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Microbiota, renal disease and renal transplantation

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Abstract

Aim of this frontier review has been to highlight the role of microbiota in healthy subjects and in patients affected by renal diseases with particular reference to renal transplantation. The microbiota has a relevant role in conditioning the healthy status and the diseases. In particular gut microbiota is essential in the metabolism of food and has a relevant role for its relationship with the immune system. The indigenous microbiota in patients with chronic renal failure is completely different than that of the healthy subjects and pathobionts appear. This abnormality in microbiota composition is called dysbiosis and may cause a rapid deterioration of the renal function both for activating the immune system and producing large quantity of uremic toxins. Similarly, after renal transplantation the microbiota changes with the appearance of pathobionts, principally in the first period because of the assumption of immunosuppressive drugs and antibiotics. These changes may deeply interfere with the graft outcome causing acute rejection, renal infections, diarrhea, and renal interstitial fibrosis. In addition, change in the microbiota may modify the metabolism of immunosuppressive drugs causing in some patients the need of modifying the immunosuppressant dosing. The restoration of the indigenous microbiota after transplantation is important, either to avoiding the complications that impair the normal renal graft, and because recent studies have documented the role of an indigenous microbiota in inducing tolerance towards the graft. The use of prebiotics, probiotics, smart bacteria and diet modification may restore the indigenous microbiota, but these studies are just at their beginning and more data are needed to draw definitive conclusions.

Key Words: Gut commensals; Microbioma; Microbiota; Renal disease; Renal transplantation; Transplant outcomes

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Core Tip: Recent studies on the microbiota have documented that a microbiota modification, related to the assumption of immunosuppressive drugs and of antibiotics, as happens in the first period after transplantation may modify the outcomes of the graft. Indeed, dysbiosis may cause acute rejections and reduce the possibility of a tolerance status. In addition, dysbiosis is often the cause of infections and renal fibrosis. Dysbiosis may also cause diarrhea that is a frequent and severe complication in the transplanted patient. Modification of dysbiosis is possible with an appropriate treatment, but studies on this topic are just at their beginning.

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INTRODUCTION

The microbiota is defined as the micro-organisms that live in the human body without damaging it in healthy conditions. The most important and the best studied is the microbiota of the digestive system. In particular, the urinary microbiota has also been studied in studies concerning renal diseases and renal transplants.

In recent years the function of the microbiota, particularly the gut microbiota has been extensively examined and the relationship between the microbiota and diseases has been elucidated with particular reference to organs such as the kidney. In this frontier review, the definition of the microbiota and its variety will be provided, along with descriptions of its functions and relationship with the immune system. In addition, the relationship between an abnormal microbiota or pathobionts and renal diseases and renal transplantation has been documented in several studies^[1-5]. The relationship between the microbiota and its alterations in patients with kidney disease will be elucidated with particular references to the relationship between the microbiota and renal transplantation.

DEFINITIONS

The words microbiota and microbioma are often mutually used, but they have a different meaning.

The term microbiota refers to all the microorganisms inhabiting some specific niches as gut, skin, lungs and other organs and encompasses bacteria, viruses, fungi and archaea. In this review the term microbiota refers principally to bacteria even if in general it strictly refers also to other microorganisms. In a recent study the estimated total number of bacteria for a 70 kg man is approximately 3.8×10^{13} and is approximately of the same order of the number of human cells^[6]. The gut microbiota is the most important community because of its quantity and its relationship with kidney disease. The gut microbiota is already present within the first few years of life, and its composition should remain stable in adults, where the dominant bacteria are Bacteroides, Firmicutes and Actinobacteria^[7-9]. In the healthy subject the resident microbiota is also called indigenous microbiota. When the indigenous microbiota, due to genetic or environmental factors, cause inflammatory disorders or other diseases, is generally called pathobionts and this condition is called dysbiosis. Pathobionts should be distinguished from acquired infectious agents also called pathogens^[10]. Due to the relevance of microbiota both in healthy status and diseases, several national and international scholars performed studies of gut microbiota, such as the Canadian Microbiome Initiative, The Human Meta Genome Consortium Japan, the My New Gut Project of the European Union and the International Human Microbiome Consortium^[11-13]. The composition of the gut microbiota under standard conditions is shown in Table 1.

As mentioned above, the term microbioma has a different meaning than the microbiota and refers to all the microbiota genes and is approximately 150 times larger than the human genome^[14,15]. In healthy subjects the gut microbioma is stable and

Table 1 Distribution of normal gut flora in different parts of intestine

Intestine sections	Function	Normal flora
Stomach	Acid production, pepsin, amylase, CFU < 10 ³ /mL	<i>Lactobacillus</i> ; <i>Streptococcus</i> ; <i>Helicobacter pylori</i>
Small intestine: duodenum, jejunum	Pancreatic enzymes, bicarbonate ions, bile salts, CFU: 10 ³ -10 ⁴ /mL	<i>Lactobacilli</i> ; <i>Enterococci</i> ; <i>Streptococci</i> ; <i>Actinobacteria</i>
Small intestine: ileum	CFU: 10 ³ -10 ⁹ /mL	<i>Enterococcus</i> ; <i>Bacteroidetes</i> ; <i>Lactobacillus</i> ; <i>Clostridium</i> ; <i>Corynebacteria</i>
Large intestine: caecum, colon	Mucus and bicarbonate, CFU:10 ¹⁰ -10 ¹² /mL	<i>Bacteroidetes</i> ; <i>Clostridium</i> ; <i>Eubacterium</i> ; <i>Ruminococcus</i> ; <i>Streptococcus</i> ; <i>Enterococcus</i> ; <i>Lactobacillus</i> ; <i>Fusobacteria</i>

CFU: Colony forming units.

exerts important functions throughout the body as shown in Table 2.

FUNCTIONS OF THE MICROBIOTA

Metabolic functions

Dietary fibers produce energy when metabolized, but not all dietary fibers are metabolized by digestive enzymes^[16]. The gut microbiota of the large intestine contains enzymes that are able to metabolize these fibers and recover additional energy^[17,18].

