Drugs: A Systematic Review. *Biomedicines* 2023; **11** [PMID: 37761003 DOI: 10.3390/biomedicines11092562]

61 **Zimmermann M**, Zimmermann-Kogadeeva M, Wegmann R, Goodman AL. Mapping human microbiome drug metabolism by gut bacteria and their genes. *Nature* 2019; **570**: 462-467 [PMID: 31158845 DOI: 10.1038/s41586-019-1291-3]

62 **So SY**, Savidge TC. Sex-Bias in Irritable Bowel Syndrome: Linking Steroids to the Gut-Brain Axis. *Front Endocrinol (Lausanne)* 2021; **12**: 684096 [PMID: 34093447 DOI: 10.3389/fendo.2021.684096]

63 **Lee JR**, Muthukumar T, Dadhania D, Taur Y, Jenq RR, Toussaint NC, Ling L, Pamer E, Suthanthiran M. Gut microbiota and tacrolimus dosing in kidney transplantation. *PLoS One* 2015; **10**: e0122399 [PMID: 25815766 DOI: 10.1371/journal.pone.0122399]

64 **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, Uhlemann AC, Colombo PC, Demmer RT, Yuzefpolskaya M. Gut

microbial diversity, inflammation, and oxidative stress are associated with tacrolimus dosing requirements early after heart transplantation. *PLoS One* 2020; **15**: e0233646 [PMID: 32469966 DOI: 10.1371/journal.pone.0233646]

65 **Degraeve AL**, Haufroid V, Loriot A, Gatto L, Andries V, Vereecke L, Elens L, Bindels LB. Gut microbiome modulates tacrolimus pharmacokinetics through the transcriptional regulation of ABCB1. *Microbiome* 2023; **11**: 138 [PMID: 37408070 DOI: 10.1186/s40168-023-01578-y]

66 **Kim DS**, Park Y, Choi JW, Park SH, Cho ML, Kwok SK. Lactobacillus acidophilus Supplementation Exerts a Synergistic Effect on Tacrolimus Efficacy by Modulating Th17/Treg Balance in Lupus-Prone Mice *via* the SIGNR3 Pathway. *Front Immunol* 2021; **12**: 696074 [PMID: 34956169 DOI: 10.3389/fimmu.2021.696074]

67 **Zhou J**, Zhang R, Guo P, Li P, Huang X, Wei Y, Yang C, Zhou J, Yang T, Liu Y, Shi S. Effects of intestinal microbiota on pharmacokinetics of cyclosporine a in rats. *Front Microbiol* 2022; **13**: 1032290 [PMID: 36483198 DOI: 10.3389/fmicb.2022.1032290]

68 **Khan MH**, Onyeaghala GC, Rashidi A, Holtan SG, Khoruts A, Israni A, Jacobson PA, Staley C. Fecal β-glucuronidase activity differs between hematopoietic cell and kidney transplantation and a possible mechanism for disparate dose requirements. *Gut Microbes* 2022; **14**: 2108279 [PMID: 35921529 DOI: 10.1080/19490976.2022.2108279]

69 **Faucher Q**, Jardou M, Brossier C, Picard N, Marquet P, Lawson R. Is Intestinal Dysbiosis-Associated With Immunosuppressive Therapy a Key Factor in the Pathophysiology of Post-Transplant Diabetes Mellitus? *Front Endocrinol (Lausanne)* 2022; **13**: 898878 [PMID: 35872991 DOI: 10.3389/fendo.2022.898878]

70 **Bromberg JS**, Hittle L, Xiong Y, Saxena V, Smyth EM, Li L, Zhang T, Wagner C, Fricke WF, Simon T, Brinkman CC, Mongodin EF. Gut microbiota-dependent modulation of innate immunity and lymph node remodeling affects cardiac allograft outcomes. *JCI Insight* 2018; **3** [PMID: 30282817 DOI: 10.1172/jci.insight.121045]

71 **Kato K**, Nagao M, Miyamoto K, Oka K, Takahashi M, Yamamoto M, Matsumura Y, Kaido T, Uemoto S, Ichiyama S. Longitudinal Analysis of the Intestinal Microbiota in

Liver Transplantation. *Transplant Direct* 2017; **3**: e144 [PMID: 28405600 DOI: 10.1097/TXD.0000000000000661]

72 **Oh PL**, Martínez I, Sun Y, Walter J, Peterson DA, Mercer DF. Characterization of the ileal microbiota in rejecting and nonrejecting recipients of small bowel transplants. *Am J Transplant* 2012; **12**: 753-762 [PMID: 22152019 DOI: 10.1111/j.1600-6143.2011.03860.x]

73 **Lei YM**, Chen L, Wang Y, Stefka AT, Molinero LL, Theriault B, Aquino-Michaels K, Sivan AS, Nagler CR, Gajewski TF, Chong AS, Bartman C, Alegre ML. The composition of the microbiota modulates allograft rejection. *J Clin Invest* 2016; **126**: 2736-2744 [PMID: 27322054 DOI: 10.1172/JCI85295]

