

Clinical utility of characterizing intestinal flora in septic kidney injury

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Abstract

The incidence of septic acute kidney injury (AKI) is increasing, it has become a major threat to human health because of its acute onset, poor prognosis, and high hospital costs. The most common cause of AKI in critical-care units is sepsis. Septic AKI is a complex and multi-factorial process; its pathogenesis is not fully understood. In sepsis, the destruction of mucosal barriers, intestinal flora disorders, intestinal ischemia/reperfusion injury, use of antibiotics, and lack of intestinal nutrients lead to an inflammatory reactions that in turn affects the metabolism and immunity of the host. Such changes further influence the occurrence and development of AKI. New technology is enabling various detection methods for intestinal flora. Clinical application of these methods in septic renal injury is expected to clarify the relationship among pathogenesis, disease progression mechanism, and intestinal flora.

Keywords: Intestinal flora; Kidney injury; Sepsis

Introduction

The trillions of microorganisms in the human intestinal tract are in a symbiotic relationship with the human body and play an important role in immunity, metabolism, digestion, and other processes. The gut flora also participates in information exchange between the brain and intestinal tract. Currently, it is thought that microorganisms are gathered outside the host itself and the body forms super symbionts.^[1] Moreover, microbial genomes are considered the second genomes in our cells. Decomposition and transformation of food constituents by the intestinal flora produces a series of materials that are involved in host energy metabolism, immune regulation, neuroendocrine activity, and other physiological activities. The intestinal flora can be viewed as a virtual organ with important functions in human physiology.^[2] There are various technologies available for characterizing the intestinal flora, which should facilitate the treatment of critical diseases.

Septic Acute Kidney Injury (AKI)

Septic AKI, a clinical syndrome with many possible causes and symptoms, is a common and serious disease in intensive-care units (ICU).^[3] The most common cause of AKI is sepsis. Septic AKI is a complex, multifactorial process and its pathogenesis is not fully understood. In sepsis, destruction of mucosal barriers, imbalance of the

intestinal flora, intestinal ischemia/reperfusion injury, use of antibiotics, and lack of intestinal nutrients can lead to an inflammatory reaction, which in turn affect host metabolism and immunity, thus promoting AKI.^[4] Some studies have reported an incidence of AKI in the ICU of 10.8% to 67.0%. The death rate of AKI patients receiving renal replacement therapy (RRT) exceeds 50%. Great progress has been made in medical care for AKI and RRT technology, but the reported death rate for the disease among hospitalized adult patients remains high, at 14%–60%.^[5] Several studies have shown a relationship between the intestinal flora and renal insufficiency, which by extension shows the close relationship between the kidney and the gastrointestinal tract (known as the gastrointestinal axis).^[6] Therefore, studies on the intestinal flora and sepsis-induced kidney injury are of importance to guide follow-up treatment and reverse gastrointestinal dysfunction in patients with kidney disease.

Intestinal Flora and Kidney Injury

The intestinal flora shows changes under conditions of kidney injury. In particular, most patients with end-stage renal disease exhibit intestinal dysfunction.^[7] There are several reasons why septic AKI patients show obvious changes in the intestinal flora, as follows. (1) Metabolic waste cannot be fully excreted by the kidneys and accumulates in the body during kidney injury, eventually changes the structure, quantity, and distribution of the intestinal flora, resulting in a serious imbalance in

Access this article online

Quick Response Code:



Website:
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DOI:
10.1097/CM9.0000000000000724

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Chinese Medical Journal 2020;133(7)

Received: 04-12-2019 Edited by: Yuan-Yuan Ji

intestinal microecology that may manifest in a decrease in probiotic bacteria and overgrowth of saprophytic bacteria. (2) The type and quantity of intestinal flora are closely related to vitamin K, a deficiency of which in patients with renal injury can lead to changes in intestinal microecology. (3) Iatrogenic factors may be involved in AKI,^[8,9] whereby the intestinal flora plays a vital role in the development and treatment of kidney diseases; this is currently a hot topic of research.