Undigested proteins are degraded into peptides, amino acids and other metabolites in the large intestine. Some of these metabolites are dangerous to the body and could cause diseases as colorectal cancers and kidney dysfunction^[19]. The MEROPS database documented that the composition of the large intestine microbiota may contains different proteases responsible for inducing the production of different metabolites^[20,21]. The gut microbiota also exerts important actions on lipids, bile salts and polyphenols.

Structural functions

The structural integrity of the intestinal epithelium is essential to avoid a dangerous increase in permeability. The maintenance of structural integrity is essential for the microbiota. In normal conditions, cytokines produced in the gut may back diffuse in small quantities passing through the gut barrier. The barrier function of the tight junction in dysbiosis condition, may be weakened by several endotoxins of some pathogens as *Escherichia coli* (*E. coli*), *Clostridium difficile* and *Clostridium perfringens*. In this condition of dysbiosis, the diffusion of cytokines such as interleukin 4, interleukin 1 beta, tubular necrosis factor alpha and interferon gamma is increased^[22-26].

Protective function

The gastrointestinal tract represents a bidirectional barrier between the gut microbiota and the gut immune system^[27]. The barrier is composed of three layers: the mucus layer, the antimicrobial peptides (AMPs) and the IgA system.

Mucin glycoproteins secreted by goblet cells form a layer over the epithelia to restrict bacterial adhesion. This layer prevents the adherence of commensal microbiota to gut epithelial cells, limiting the bacterial adhesion^[28]. A second layer is represented by AMPs secreted by epithelial cells. AMPs include α and β defensins secreted by the epithelium and mediated by cytosolic nucleotide-binding oligomerization domain-containing protein 2^[29,30]. C-type lectins activate Toll-like receptors to limit bacterial penetration through the gut barrier^[31].

The third layer is composed of the IgA system. Dendritic cells (DCs) located beneath the epithelial dome of Peyer's patches take up bacteria, migrate to mesenteric lymph nodes and induce B cells to differentiate into IgA plasma cells that secrete IgA^[32,33].

THE MICROBIOTA AND THE IMMUNE SYSTEM

The indigenous microbiota, pathobionts and pathogens promote in the gut the generation of several Th cells among which Th1, Th2, Th17 and Treg. At mucosal sites this may also be due to the production of microbiota metabolites. In particular, the

Table 2 Functional activities of normal gut flora

Protective function	Metabolic function	Structural function
Nutrient competition; Barrier fortification; Innate and adaptive immunity activation; Antimicrobial compounds secretion	Vitamin and amino acid biosynthesis; Bile acid biotransformation; Dietary fiber fermentation; Short chain fatty acids production	Mucus layer properties; Crypt and villi development; Villi microvascularization; Tight junction regulation

Seven division of bacteria (*Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Fusobacteria*, *Verrucomicrobia*, *Actinobacteria*, *Cynobacteria*), 300-1000 species.

microbiota stimulate epithelial cells to the generation and accumulation of Treg by increase of TGF β , stimulate macrophages to induce Th17 cells by increase of interleukin 1 beta, and through DNA methylation can induce proliferation of colonic Treg cells. Other actions on immune cells are due to microbiota metabolites as butyrate. Butyrate down regulates IL-10 production from neutrophils and generates an anti-inflammatory activity. Butyrate, down regulating IL-6 from macrophages, induces increased levels of histone acetylation. On the other hand, butyrate, by inhibition of histone deacetylase, inhibits the activation of NF- κ B inducing a Th1 cell response^[34,35]. The balance of Treg cells and the effector T cells in the intestinal mucosa is related to the ratio between the indigenous microbiota and the pathobionts. In particular the subset of Th1 and Th2 cells activation is characterized by the expression of proinflammatory cytokines including IFN γ , IL4, IL5 and IL13, and IL23^[22]. Th 17 cells are characterized by the synthesis of IL-17, which stimulates cells to express the proinflammatory cytokines as IL-6, IL-8, and IL-22^[36,37].

The indigenous microbiota plays a fundamental role in the induction, education and function of the immune system (Figure 1).

The microbiota composition may be modified by several conditions, among which the use of antibiotics, immunosuppressants or diet alterations. In such conditions pathobionts appear and modify the immune system and promote the development of inflammatory diseases^[38].

Microbiota-derived Toll-like receptors and NOD ligands and metabolites [such as short-chain fatty acids (SCFAs) and aryl hydrocarbon receptors] may act on local gut cells but also penetrate beyond the mucosa to tune immune cells in peripheral tissues^[39].

SCFAs promote DC precursor activation and release into the bloodstream. Microbiota-derived NOD1 Ligands induce mesenchymal cells to produce hematopoietic growth factors as IL7, stem cell factor (SCF), thrombopoietin, recombinant human flt3-Ligand, IL6^[40-42].

In addition, microbiota-derived riboflavin metabolites promote the development of mucosal-associated invariant T cells^[43], and commensal bacterial-induced cytokines IL1 β and IL23 promote IL17A production from gamma delta T cells^[44,45].

Finally, commensal bacterial colonization promotes effector and regulatory T cell responses.

Clostridia colonization promotes retinoic acid receptor-related orphan nuclear receptor gamma (ROR γ t)^[46], and Foxp3+ Treg cell accumulation, which in turn limits colonic Th2 and Th17 cell responses.

Foxp3+ Tregs cells localize in Peyer's patches and promote B class switching and the production of IgA, which fosters a different microbiota and ensures commensal bacteria compartmentalization from the intestinal epithelium^[47].

Under healthy conditions, a balance between antigenic stimuli exists due to the microbiota and the immune response.

However, an aggressive immune response due to the appearance of pathobionts or pathogens in some subjects may cause inflammatory diseases, and a weak response may cause the overgrowth and diffusion of the pathobionts themselves.

Commensal bacteria induce CD4+ cells to differentiate into 4 main subtypes: Th1, Th2, Th17 and Treg. The indigenous microbiota contributes to normalizing the ratio of these subtypes.

Additionally, IgA production contributes to controlling excessive microbiota growth and limiting the growth of pathobionts.