74 **Rey K**, Manku S, Enns W, Van Rossum T, Bushell K, Morin RD, Brinkman FSL, Choy JC. Disruption of the Gut Microbiota With Antibiotics Exacerbates Acute Vascular Rejection. *Transplantation* 2018; **102**: 1085-1095 [PMID: 29538261 DOI: 10.1097/TP.0000000000002169]

75 **Corr SC**, Li Y, Riedel CU, O'Toole PW, Hill C, Gahan CG. Bacteriocin production as a mechanism for the antiinfective activity of Lactobacillus salivarius UCC118. *Proc Natl Acad Sci U S A* 2007; **104**: 7617-7621 [PMID: 17456596 DOI: 10.1073/pnas.0700440104]

76 **Macpherson AJ**, Gatto D, Sainsbury E, Harriman GR, Hengartner H, Zinkernagel RM. A primitive T cell-independent mechanism of intestinal mucosal IgA responses to commensal bacteria. *Science* 2000; **288**: 2222-2226 [PMID: 10864873 DOI: 10.1126/science.288.5474.2222]

77 **Mathewson ND**, Jenq R, Mathew AV, Koenigsknecht M, Hanash A, Toubai T, Oravecz-Wilson K, Wu SR, Sun Y, Rossi C, Fujiwara H, Byun J, Shono Y, Lindemans C, Calafiore M, Schmidt TM, Honda K, Young VB, Pennathur S, van den Brink M, Reddy P. Gut microbiome-derived metabolites modulate intestinal epithelial cell damage and mitigate graft-versus-host disease. *Nat Immunol* 2016; **17**: 505-513 [PMID: 26998764 DOI: 10.1038/ni.3400]

78 **Annavajhala MK**, Gomez-Simmonds A, Macesic N, Sullivan SB, Kress A, Khan SD, Giddins MJ, Stump S, Kim GI, Narain R, Verna EC, Uhlemann AC. Colonizing multidrug-resistant bacteria and the longitudinal evolution of the intestinal microbiome

after liver transplantation. *Nat Commun* 2019; **10**: 4715 [PMID: 31624266 DOI: 10.1038/s41467-019-12633-4]

79 **Baghai Arassi M**, Zeller G, Karcher N, Zimmermann M, Toenshoff B. The gut microbiome in solid organ transplantation. *Pediatr Transplant* 2020; **24**: e13866 [PMID: 32997434 DOI: 10.1111/petr.13866]

80 **Cheng YW**, Phelps E, Ganapini V, Khan N, Ouyang F, Xu H, Khanna S, Tariq R, Friedman-Moraco RJ, Woodworth MH, Dhere T, Kraft CS, Kao D, Smith J, Le L, El-Nachef N, Kaur N, Kowsika S, Ehrlich A, Smith M, Safdar N, Misch EA, Allegretti JR, Flynn A, Kassam Z, Sharfuddin A, Vuppalanchi R, Fischer M. Fecal microbiota transplantation for the treatment of recurrent and severe Clostridium difficile infection in solid organ transplant recipients: A multicenter experience. *Am J Transplant* 2019; **19**: 501-511 [PMID: 30085388 DOI: 10.1111/ajt.15058]

81 **Huang J**, Zhou H, Song T, Wang B, Ge H, Zhang D, Shen P, Qiu X, Li H. Fecal microbiota transplantation from sodium alginate-dosed mice and normal mice mitigates intestinal barrier injury and gut dysbiosis induced by antibiotics and cyclophosphamide. *Food Funct* 2023; **14**: 5690-5701 [PMID: 37272879 DOI: 10.1039/d3fo01193c]

82 **García-Martínez Y**, Borriello M, Capolongo G, Ingrosso D, Perna AF. The Gut Microbiota in Kidney Transplantation: A Target for Personalized Therapy? *Biology (Basel)* 2023; **12** [PMID: 36829442]

83 **Nobakht E**, Jagadeesan M, Paul R, Bromberg J, Dadgar S. Precision Medicine in Kidney Transplantation: Just Hype or a Realistic Hope? *Transplant Direct* 2021; **7**: e650 [PMID: 33437865 DOI: 10.1097/TXD.0000000000001102]

Figure Legends

Figure 1 Factors affecting the intestinal microbiota after kidney transplantation.

Figure 2 Impact of glucocorticoids on the gut microbiota. MUC: Mucin; RegIII: Regenerating protein; Muc2: Mucine 2; GC: Glucocorticoids; TNF-α: Tumor necrosis factor α; MLCK: Myosin light chain kinase; MLC2: Myosin light chain 2.

Figure 3 Impact of Tacrolimus on the gut microbiota. SCFA: Short chain fatty acids.

