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EDITORIAL

Lindner C, Riquelme R, San Martín R, Quezada F, Valenzuela J, Maureira JP, Einersen M. Improving the radiological diagnosis of hepatic artery thrombosis after liver transplantation: Current approaches and future challenges. *World J Transplant* 2024; 14(1): 88938 [DOI: [10.5500/wjt.v14.i1.88938](https://doi.org/10.5500/wjt.v14.i1.88938)]

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MINIREVIEWS

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ORIGINAL ARTICLE**Retrospective Cohort Study**

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SYSTEMATIC REVIEWS

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CASE REPORT

Sánchez Pérez B, Pérez Reyes M, Aranda Narvaez J, Santoyo Villalba J, Perez Daga JA, Sanchez-Gonzalez C, Santoyo-Santoyo J. New therapeutic strategy with extracorporeal membrane oxygenation for refractory hepatopulmonary syndrome after liver transplant: A case report. *World J Transplant* 2024; 14(1): 89223 [DOI: [10.5500/wjt.v14.i1.89223](https://doi.org/10.5500/wjt.v14.i1.89223)]

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

Maurizio Salvadori, Giuseppina Rosso

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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

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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.

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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 prausnitzii*[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 metabolomic 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 prausnitzii*[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-octadecate by produced by *Lactobacillus* by lipid metabolism maintains the intestinal barrier function and decreases inflammation[25].

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)	↑ <i>Faecalibacterium prausnitzii</i>	Increased abundance positively correlated with increased TAC dose requirements
Rejection	KTRs (n = 55)	↑ <i>Lactobacillales</i> ; ↓ <i>Clostridiales</i> ; ↑ <i>Enterococcus</i> ; ↓ <i>Barnesiellaceae</i> ; ↑ <i>Anaerofilum</i> ; ↓ <i>Paraprevotellaceae</i> ; ↑ <i>Clostridium</i> ; ↓ <i>Pasteurellaceae</i> ; <i>Tertium</i> ; ↓ <i>Roseburia</i> ; ↓ <i>Haemophilus</i> ; ↓ <i>Faecalibacterium</i>	Gut microbiota alterations associated with ABMR
TAC metabolism	<i>In vitro</i>	<i>Faecalibacterium prausnitzii</i> ; <i>Erysipelotriches</i> ; <i>Bacteroidales</i>	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)	↓ <i>Clostridiales</i> ; ↓ <i>Mogibacterium</i> ; ↓ <i>Peptoniphilus</i> ; ↓ <i>Coriobacterineae</i>	Changes in the relative abundance associated with the development of infections after six months post transplantation
Infection	KTRs (n = 168)	↑ <i>Escherichia</i> ; ↑ <i>Enterococcus</i>	Increased abundance associated with the development of <i>Escherichia</i> and <i>Enterococcus</i> bacteriuria
Infection	KTRs (n = 168)	↑ <i>Faecalibacterium</i> ; ↑ <i>Romboutsia</i>	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)	↑ <i>Enterococcus</i> ; ↓ <i>Eubacterium</i> ; ↑ <i>Escherichia</i> ; ↓ <i>Anaerostipes</i> ; ↑ <i>Lachnospirillum</i> ; ↓ <i>Coprococcus</i> ; ↓ <i>Romboutsia</i> ; ↓ <i>Ruminococcus</i> ; ↓ <i>Dorea</i> ; ↓ <i>Faecalibacterium</i> ; ↓ <i>Fusicatenibacter</i> ; ↓ <i>Oscillibacter</i> ; ↓ <i>Blautia</i> ; ↓ <i>Bifidobacterium</i> ; ↓ <i>Bacteroides</i>	Changes in the relative abundance associated with the development of diarrhea
Diarrhea	KTRs (n = 79)	↓ <i>Eubacterium</i> ; ↓ <i>Anaerostipes</i> ; ↓ <i>Ruminococcus</i> ; ↓ <i>Dorea</i> ; ↓ <i>Fusicatenibacter</i> ; ↓ <i>Bifidobacterium</i>	Decreased relative abundance associated with the development of non-infectious diarrhea
NODAT	KTRs (n = 50)	↑ <i>Lactobacillus</i> ; ↓ <i>Akkermansia muciniphila</i>	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.