In healthy conditions, segmental filamentous bacteria induce the growth and differentiation of Th17 and Th1 cells^[48]. In animal studies has been documented that this is impaired in animals treated with antibiotics while is normal in germ free conditions. Still in the animals, in healthy conditions, Clostridia promote the accumulation of Tregs and production of IL10, which exerts anti-inflammatory effects^[49].

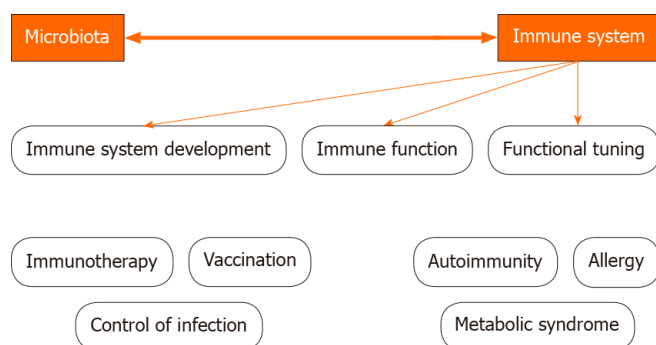


Figure 1 Role of microbiota in the induction, education and function of the immune system.

Bacterioides fragilis also contributes to maintaining a correct equilibrium between the microbiota and immune system by producing of polysaccharide A and inducing the production of IL10 and Tregs^[50].

When the microbiota loses its richness and its correct composition, pathobionts appear and dysbiosis occurs. This change may lead to diseases and kidneys and kidney grafts are among the main targets.

THE INTESTINAL MICROBIOTA AND THE KIDNEY

Communication between the gut and kidney occurs either by the activation of the immune system and by microbiota-derived metabolites.

Several studies have documented that the activation of Th17 cells in the gut by the microbiota leads to activation of Th17 cells in the kidney^[51]. Chemokine ligand 20/C-C^[52] recruits Th17 cells to the kidney.

In animals, the addition of antibiotics reduces Th17 levels and renal damage^[53]. The crucial role of Th17 cells in inducing tissue injury is also evidenced by the high levels of Th17 cells in humans with auto-immune kidney diseases and in glomerulonephritis^[54].

This phenomenon is bidirectional because acute kidney injury (AKI) determines intestinal dysbiosis and T helper Th17 cells, neutrophils and M1 macrophages mediate intestinal inflammation, as well as leaky gut with bacterial translocation. On the other hand, dysbiotic microbiota may exert an adverse effect on kidney injury and the depletion of the pathobionts may mitigate kidney injury^[55].

Microbiota-derived metabolites may affect kidney and other organ functions. Indeed, the microbiota may interact with a large number of vital functions in the health body *via* several metabolites. The targets are host metabolism and immunity as well as cardiovascular and brain functions. Additionally, the microbiota metabolism utilizes enzymes not encoded by the human genome and generates biological products relevant to the host's health as bile acids, choline, vitamins and SCFAs^[56].

SCFAs are among the most relevant metabolites produced by microbiota^[57].

SCFAs activate G protein-coupled receptors (GPR) including GPR41, GPR43 and GPR109A.

The binding of SCFAs to their receptors exerts beneficial effects on the kidney. Indeed, this signaling pathway regulates energy homeostasis^[58], stimulates glucagon-like peptide 1 secretion^[59], and inhibits the progression of atherosclerosis in mice^[60]. The binding of SCFAs to another receptor, Olfr78 exerts beneficial effects on blood pressure^[61]. These and other data support a beneficial effect of SCFAs on kidney injury (Figure 2).

In addition, SCFAs also regulate cytokine expression in T cells and the generation of Tregs through histone deacetylase inhibition.

Overall, SCFAs exert a beneficial effect on AKI by reducing the production of cytokines and chemokines such as IL1 β , IL6, TNF α and monocyte chemoattractant protein 1^[62].

In addition, SCFAs have also extraintestinal actions controlling appetite regulation, glucose and lipid metabolism. This is due to the fact that the above mentioned receptors have also been found in cells as adipocytes, neurons and immune and vascular cells^[63].

Equol, produced by certain microbiota subtypes has several beneficial effects,

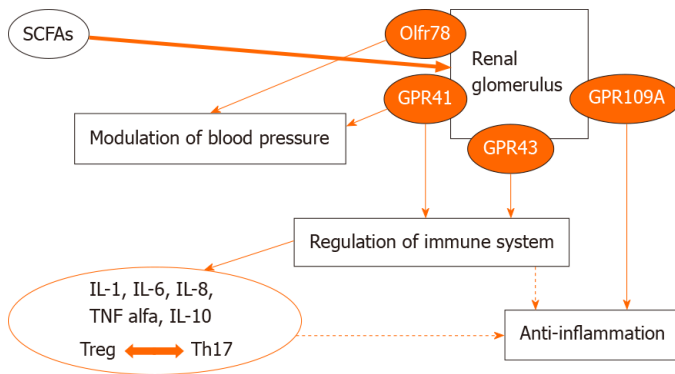


Figure 2 Short-chain fatty acids and the receptors in the kidney. Olf78: Olfactory receptor 78; GPR41: G protein receptor 41; GPR43: G protein receptor 43; GPR109A: G protein receptor 109A; SCFA: Short chain fatty acid.

including antiapoptosis, antioxidation, and anti-atherosclerosis, the production of nitric oxide in endothelial cells, antiproliferation and/or migration, and promotion of vascular smooth cells relaxation^[64].

On the contrary, negative effects on vascularization are exerted by metabolites as indoxylsulfate and trimethylamine N oxide (TMAO).

Indoxylsulfate produced by pathobionts as *E. coli* has deleterious effect on the vascular system. Indoxylsulfate induces apoptosis, senescence, prothrombotic events, proliferation and/or migration and modulation of vascular tone in vascular smooth muscle cells. Similar negative vascular effects are exerted by TMAO.

TMAO is a product of gut bacterial metabolism of choline. Differently from SFCAs it promotes renal interstitial fibrosis^[65].