Methods to Characterize Intestinal Flora in Sepsis-induced Kidney Injury

Probiotics and synbiotics

Studies reporting benefits of probiotics

The word probiotic is derived from the Greek “beneficial to life.” Li et al^[10] found that supporting enteral nutrition through probiotics effectively reduces the inflammatory response, and improves immune function and the serum albumin index in septic patients. Probiotics can also improve nutritional status, and shorten the mechanical ventilation and hospitalization times of patients with sepsis. Shimizu et al^[11] reported on 35 patients who received synbiotics and 37 patients who did not, there was no significant difference in the incidence of sepsis or mortality between the two groups, but analysis of fecal bacteria showed that the amounts of beneficial bifidobacteria and lactobacilli were significantly higher in the probiotic group than in the control group. Moreover, the concentration of organic acids in the probiotic group, particularly the amount of acetate during the first week, was significantly higher than in the control group. Overall, the results implied that prophylactic probiotics can regulate host immunity and digestion, balance the intestinal flora, and decrease the incidence of enteritis and ventilator-associated pneumonia in patients. Vitetta et al^[12] also investigated the efficacy of probiotics, and found that *Streptococcus thermophilus* (*S. thermophilus*) is an important regulator of uremic toxins in the intestinal tract of patients with chronic kidney disease (CKD). Using probiotics containing *S. thermophilus* may delay the progression of CKD by downregulating the proinflammatory response of the mucosa. Zhang et al^[13] studied the intestinal microflora of 25 CKD patients (CKD group) and 25 healthy subjects (control group). The results showed that the intestinal microflora of the CKD patients differed significantly from that of the healthy subjects, and probiotic levels were negatively correlated with inflammatory factors; moreover, rumen microflora was positively correlated with inflammatory factors. Wu et al^[14] reported that probiotics alter the host’s response to bacterial infection by directly regulating the transmission of mucosal signals. Once intestinal epithelial cells are exposed, pathogen-induced filaments are present due to kinin profiles associated with multiple innate immune signaling pathways. Activation of mitogen-activated protein kinase and nuclear factor kappa B decreased in response to probiotics. Consistent with this, the gut microbiota of mice fed oral probiotics was not changed, but the inflammatory response to lipopolysaccharide (LPS) was reduced. It may be because that

probiotics inhibit the inflammatory response triggered by LPS.

Studies reporting no benefits of probiotics

Among critically ill patients, the infection rate was lower in those who were administered with probiotics, compared with that than in the patients without, but probiotics had no effect on mortality, average hospital stay, or the incidence of diarrhea.^[15] More clinical studies are needed to confirm these findings. Borges et al^[16] assigned 46 hemodialysis (HD) patients to *S. thermophilus*-treated ($n = 23$) and placebo ($n = 23$) groups: probiotics failed to significantly reduce uremic toxins or inflammatory markers. Therefore, further study is needed to determine whether probiotics should be administered to HD patients. Another study found that a 6-week of administration of lactobacilli or bifidobacteria before dialysis in patients with chronic kidney disease reduced levels of uric acid toxin in plasma and the occurrence of constipation and systemic inflammatory reactions.^[17] However, further research is needed to determine whether there are long-term benefits. Suez et al^[18] reported that although probiotics have been widely used, and probiotic colonization, activity at the strain level, safety, interactions with the local microbiome and effects on the host have been assessed, the clinical outcomes associated with the use of many probiotic strains and preparations are unsatisfactory. At present, the clinical data are insufficient to support the use of probiotics in the perioperative and ICU environments.^[19] More research is needed to understand the complex two-way relationship between microorganisms and the host. A decrease in the number of beneficial microorganisms, and an increase in pathogenic bacteria (a condition known as dysbiosis), in the ICU, may promote the onset of worsening of intestinal sepsis. Although oral probiotics prevent nosocomial infections, the underlying mechanisms remain to be explored.^[20] Overall, whether probiotics are beneficial for severely ill patients still requires clinical validation.