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 (SOT), 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

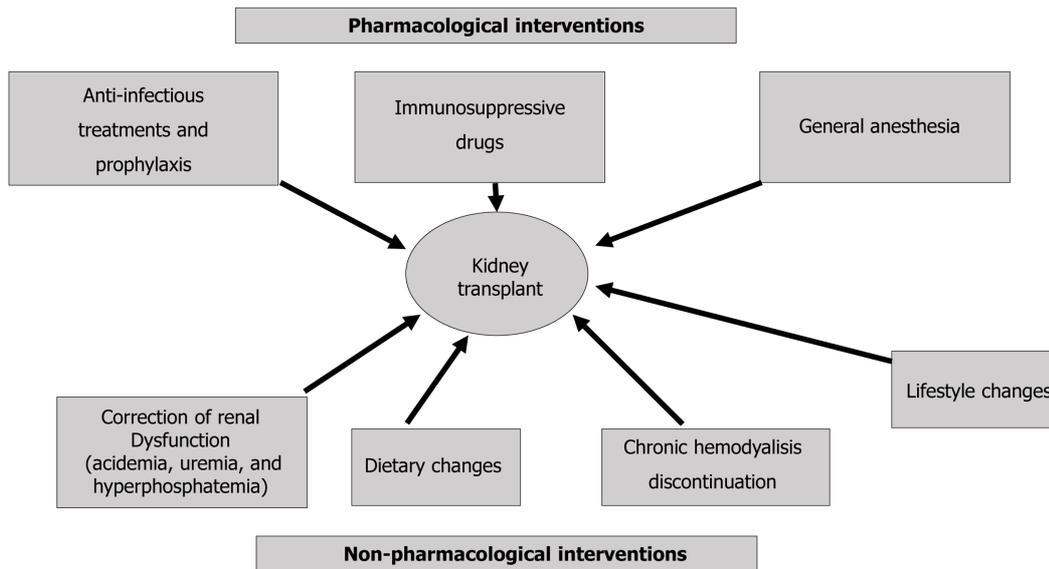


Figure 1 Factors affecting the intestinal microbiota after kidney transplantation.

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 lead 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 SOT, 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].

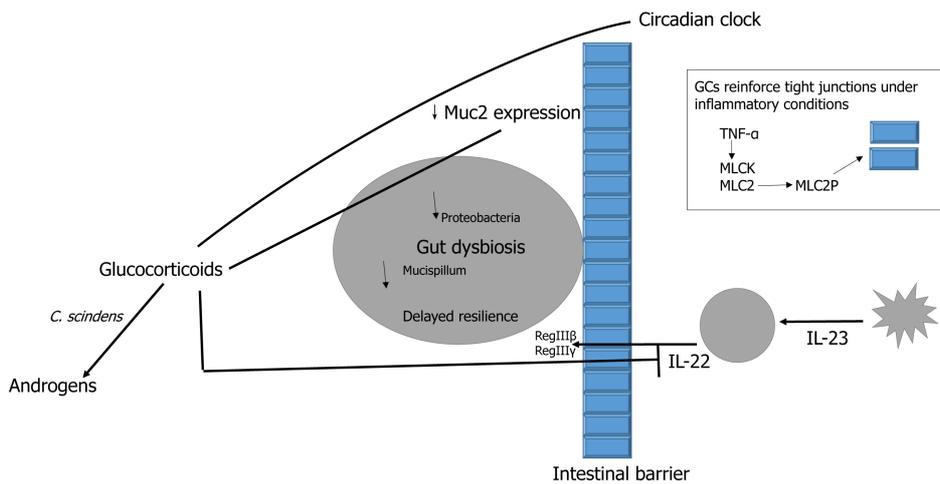


Figure 2 Impact of glucocorticoids on the gut microbiota. MUC: Mucin; RegIII: Regenerating protein; Muc2: Mucine 2; GC: Glucocorticoids; TNF- α : Tumor necrosis factor α ; MLCK: Myosin light chain kinase; MLC2: Myosin light chain 2.

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 RegIII β levels, participating in dysbiosis[40].