The different effects of these metabolites are shown in Figure 3.

The gut microbiota may also produce uremic toxins that, in the case of dysbiosis, may be produced in high quantities and may damage the kidney^[66].

The quorum sensing signals (QS) may be produced either by pathobionts or by indigenous microbiota. Indeed, QS may be divided into two types. Those produced by GRAM⁺ bacteria such as *Pseudomonas aeruginosa* have negative immune-related processes such as IκK phosphorylation, and activation of mitogen activated protein kinase (MAPK) pathways. These induce NF-κB signaling and chemotaxis. As a result they increase inflammatory genes expression. Differently, the QS signals induced by *Bacillus subtilis*, have beneficial effects through the induction of p38 MAPK on protein kinase B^[57].

Dysbiosis may facilitate AKI either by modifying the SCFAs composition or generating higher quantities of TMAO and uremic toxins. This modification may facilitate the transition from AKI to chronic renal disease (CKD). Indeed, a cross-talk between the intestinal microbiota and the kidney has been observed. During experimental AKI, gut pathobionts may modify immune cells and other pathophysiological mediators to alter the course of AKI. AKI may in turn modify the gut bacterial composition^[67,68]. This topic has been extensively studied by Vaziri *et al.*^[68] who observed substantial differences in the gut microbiota composition between patients with end stage renal disease and control patients.

This result has been confirmed by Cigarran Guldreis *et al.*^[69], who substantially found dysbiosis in patients affected by end stage renal disease, due to the presence of pathobionts. Pathobionts modify protein absorption, reduce the utilization of alimentary fibers and are frequently associated with the use of antibiotics^[70,71].

In summary, in the healthy subject the indigenous microbiota provides benefits to our health. Indigenous microbiota affects the host by production of metabolites and gut neuropeptides. By sending the informations about the state of inner organs to the brain, they control many important functions as mood, immune response, digestion and heart rate. By this way a bidimensional communication between the gut, its microbioma and the nervous and neuroendocrine systems is established^[72].

THE MICROBIOTA AND RENAL TRANSPLANTATION

Different factors, including immunosuppressant and antibiotic therapy, lifestyle and diet, may alter the microbiota and lead to generation of pathobionts and dysbiosis.

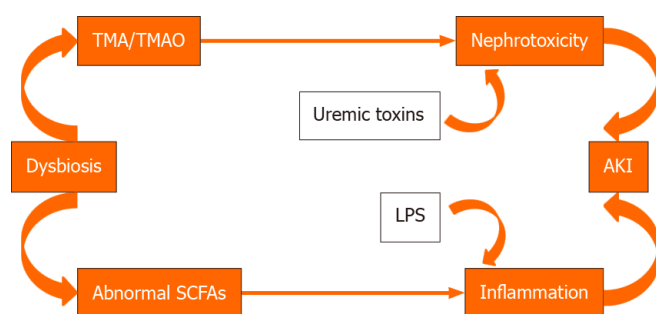


Figure 3 Dysbiosis during acute kidney injury. TMA: Trimethylamine; TMAO: Trimethylamine N oxide; AKI: Acute kidney injury; SCFA: Short chain fatty acid; LPS: Lipopolysaccharide.

Dysbiosis disrupts the gut epithelial barrier, induces a loss of barrier integrity and leads to pathogen overgrowth. The leaky gut and increased permeability facilitate the translocation of bacteria and their components into the inner environment. In this dysbiosis situation, the proinflammatory response triggers the elimination of pathogens by intestinal epithelial cells (IL-1, IL-6 and IL-18 secretion), DCs and macrophages that induce the development of the effector CD4⁺ cells, Th1 and Th17. Innate immune responses lead to a systemic and allograft inflammation. Moreover, dysbiosis decreases the number of regulatory T cells and increases the number of effector T cells that activate innate immunity. On the other hand, in the colon and liver, dysbiotic gut-derived uremic toxins are further metabolized to TMAO. The accumulation of p-cresyl sulfate in the kidney generates reactive oxygen species that lead to the production of inflammatory cytokines and profibrotic factors. In addition, indoxylsulfate induces inflammation and nephrotoxicity^[73-77].

Characteristics of the microbiota after renal transplantation

Renal transplant patients, in addition to receiving relevant immunosuppressive therapy in the first period after transplantation, receive several antibiotic treatments as a prophylactic measure to avoid infections.

All these drugs extensively modify the human microbiota, principally at the gut and urinary tract levels. Historically, since the initiation of renal transplantation, when very high doses of cyclosporine A were used, gingival overgrowth was observed as an important side effect. This change was related to modifications of the oral microbiota and generation of pathobionts^[78].

In a pilot study, Lee *et al*^[79], performed polymerase chain reaction in samples from 26 kidney transplant recipients and documented a change in the microbiota between the pre- and posttransplant periods. The results are shown in Table 3.

Firmicutes were the most abundant bacteria detected pre- and posttransplantation, but their quantity posttransplantation was lower than in healthy subjects^[80]. The same study reported posttransplantation an increase in the abundance of Bacteroides that included infective pathogens such as *E. coli* and *Klebsiella pneumoniae*^[81].

Overall, the study by Lee and colleagues documented a dysbiosis that was later confirmed by other studies. A recent review from Xiao *et al*^[82] on microbiota modifications in response to solid organ transplantation highlighted an increase in the abundance of pathogenic Proteobacteria, which might represent the cause of infectious diseases occurring after transplantation.

These data were confirmed by a recent study by Swarte *et al*^[83] that confirmed a reduction in the abundance of Firmicutes with variability among the species. The most significant reduction was observed for *Streptococcus thermophilus* and *Blautia wexlerae*.

Overall these authors observed an increase in the abundance of Proteobacteria (*E. coli*) and a decrease in the abundance of Actinobacteria posttransplantation. The increase in Proteobacteria has already been proposed as a marker of dysbiosis^[84]. Additionally, the same study observed a reduction in SCFAs producing bacteria after transplantation. In particular, reductions in the abundance of *Eubacterium rectale*, *Coprococcus* and *Roseburia* were observed. All these bacteria produce SCFAs^[85] that exert beneficial effects on the kidney and increase the number of Tregs, reducing systemic inflammation^[86,87]. The use of proton pump inhibitors, of MMF and aging were the prevalent determinants of this form of dysbiosis^[88,89].