Next-generation sequencing

With the rapid development of next-generation sequencing technology, the throughput of genome sequencing has increased, while the sequencing time and costs continue to decrease. Due to the close relationship between intestinal microorganisms and the physiological functions of the human body such as nutrition, immunity, metabolism, research of intestinal microbial genomics has good application prospects in host physiology, disease pathology, drug pharmacology, and etc.^[21] Marker genes have recently been used in clinical practice to better understand the structure and function of the microbiota, and the relationship between the microbiome and disease.^[22] The 16S ribosomal RNA gene is commonly used as a marker of microbial diversity. The highly variable regions within this gene can be amplified and sequenced. Currently, high-throughput sequencing involves polymerase chain reaction amplification of the target region of the genome after amplifying the DNA of the target region. Then, the sequence is compared against a database to identify the species, followed by biological information analysis.^[23]

Muhawang *et al*^[24] acquired fecal samples from 20 healthy adults in Taiyuan, China. DNA was extracted and a 16S rRNA gene clone library was prepared. The high-throughput sequencing and bioinformatics analyses demonstrated that the intestinal microflora of healthy adults is complex, but relatively stable. Nycz *et al*^[25] analyzed 16S rRNA gene sequences to determine the bacteria present in patients' feces. The analysis revealed that the gut microbiota was not only related to cancer types and the response to chemotherapy, but could also be used to predict subsequent bloodstream infections. Lankelma *et al*^[21] compared the fecal bacterial compositions of critically ill septic and non-septic patients with those of controls. The results showed that bacterial diversity was significantly decreased in half of the patients compared with the controls. However, microbial diversity, the thick-walled bacteria/bacteroides ratio, and the Gram-positive/Gram-negative bacteria ratio were not associated with complications or survival. Further study is needed to understand the effect of major changes in intestinal bacterial communities on short- and long-term health.

Determination of organic acid concentrations

Carboxylic acids are produced through anaerobic fermentation of carbohydrates, fats, and proteins, particularly short-chain fatty acids (SCFAs; e.g., formate, acetate, propionate, and butyrate), which play an important role in anaerobic digestion.

One study showed that acetic acid improves sepsis-induced AKI by lowering the ratio of serum creatinine to blood urea nitrogen and renal myeloperoxidase activity to lipid peroxide, as well as by restoring the tubular structure. Moreover, administration of acetate was associated with an oxidative-antioxidant imbalance in the T cells of patients with AKI. During AKI, acetic acid inhibits the activity of nicotinamide adenine dinucleotide phosphate oxidase 2 and reactive oxygen species, by inhibiting histone deacetylase activity in T cells.^[26] These data imply that acetate may be able to induce T cells to restore the oxidative-antioxidant balance in patients with sepsis-induced AKI.

Weng *et al*^[27] reported that propionate is an independent predictor of sepsis (odds ratio [OR]: 1.279; 95% confidence interval [CI]: 1.069–1.530; $P = 0.007$), ICU mortality (OR: 1.331; 95% CI: 1.107–1.600; $P = 0.002$), 28-day mortality (OR: 1.259; 95% CI: 1.046–1.514; $P = 0.015$), and 90-day mortality (OR: 1.304; 95% CI: 1.092–1.558; $P = 0.003$). Thus, propionate can be useful to diagnose and predict the prognosis of septic shock.

Wang *et al*^[28] evaluated the utility of SCFAs in terms of survival rate in an LPS-induced septic model. They found that butyrate (but not acetate or propionate) significantly reduced the mortality rate of infected mice. Further studies found that butyrate reduced the inflammatory response induced by sepsis by upregulating the anti-inflammatory cytokine interleukin-10. Ty *et al*^[29] showed that carboxylic acid is an evolutionary precursor of amino acids that regulates cell proliferation and apoptosis. Preparation containing butyrate and propionate can be used to study

the mechanisms of action of probiotic strains and metabolomics, and could aid in the development of innovative drugs.

