·标准与指南·

代谢相关脂肪性肝病患者微生态治疗指南

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【摘要】 本指南针对代谢相关脂肪性肝病(MAFLD)的微生态治疗提出规范建议。指南系统阐述了"肠-肝轴"紊乱在MAFLD发病机制中的核心作用,并明确了肠道微生态失衡的诊断方法。重点推荐了益生菌、益生元、合生元、后生元等多种微生态制剂的应用,并详细规范了粪菌移植的供体筛选、制剂制备、适应证、操作流程、随访监测及疗效评估标准。本指南旨在为临床医师应用微生态疗法治疗MAFLD提供基于循证医学的决策依据,以改善患者管理并确保治疗安全有效。

【关键词】 代谢相关脂肪性肝病; 微生态; 肠肝轴; 粪菌移植; 诊断; 治疗; 管理; 指南
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Guidelines for microecological therapy in patients with metabolic associated fatty liver disease

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【Abstract】 These guidelines present standardized recommendations for the microecological therapy of metabolic dysfunction-associated fatty liver disease (MAFLD). The core role of gut-liver axis dysfunction in the pathogenesis of MAFLD is systematically elaborated, and the diagnostic methods for intestinal microecological imbalance are clearly defined herein. The application of various microecological preparations, including probiotics, prebiotics, synbiotics and postbiotics, is emphatically recommended, and the donor screening, product preparation, indications, operation procedures, follow-up monitoring and efficacy evaluation criteria for fecal microbiota transplantation are standardized in detail. The authors formulated these guidelines to provide evidence-based decision-making references for clinicians applying microecological therapy for MAFLD, with the aim of optimizing patient management and ensuring the safety and efficacy of treatment.

【Key words】 Metabolic associated fatty liver disease; Microbiome; Gut-liver axis; Fecal microbiota transplantation; Diagnosis; Therapeutic; Management; Guideline

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Metabolic dysfunction-associated fatty liver disease (MAFLD) is a chronic progressive disease caused by excessive lipid deposition in the liver[1], with a global prevalence exceeding 30%. In a subset of patients, the disease can progress to steatohepatitis, liver cirrhosis, and even hepatocellular carcinoma, imposing a substantial socioeconomic burden[2]. Studies have shown that gut-liver axis dysfunction is the core link in the progression of MAFLD. However, the interactive mechanisms between inflammation and immunity remain poorly elucidated, and there are still key bottlenecks including difficulties in early warning and a lack of effective therapeutic drugs and strategies.

Recent studies have found that intestinal microbiota dysbiosis not only impairs the intestinal mechanical and biological barriers, but also alters the immunochemical barrier, thereby accelerating the progression of MAFLD[3]. Following microbiota dysbiosis, the levels of key metabolites including tryptophan, fatty acids, and secondary bile acids are significantly decreased, while the levels of branched-chain amino acids are elevated. Once the intestinal barrier is damaged, endotoxin and other microbial products can enter the liver through the portal vein to activate pattern recognition receptors, which in turn drive the inflammatory cascade of innate immune cells including macrophages, dendritic cells, and natural killer cells[4]. This lays a theoretical foundation for intestinal microecological therapy for MAFLD. At present, considerable progress has been made in mechanistic and clinical research on microecological regulation as a therapeutic strategy for MAFLD. However, there is still a lack of unified standards for key links including the specific strain selection, dosage range, administration route, and efficacy evaluation of probiotics.

To promote the standardized application of microecological therapy in the clinical practice of MAFLD, improve the therapeutic effect and ensure patient safety, these guidelines were jointly developed under the leadership of the Professional Committee of Hepatology (Integrated Traditional Chinese and Western Medicine) of the Chinese Research Hospital Association, in conjunction with experts in related fields. A systematic literature search was conducted in databases including China National Knowledge Infrastructure, VIP Database, Wanfang Data, China Science and Technology Paper Online, PubMed, and ScienceDirect from October 2015 to October 2025, with the keywords of non-alcoholic fatty liver disease (NAFLD), MAFLD, metabolic dysfunction-associated fatty liver disease, fecal microbiota transplantation (FMT), intestinal microbiota transplantation, gut microbiota transplantation, intestinal microecology, and microecological preparations. A total of 81 articles were finally included as references after screening and evaluation. These guidelines strictly follow the PICO principle, take clinical problems as the core and evidence-based evidence as the foundation, and focus on clarifying the applicable population and clinical value of microecological therapy for MAFLD. These guidelines were compiled by a multidisciplinary expert panel in the fields of hepatology, microecology, evidence-based medicine and other related areas. After multiple rounds of review and discussion, the final recommendations for divergent viewpoints were formed through collective voting.