Another study^[90] analyzed the gut microbiota in 142 kidney transplant recipients. The authors detected potential pathogens, such as *Clostridium difficile* and *E. coli* in 30% of patients. These pathogens were not associated with diarrhea, as expected.

Table 3 Alterations in the gut microbiota following kidney transplantation according phylum and order

Phylum	Pre Tx cohort	Post Tx cohort
<i>Firmicutes</i>	91.8%	87.7%
<i>Actinobacteria</i>	2.0%	7.6%
<i>Proteobacteria</i>	0.9%	4.1%
<i>Bacteroidetes</i>	2.8%	0.6%
Order		
<i>Clostridiales</i>	64.8%	64.3%
<i>Lactobacillales</i>	19.1%	12.0%
<i>Erysipelotrichales</i>	5.6%	10.2%
<i>Bifidobacteriales</i>	1.6%	6.6%
<i>Enterobacteriales</i>	0.4%	3.9%
<i>Bacteroidales</i>	2.8%	0.6%

A different study^[91] observed that major changes in the microbioma occur in the first month after transplantation, with substantial differences among patients. The authors concluded that longitudinal analyses should be performed to provide more information.

In conclusion, dysbiosis after renal transplantation is related to an imbalance between the indigenous microbiota and the pathobionts. This imbalance is related principally to the need for immunosuppressant and prophylactic and therapeutic antimicrobial agents^[92].

The metabolic and clinical consequences of dysbiosis are represented by a higher incidence of acute rejections, acute infections, interstitial fibrosis, posttransplant diarrhea, reduced production of protective agents such as SCFAs by the gut microbiota, and modification of immunosuppressant levels in the blood.

Dysbiosis and acute rejection

Several experimental studies conducted in animals have documented an effect of the gut microbiota on immune responses that lead to transplant rejection^[93].

Few studies have been conducted in the humans on this topic.

In the aforementioned study by Lee *et al*^[79], the differences in the fecal bacteria composition of patients with and without rejection are shown in Table 4.

In one recent study^[84], the microbiota was evaluated pre- and posttransplant in 60 patients who received a renal transplant.

Samples from urine, oral swabs, rectal swabs and blood were evaluated for up to 6 mo after transplantation.

In the study, the most relevant changes in the microbiota principally verified in the first month after transplant, when the immunosuppressive treatment was heavier because of the induction therapy. Further modifications in the microbiota were verified in the first six months after transplantation. In urine samples and in oral swab samples, changes were verified principally in the phylum *Proteobacteria*. In the rectal swab samples, *Firmicutes* were the bacteria whose composition changed more frequently.

Significant changes in *Leptotrichia*, *Neisseria* and *Actinobacteria* were observed in five patients who experienced acute rejection. Four patients experienced late acute rejection and displayed significant changes in *Anaerotruncus*, *Coprobacillus* and *Coprococcus*.

Dysbiosis and infections

The same authors of the study on acute rejection^[94] documented that similar changes in the microbiota were also associated with a higher incidence of urinary tract infections.

In particular, in four patients with posttransplant infections, the abundance of the genus *Anaerotruncus* of *Firmicutes* was markedly decreased compared to the other patients.

Several factors may cooperate with dysbiosis to generate infections, as shown in Table 5. This higher incidence of both urinary and gastrointestinal infections was also reported in the aforementioned studies by Lee *et al*^[79] and Chan *et al*^[95].

In a recent study^[96], a transplant patient with recurrent urinary infections recovered

Table 4 Microbial composition of fecal specimens from patients with or without acute rejection, by Phylum and Order

Phylum	No AR cohort	AR cohort	P value
<i>Firmicutes</i>	91.4%	76.6%	0.40
<i>Actinobacteria</i>	3.7%	8.2%	0.60
<i>Proteobacteria</i>	1.3%	15.2%	0.33
<i>Bacteroidetes</i>	3.1%	0.02%	0.03
Order			
<i>Clostridiales</i>	63.1%	16.9%	0.01
<i>Lactobacillales</i>	12.7%	49.9%	0.04
<i>Erysipelotrichales</i>	13.3%	9.2%	0.32
<i>Bifidobacteriales</i>	3.1%	7.9%	0.44
<i>Enterobacteriales</i>	1.0%	14.7%	0.17
<i>Bacteroidales</i>	3.1%	0.02%	0.03

AR: Acute rejection.

Table 5 Potential transplant associated factors that may lead to changes in the gastrointestinal microbiota and cause infections

Risk factors	Microbiota changes	Consequences	Interventions
Dietary patterns	Increase in bacteria translocation	Gastrointestinal upset <i>e.g.</i> , diarrhea	Diet
Changes to colonic and bowel transit time	Increase in metabolic endotoxemia	Urinary tract infections	Prebiotics
Immunosuppression	Increase in gut-derived microbial toxin formation	Other infections not yet explored	Probiotics
Antibiotics			Synbiotics
Lifestyle (sedentary, smoking, alcohol)			

after fecal microbiota transplantation (FMT), which induced a marked decrease in the abundance of *E. coli* in the urinary microbiota.

In conclusion, according to these studies, some microbial species may exert a protective effect on the mucosal surface under normal conditions, and when the microbiota changes, pathobionts and aggressive phenotypes appear to induce renal dysfunction.

Dysbiosis and interstitial fibrosis

The hypothesis that urinary dysbiosis is principally responsible for the development of interstitial fibrosis of the graft was based on the findings that patients affected by interstitial fibrosis/tubular atrophy (IF/TA) had abnormalities in the urinary microbiota with appearance of pathobionts and, consequently, in the immune response. Two studies, conducted in humans^[97,98] detected antibodies directed against *E. coli* LPS, a powerful activator of the immune system *via* TLR4 receptor in the biopsies of patients affected by IF/TA.