Figure 4 Impact of mycophenolate mofetil on the gut microbiota. MMF: Mycophenolate mofetil; MPA: Mycophenolic acid; MPAG: Mycophenolic acid glucuronated; LPS: Lipopolysaccherides; MLCK: Myosin light chain kinase; MLC2: Myosin light chain 2; MLC2P: Myosin light chain 2 phosphorilated; KT: Kidney transplantation.

Table 1 Role of gut microbiota in kidney transplantation[6-16]

Post-transplant Setting	Study population	Gut bacteria involved	Outcome
TAC dosing	KTRs (*n* = 19)	↑*Faecalibacterium prausnizii*	Increased abundance positively correlated with increased TAC dose requirements
Rejection	KTRs (*n* = 55)	↑*Lactobacillales*; ↓*Clostridiales*; ↑*Enterococcus*; ↓*Barnesiellaceae*; ↑*Anaerofilum*; ↓*Paraprevotellaceae*; ↑*Clostridium*; ↓*Pasteurellaceae*; *Tertium*; ↓*Roseburia*; ↓*Haemophilus*; ↓*Faecalibacterium*	Gut microbiotra alterations associated with ABMR
TAC metabolism	*In vitro*	*Faecalibacterium prausnizii*; *Erysipelotricheles*; *Bacteroidales*	Taxa able to metabolize TAC into a less effective immunosuppressant metabolite
TAC metabolism	KTRs (*n* = 10)	Gut bacteria	Active metabolism of TAC by the gut bacteria. The gut microbiota could impact TAC trough variability
Infection	KTRs (*n* = 60)	↓*Clostridiales*; ↓*Mogibacterium*; ↓*Peptoniphilus*; ↓*Coriobacterineae*	Changes in the relative abundance associated with the development of infections after six months post transplantation
Infection	KTRs (*n* = 168)	↑*Escherichia*; ↑*Enterococcus*	Increased abundance

			associated with the development of *Escherichi*a and *Enterococcus* bacteriuria
Infection	KTRs (*n* = 168)	↑*Faecalibacterium*; ↑*Romboutsia*	Increased abundance associated with lower risk of Enterobacteriaceae bacteriuria and UTI
Infection	KTRs (*n* = 168)	Butyrate-producing bacteria	A relative abundance than 1% associated with lower risk of respiratory viral infection and CMV viremia
Diarrhea	KTRs (*n* = 64)	↑*Enterococcus*; ↓*Eubacterium*; ↑*Escherichia*; ↓*Anaerostipes*; ↑*Lachnoclostridium*; ↓*Coprococcus*; ↓*Romboutsia*; ↓*Ruminococcus*; ↓*Dorea*; ↓*Faecalibacterium*; ↓*Fusicatenibacter*; ↓*Oscillibacter*; ↓*Blautia*; ↓*Bifidobacterium*; ↓*Bacteroides*	Changes in the relative abundance associated with the development of diarrhea
Diarrhea	KTRs (*n* = 79)	↓*Eubacterium*; ↓*Anaerostipes*; ↓*Ruminococcus*; ↓*Dorea*; ↓*Fusicatenibacter*; ↓*Bifidobacterium*	Decreased relative abundance associated with the development of non.infectious diarrhea
NODAT	KTRs (*n* = 50)	↑*Lactobacillus*; ↓*Akkermansia muciniphila*	Changes in the relative abundance associated with the

									development of NODAT

TAC: Tacrolimus; KTR: Kidney transplant recipient; ABMR: Antibody mediated rejection; UTI: Urinary tract infection; CMV: Cytomegalovirus; NODAT: New onset diabetes after transplantation.

90194_Auto_Edited.docx

ORIGINALITY REPORT

13%
SIMILARITY INDEX

PRIMARY SOURCES

1	www.mdpi.com Internet	121 words — 3%
2	www.wjgnet.com Internet	91 words — 2%
3	www.esp.org Internet	83 words — 2%
4	coek.info Internet	68 words — 2%
5	www.emjreviews.com Internet	52 words — 1%
6	Joshua S. Kim, Christina Sze, Tarek Barbar, John R. Lee. "New insights into the microbiome in kidney transplantation", Current Opinion in Organ Transplantation, 2021 Crossref	28 words — 1%
7	Alexandra L. Degraeve, Laure B. Bindels, Vincent Haufroid, Serge Moudio et al. "Tacrolimus pharmacokinetics is associated with gut microbiota diversity in kidney transplant patients: results from a pilot cross-sectional study", Clinical Pharmacology & Therapeutics, 2023 Crossref	19 words — < 1%

8	Rinse K Weersma, Alexandra Zhernakova, Jingyuan Fu. "Interaction between drugs and the gut microbiome", Gut, 2020 Crossref	16 words — < 1%
9	kidney360.asnjournals.org Internet	15 words — < 1%
10	www.rj-robbins.com Internet	15 words — < 1%

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	< 15 WORDS
EXCLUDE BIBLIOGRAPHY	ON	EXCLUDE MATCHES	< 10 WORDS