Hecker *et al*^[30] reported that SCFAs and medium-chain fatty acids (MCFAs) increase the mitochondrial respiration capacity under baseline and inflammatory conditions, without influencing the mitochondrial DNA content or production of proinflammatory cytokines. Thus, they concluded that SCFAs and MCFAs are a suitable and safe energy source under inflammatory conditions, and have the ability to partially restore mitochondrial respiration. The influx of urea and other residual toxins affects the gut microbiota in patients with CKD, resulting in a decrease in the number of beneficial bacteria producing SCFAs and an increase in the number of bacteria producing uremic toxins (e.g., barium sulfate, armor phenol sulfate, and trimethylamine-n-oxide), which further aggravates intestinal wall inflammation and degradation of tight junctions between cells, and also accelerates the release of intestinal uremic toxins into the blood.^[31]

Fecal microbiota transplantation (FMT)

Gaines *et al*^[32] found that the intestinal microbiota varied among experimental mice, and was associated with phenotypes of peritoneal sepsis in a bacterial inoculation model (intraperitoneal injection of feces). Wide variation in bacterial composition among the animals was revealed by fecal analysis, and the differences in clinical phenotype disappeared by 16 months after the injections. Wei *et al*^[33] showed that multiple organ dysfunction syndrome (MODS) and severe diarrhea were resolved in two male patients following FMT, and their defecation volume and body temperature also either decreased significantly or were restored to normal. These outcomes were in accordance with significant changes in the bacterial profiles of the patients; a significant increase in the symbiosis of Firmicutes and a decrease in the opportunistic microbial population of Proteobacteria were observed. In addition, a recombinant bacterial community rich in Firmicutes was found; however, it lacked Proteobacteria, which was associated with decreased fecal excretion and plasma inflammatory markers. In both patients, repairing the intestinal flora barrier not only reduced infection but also regulated the immune response. These findings lay the foundation for further research on FMT as a new treatment for microbial-related diseases, including MODS.

Analysis of volatile organic compounds (VOCs) in feces

Fecal VOCs reflect the composition and activity of intestinal microbial communities. Berkhout *et al*^[34] hypothesized that VOCs could serve as non-invasive biomarkers of late-onset sepsis (LOS) at the pre-clinical stage in septic patients. Notably, VOC spectral analysis is clinically feasible, but the utility of this technique for early detection of LOS needs to be confirmed in future studies.

Discussion and Prospects

Lankelma *et al*^[35] determined that although broad-spectrum antibiotics may disrupt the intestinal flora, the

innate immune response in healthy individuals during endotoxemia is not affected. Metabolites produced by the intestinal microflora, especially SCFAs, are proven to improve kidney diseases by reducing inflammatory response, antioxidant, anti-fibrosis; regulating blood pressure and metabolism; and enhancing immune function.^[36] However, the effects of different types of SCFAs on kidney physiology are controversial. New research^[37] suggests that intestinal floral disorders can exacerbate non-intestinal infectious diseases through the loss of bacterial and intestinal bacterial diversity and an increase in the number of virulent bacteria. According to the existing information, regulating the microbiome is a necessary part of CKD management. The combination of a low-protein diet with probiotic and symbiotic supplements is promising for controlling disease progression and comorbidities, although validation in large clinical trials is needed.

Powerful metagenomic and metatranscriptome analysis techniques have provided new insight into microbial communities. However, the mechanisms underlying the association of microorganisms with the health and disease states of the host remain unknown. High-throughput sequencing technology and correlation analyses of different flora revealed a correlation between intestinal flora and septic renal injury, thus providing a rationale for interventions targeting the intestinal flora. Probiotics and FMT can be effective for improving the intestinal microbiota of patients with septic renal injury and CKD, but interventions have mainly been limited to probiotics targeting certain microbial groups. However, knowledge is expanding rapidly, and microbial treatments based on SCFAs, for example, may eventually be included in strategies for preventing systemic infection. Nevertheless, clinical data supporting the use of FMT are currently lacking. The microbiome may play an important role in the perioperative period and the ICU environment, but existing data to support this are mostly descriptive. Better understanding of the imbalance in intestinal flora in patients with renal diseases will facilitate the development of new therapeutic strategies to prevent or reduce these diseases and their complications.

Funding

This work was supported by a grant from the Scientific Research Program of the Health Industry, Gansu Province, China (No. GSWSKY-2014-32).

Conflicts of interest

None.

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How to cite this article: Yuan JJ, Chang XN, Li M, Yuan QX, Yang XL. Clinical utility of characterizing intestinal flora in septic kidney injury. *Chin Med J* 2020;133:842–846. doi: 10.1097/CM9.0000000000000724