In a recent study of transplant patients, Modena *et al*^[99] collected urine samples from 25 patients at two time points after kidney transplantation (approximately 1 mo and 6 mo after transplantation). All these patients demonstrated developed IF/TA in surveillance biopsies collected 6 mo after transplantation.

These samples were compared with 23 patients with normal surveillance biopsies and stable renal function at 6 mo after transplantation.

At six months after transplantation, patients affected by IF/TA displayed decreased abundances in the *Lactobacillus* and *Streptococcus* genera along with an increase in the abundance of no dominant species.

The authors concluded that the urinary microbiota, modified posttransplantation, may contribute to IF/TA development by altering the host immune response.

IF/TA is associated with a loss of the indigenous dominant resident urinary microbiota and an increase in the abundance of pathobionts or nonresident, pathogenic bacteria.

The phenomenon of IF/TA may be mediated by myofibroblasts, as has already been documented in the gut, where gut dysbiosis potentially leads to intestinal fibrosis^[100]. Myofibroblasts may be derived from transdifferentiation processes such as the epithelial to mesenchymal transition or endothelial to mesenchymal transition. These processes may be induced and aggravated by modifications in the indigenous microbiota.

In conclusion, myofibroblasts may play a relevant role in inducing IF/TA either at the gut or renal level, and the indigenous microbiota might have regulatory and protective functions under normal conditions.

Dysbiosis and diarrhea

Diarrhea represents a severe complication after kidney transplantation, affecting approximately 20% of patients^[101], and it represents an important cause of graft loss and death^[102]. However, its etiology is still being discussed, and a clear diagnosis not available for approximately 85% of transplanted patients affected by diarrhea. With the exception of the few cases that are ascribed to a specific infection and the presence of pathogens, the diarrhea etiology is often ascribed to the use of immuno-suppressants, in particular MMF. However, a reduction in the MMF dose is dangerous and may lead to an increased risk of allograft rejection^[103].

In the pilot study by Lee *et al.*^[79], the authors observed a reduction in the commensal indigenous microbiota, such as *Ruminococcus*, *Dorea* and *Coprococcus*, in 26 renal transplant patients affected by diarrhea. In addition, they did not detect pathogens such as *Clostridium difficile* or norovirus in fecal specimens. These findings prompted the hypothesis that in the majority of patients, gut dysbiosis rather than the presence of pathogens may represent an important cause of posttransplant diarrhea. In a recent study by Lee *et al.*^[104], fecal specimens from 25 patients presenting diarrhea in the first three months after transplantation were compared with 46 patients who did not develop diarrhea. In the diarrhea group, the abundance of the genera *Eubacterium*, *Anaerostipes*, *Coprococcus*, *Romboutsia*, *Ruminococcus*, *Dorea*, and *Faecalibacterium* were significantly decreased, while the abundance of the genera *Lachnospiraceae*, *Escherichia* and *Enterococcus* were significantly increased. Table 6 provides a detailed description of the data. Many of the bacteria that were present at lower abundance in the diarrhea group belong to the *Lachnospiraceae* and *Ruminococcaceae* families^[105] and contribute to metabolic functions essential for gut health^[106]. Utilizing the Phylogenetic Investigation of Communities by Reconstruction of Unobserved States Analysis^[107], 9 metabolism-related pathways were decreased in the diarrhea group. The decrease in the abundance of these indigenous microbiota bacteria in the subjects affected by diarrhea contributes to the development of an abnormal metabolic status, which might lead to diarrhea.

Interestingly, a similar decrease in the abundance of protective bacteria was also observed in nontransplant patients affected by diarrhea^[108].

Notably, the specimens from transplanted patients with diarrhea were negative for known bacterial and protozoan pathogens that cause diarrhea.

Finally, two transplanted patients affected by persistent diarrhea underwent FMT from allogeneic donors. Diarrhea resolved in the first month after FMT, and the abundances of 13 protective bacteria taxa increased with a simultaneous decrease in the abundances of the 3 identified pathobionts or pathogenic bacterial taxa^[96,108].

Short Chain Fatty Acids and other metabolites in renal transplantation

SCFAs are produced in the gut by the indigenous microbiota and have a trophic action on the gut epithelium. In addition, these substances exert an anti-inflammatory effect on the whole body and regulate immune cells.

Ninety-five percent of SCFAs are represented by acetic acid, propionic acid, butyric acid and valeric acid, all of which are derived from saccharolytic fermentation. Under normal conditions with a microbiota producing normal quantities of SCFAs, several beneficial effects have been documented after transplantation both in animals and in humans.

In humans, SCFAs increase the expression of antimicrobial peptides secreted to the external surface by epithelial cells^[109]. Studies *in vitro* or in animals documented that SCFAs modulate the production of immune mediators, including IL-18 and other cytokines and chemokines^[110], regulate the differentiation, recruitment and activation of immune cells, including neutrophils^[111], DCs, macrophages^[112] and T lymphocytes^[113].

Finally, Wu *et al.*^[114] documented, in a murine kidney transplantation model, that SCFAs are able to induce donor-specific tolerance by inducing the production of T regulatory cells^[114].

Table 6 Most significant genus level composition in the fecal specimens from the diarrhea group and the no diarrhea group

Bacterial Taxonomy Genus	Median relative abundance in the diarrhea group	Median relative abundance in the no diarrhea group	P value
<i>Eubacterium</i>	0.002	0.017	1.5E-09
<i>Anaerostipes</i>	0.000	0.005	2.7E-08
<i>Coprococcus</i>	0.000	0.004	3.0E-08
<i>Romboutsia</i>	0.000	0.014	4.2E-06
<i>Ruminococcus</i>	0.007	0.025	8.3E-06
<i>Dorea</i>	0.000	0.007	3.4E-05
<i>Enterococcus</i>	0.002	0.000	1.3E-04
<i>Faecalibacterium</i>	0.000	0.019	1.4E-04
<i>Fusicatenibacter</i>	0.000	0.006	0.001
<i>Oscillibacter</i>	0.001	0.008	0.001
<i>Ruminiclostridium</i>	0.005	0.021	0.002

Andrade-Oliveira *et al*^[115] evaluated the effect of SFCAs on a mouse model of ischemia-reperfusion^[115].