In a large study conducted in liver transplant patients, tacrolimus decreased *Bifidobacterium*, *Lactobacillus* and *Faecalibacterium prausnitzii* 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 prausnitzii*, 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 glucuronated 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

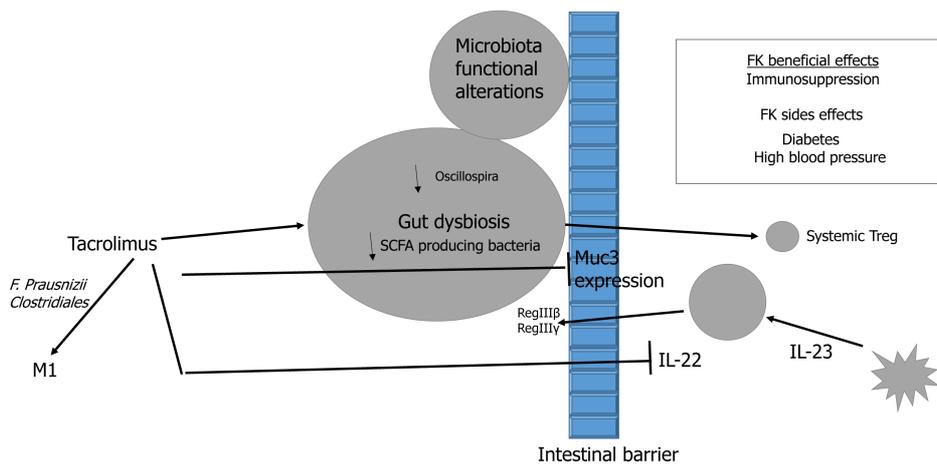


Figure 3 Impact of Tacrolimus on the gut microbiota. SCFA: Short chain fatty acids.

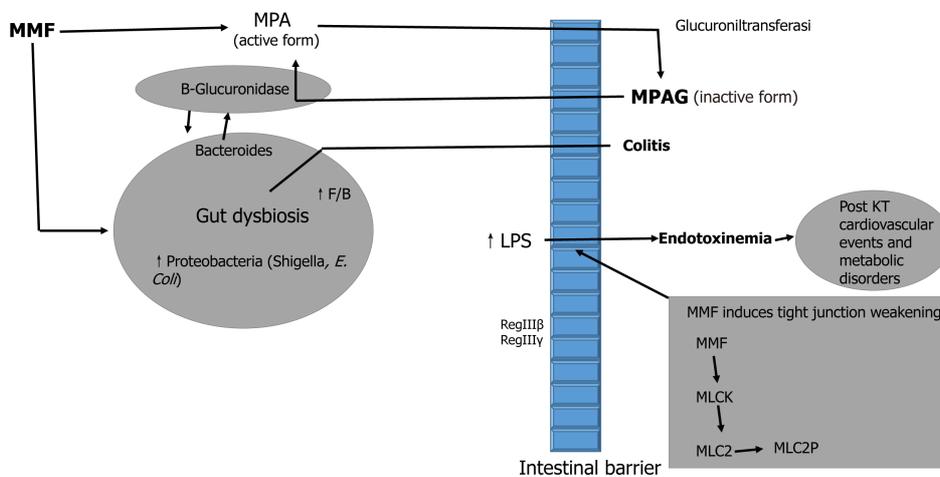


Figure 4 Impact of mycophenolate mofetil on the gut microbiota. MMF: Mycophenolate mofetil; MPA: Mycophenolic acid; MPAG: Mycophenolic acid glucuronated; LPS: Lipopolysaccharides; MLCK: Myosin light chain kinase; MLC2: Myosin light chain 2; MLC2P: Myosin light chain 2 phosphorylated; KT: Kidney transplantation.

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 prausnitzii* 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 inpatient 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 *Alloprevolletta* 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 SOTS

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*, *Tyzzera*, and *Erysipelotrichaceae*. Clearly, this finding is related to the active form of MPA as a cause of diarrhea.

CONCLUSIONS

Our study has well documented that 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.

In addition, the clinical consequences of the dysbiosis 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.

A main problem without a definitive conclusion is the treatment of a severe dysbiosis. Indeed, few studies have been conducted in patients transplanted and most of them are still in phase II level.

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].

FOOTNOTES

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