In the animals, the treatment with SCFAs improved renal function after ischemia-reperfusion injury, reduced the apoptosis, inhibited NFkB activation and nitric oxide production and reactive oxygen species production. All these actions of SCFAs are summarized in Table 7.

In mice, SCFAs decrease the activation of bone marrow-derived DCs and inhibit their function as antigen presenting cells^[115].

In conclusion, the authors showed that SFCA supplementation reduces inflammation in their model and improves ischemia-reperfusion injury.

To our knowledge, few studies have been conducted in humans. A recent study by Lee *et al*^[116] studied 168 kidney transplant recipients and divided the patients according to whether they had higher levels of butyrate-producing bacteria (BPG) or low levels of BPG. The posttransplant administration of antibiotics was associated with a decrease in BPG levels. These patients have a higher incidence of respiratory tract infections.

For the first time, the clinically beneficial effects of higher butyrate levels and posttransplant-induced dysbiosis were documented in transplanted men and may induce higher infection rates.

Similarly, in another study on transplanted humans, 51 renal transplanted recipients have been followed up to 12 mo after transplantation to study the serum levels of uremic toxins as p cresyl sulfate, p cresyl glucuronide, indoxyl sulfate, TMAO and phenylacetylglutamine. The results were compared with CKD control patients with similar renal function. The study documented that after transplantation the colonic microbiota derived uremic retention solutes decreases. As the urinary excretion is lower in transplanted patients, this fact suggests an independent effect after transplantation on intestinal uptake and a different colonic microbial metabolism and absorption^[117].

The microbiota and tolerance

The aforementioned hypothesis that gut microbioma metabolites such as SCFAs could induce donor-specific tolerance through the induction of regulatory T cell differentiations^[114], introduces the chapter on the relationship between microbiota and tolerance.

This relationship is well known in the development of immune tolerance in children. Indeed, in the first 1000 d of life, the early exposure of food allergens to indigenous intestinal microbiota induces tolerance through activation of Tregs and subsequent production of TGFβ and IL-10^[118].

In a recent study, Colas *et al*^[119] examined the urinary microbiota of 86 renal transplant patients. Patients were divided into 3 groups: Normally immunosuppressed with stable renal function, minimally immunosuppressed, and spontaneously tolerant patients. Differences in microbiota profiles were observed, and a unique and specific urinary microbiota was detected in patients with spontaneous

Table 7 Actions of short-chain fatty acids on a model of ischemia reperfusion syndrome

Actions
SCFAs improve renal function
SCFAs decrease apoptosis and increase tubular proliferating cells
SCFAs decrease activation of bone marrow derived dendritic cells and inhibit their function as antigen presenting cells
SCFAs inhibit NFkB activation and nitric oxide production
SCFAs inhibit ROS production

SCAF: Short chain fatty acid; ROS: Reactive oxygen species; NFkB: Nuclear factor kappa-light-chain-enhancer of activated B cells.

tolerance characterized by a clear *Proteobacteria* profile. The profile was different in patients stratified according to gender (higher in males) and inversely correlated with the quantity of immunosuppressive drugs.

The *Proteobacteria* detected in tolerant subjects included *Janthinobacterium*, *Clostridia* and *Firmicutes*. *Janthinobacterium* is known to produce an indole-derived peptide with antiproliferative and anti-inflammatory activities^[120,121]. *Clostridia* exert an anti-inflammatory effect by producing SCFAs^[122]. *Firmicutes* produce indole derivatives^[123] and polyphosphate^[124] with anti-inflammatory activities.

In conclusion, the indigenous microbiota may favor the induction of tolerance, but the use of immunosuppressants modifying the microbiota may represent an obstacle to the development of the tolerance state.

Interactions between the microbiota and immunosuppressants

Bilateral actions between the microbiota and immunosuppressive drugs have been identified. On one hand, the microbiota may modify the absorption and the metabolism of immunosuppressants; on the other hand, immunosuppressants may modify the indigenous microbiota.

The vast majority of studies on this issue have been conducted on calcineurine inhibitors.

Several studies have extensively documented that factors such as age, gender, race and CYP3A5 polymorphisms influence the absorption and metabolism of immunosuppressants and account for interindividual variability such that the individual dosing is not the same for all patients.

Recently, the gut indigenous microbiota or the pathobionts have been suspected to exert a powerful effect, justifying the different metabolism from one patient to another and in the same subject.

The assumption of other drugs, such as antibiotics, modifying the indigenous microbiota may account for this variability^[125-128].

Lee *et al*^[129] examined the microbiota in the fecal specimens of 19 patients who received a kidney transplant and were on tacrolimus (TAC) as the principal immunosuppressive therapy. All patients received the same prophylactic antibiotic therapy to avoid biases. Patients were divided into two groups according to the need to receive increasing TAC doses (Dose Escalation Group) or not (Dose Stable Group). By examining the microbiota, the authors found a significantly higher level of *Faecalibacterium prausnitzii* in patients from the Dose Escalation Group than in patients from the Dose Stable Group. In addition, *Faecalibacterium prausnitzii* was the most significant factor justifying the need to increase the TAC dose. Even if a large quantity of TAC is absorbed by the small intestine, it may also be absorbed in the colon^[130]. Although the Lee's study is a pilot one, the results raise the question of the relevance of microbiota and of *Faecalibacterium prausnitzii*, particularly on TAC trough levels, which are also important due to the narrow therapeutic index of TAC.

In a different study, Guo *et al*^[131] incubated *Faecalibacterium prausnitzii* cells *in vitro* with TAC. The authors detected a compound named M1 that is a cheto-produced metabolite of TAC with a less powerful immunosuppressant. The authors measured a large quantity of M1 in the stool samples of patients with a larger quantity of *Faecalibacterium prausnitzii* in the stool.

In addition, the same study documented that other bacteria, such as *Clostridia* and *Bacteroidales*, are able to convert TAC into M1 metabolites. The authors conclude that several commensal microbiota may metabolize TAC in the gut to less powerful compounds, explaining the differences in TAC exposure in transplant recipients.

On one hand, the microbiota may alter the metabolism of immunosuppressants; on the other hand, immunosuppressants may alter the gut indigenous microbiota. The study by Gibson *et al*^[132] reviewed this topic extensively. Unfortunately the vast majority of studies have been conducted on calcineurin inhibitors and very few have examined renal transplantation.

The studies by Zhang *et al*^[133] and by Lee *et al*^[129] documented the effect of TAC on the gut microbiota in renal transplant recipients. Other studies^[134] analyzed the same phenomenon in liver transplant recipients. Zaza *et al*^[135] examined the microbiota in patients receiving TAC + MMF or everolimus + MMF, but they did not observe any difference.

In the pilot study by Lee *et al*^[79], patients with early corticosteroid withdrawal had fewer *Clostridiales* and *Erysipelotrichaeles* in the microbiota, but the difference was not statistically significant.

Finally, a recent study^[136] documenting that encapsulated cyclosporine A does not change the composition of the human indigenous microbiota is worth mentioning.

MICROBIAL THERAPIES IN KIDNEY HEALTHY, DISEASE AND TRANSPLANTATION

The treatment of gut dysbiosis may be divided into probiotics, smart bacteria, prebiotics, a high-fiber diet and fecal microbiota transplantation.

Several of these therapies have been used in patients affected by chronic kidney disease.

Probiotics are defined by the World Health Organization as live organisms that, when administered in adequate amounts, confer a health benefit to the host^[137]. Probiotics such as *Lactobacilli* and *Streptococci*^[138,139] have been used to treat CKD. They are able to enhance gut barriers, improve mucosal immunity and modulate the host signaling pathways by reducing the activation of NFκB and the MAPK^[140,141]. Smart bacteria are genetically modified bacteria that are able to remove toxic molecules in animal studies^[142,143].

Prebiotics are nonviable food components that confer health benefits to the host associated with the modulation of the microbiota^[144]. A prebiotic must be resistant to gastric acid and digestive enzymes, allowing it to reach the small and the large intestines to stimulate the activity of beneficial microbes. To date, only insulin and trans-galacto-oligosaccharides have these characteristics and may be considered prebiotics^[145].

The principal mechanisms of action of prebiotics are to increase the production of SCFAs and to decrease the intestinal pH^[146].

Unfortunately, the vast majority of studies using these therapies have been conducted in animal models of CKD.

Few studies have assess probiotics in humans, particularly kidney transplant recipients and most studies were conducted in liver transplant patients^[5,95].

Currently, the most effective treatment for renal transplant recipients appears to be FMT, principally in patients affected by infection and/or diarrhea due to resistant *Clostridium difficile* or *E. coli*^[79,96].

FUTURE PERSPECTIVES

Two main issues are involved in the search for new perspectives: the search for new therapies and an improved knowledge of gut microbiota and pathobionts.

New therapies: Potential benefits of nutritional and supplementation approaches may target microbiota in CKD patients. In CKD, nutritional management and supplementation, including salt and protein restriction, vegetable intakes, and the use of pro-, pre-, and synbiotics, has several benefits. Modulate gut microbiota dysbiosis, decrease colonic production of proteolytic derived uremic toxins and reduce inflammation and oxidative stress^[147].

Strategies targeting the microbial source of immune regulation are also promising. The presence of *Lactobacillales* in the gut microbiota promotes Treg cells and suppresses Th17 in the kidney. The oral administration of *Lacidophilus* ATCC4356 in the animals attenuates atherosclerotic progression^[148].

Lubiprostone, a synthetic derivative of prostaglandin, in a rat model of CKD is associated with reduction of kidney inflammation and improvement of microbioma

profile with proliferation of saccharolytic bacteria.

Similarly, the trimethylamine inhibitor 3,3-dimethyl-1-butanol inhibits the atherosclerotic lesions in mice^[149].

The identification of causative bacteria in the context of kidney disease and the distinction of indigenous microbioma from pathobionts is a technical challenge.

Sequencing techniques and a wide application of metabolomics allowed us for an improved understanding of microbioma in health and diseases.

The National Institute of Diabetes and Digestive and Kidney Diseases is conducting a study (ClinicalTrials.gov Identifier: NCT02572882)^[150] aimed to Characterize the Gut Microbiome of Individuals With End-stage Renal Disease Treated With Maintenance Hemodialysis, and to Explore Effects of P-inulin on the Gut Microbiome.

Future studies should explore the interaction of microbioma with human genome and how the microbioma should be treated in the case of renal disease and renal transplantation^[137].

CONCLUSION

In the last decade, relevant importance in conditioning both the healthy status and several diseases has been assumed by the microbiota. The microbiota is defined as the microorganisms that live in our body.

Gut microbiota has an important function because can metabolize food and produce substances as SCFAs extremely useful for the body. In addition, the microbiota has important relationship with the immune system and, when modified may induce abnormal activation of the immunity that may cause disease.

Renal diseases may be induced by dysbiosis both for the activation of the immune system and for the production of an excess of uremic system.

In several renal diseases and in particular in the case of end stage renal disease the normal microbiota changes with development of pathobionts and the consequent dysbiosis is responsible for the further deterioration of the renal function.

In the case of renal transplantation, the microbiota has a relevant function.

After transplantation, because of the assumption of immunosuppressive drugs and of prophylactic antibiotics, the gut indigenous microbiota profile modifies, particularly in the first month after transplantation. This modification may influence the graft outcomes causing acute rejection, infections, renal fibrosis and modifications of the drug metabolism, immunosuppressants included. It is possible to modify an abnormal microbiota with the use of prebiotics, probiotics and diet modification.

It should be highlighted that all the studies referring to the microbiota in renal transplantation are few, refer to small number of patients, often retrospectives. In addition, many of these studies have been conducted in animals. Because of this fact the microbiota in general and in solid organ transplantation in particular may be considered a new frontier in medical studies.

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