These guidelines are intended to provide clinical references for clinicians applying microecological therapy in the intervention of MAFLD, and do not serve as mandatory specifications. Given the continuous development of this field, these guidelines cannot cover all clinical issues. In actual clinical practice, clinicians should develop individualized treatment plans based on the patient's specific conditions, personal will, and available medical resources, as well as the current best available evidence, professional experience, and indications. In these guidelines, the quality of evidence is classified into three levels: high (A), moderate (B), and

low (C), and the strength of recommendation is divided into two grades: strong recommendation and weak recommendation, as shown in Table 1.

Ⅰ. Gut-liver axis dysfunction and the pathogenesis of MAFLD

The development of MAFLD is associated with multiple factors including dysregulation of lipid metabolism, oxidative stress, insulin resistance, inflammatory response, and intestinal microbiota dysbiosis. The intestinal microecosystem is a complex ecosystem composed of trillions of microorganisms (including bacteria, fungi, viruses, etc.) in the human intestinal tract, which is closely related to human health[5]. Studies have shown that intestinal microbiota dysbiosis is prevalent in patients with MAFLD[6,7]. This imbalance impairs the integrity of the intestinal barrier, allowing harmful microbial products such as endotoxin to pass through the "leaky" gut and reach the liver via the portal vein, where they activate immune cells and trigger inflammatory responses[8]. Conversely, alterations in liver function can also affect the composition of the microbiota and the intestinal environment, thus forming a vicious circle that promotes the progression of MAFLD[9]. Therefore, the intestinal microecosystem has become a key participant in the occurrence and development of MAFLD, as well as a highly promising novel therapeutic target.

The intestinal barrier is the key line of defense that blocks harmful substances in the intestinal tract from entering the systemic circulation, which functions through the synergistic effect of the mechanical, chemical, biological, immune, and vascular barriers[10]. The mechanical barrier is mainly composed of tight junctions between intestinal epithelial cells. Endotoxin produced by microbiota dysbiosis can lead to downregulated expression or structural damage of tight junction proteins, allowing toxins originally confined to the intestinal lumen to cross the intestinal epithelium, enter the portal venous system, and directly damage the liver[11]. The chemical barrier refers to secreted chemical substances including mucus, bile, glycoproteins, mucopolysaccharides, digestive enzymes, and lysozyme, which can destroy antigens in food and resist the invasion of microorganisms into the blood circulation[12]. The intestinal mucus layer contains antimicrobial peptides that prevent bacteria from entering the portal vein. Downregulated expression of antimicrobial peptides in mice with metabolic-associated steatohepatitis can lead to intestinal lipopolysaccharide translocation, liver inflammation, and fibrosis[13]. In addition, bile acids negatively regulate the expression of sterol regulatory element-binding protein 1c by activating the farnesoid X receptor [14], and reduce the expression of lipogenesis-related genes, thereby inhibiting the occurrence of MAFLD[15]. The biological barrier refers to the normal commensal microbial community in the intestinal tract, and its metabolites are closely related to the pathogenesis and progression of MAFLD. For

Table 1 Strength of recommendation and level of evidence for recommendation statements

Grade	Description
Quality of evidence	
High quality (A)	Evidence is derived from at least one well-designed multicenter randomized controlled trial, further research is unlikely to alter the current assessment results.
Moderate quality (B)	Evidence is derived from at least one well-designed non-randomized clinical trial, cohort study, or case-control study; further research may affect the current assessment results.
Low quality (C)	Evidence is derived from clinical experience, descriptive case studies, reports of expert committees, and opinions from authoritative professional organizations; further research is very likely to alter the current assessment results.
Strength of recommendation	
Strong recommendation	The quality of evidence, potential therapeutic efficacy and prognosis are fully considered, with a favorable cost-benefit ratio, and clinical application is strongly recommended.
Weak recommendation	The value of evidence is uneven, there is uncertainty in the recommendation statement, or the cost-benefit ratio of the recommendation is not favorable, and a conservative attitude towards the recommendation is adopted.

example, butyrate inhibits the development of MAFLD by upregulating the expression of intestinal tight junction proteins[16]. Endogenous ethanol produced by yeasts and certain bacteria in the intestinal microbiota (such as Escherichia coli, Staphylococcus aureus, and Klebsiella pneumoniae) can induce severe liver injury, inflammation, and fibrosis in mice, thereby accelerating the progression of MAFLD[17]. The immune barrier is composed of secretory immunoglobulin A (sIgA) secreted by lymphocytes and plasma cells[10]. Since sIgA has a specific inhibitory effect on Gram-negative bacteria in the intestinal tract, the function of sIgA is significantly inhibited when the intestinal mucosa is damaged, which in turn promotes bacterial translocation in the intestinal tract, stimulates the production of inflammatory factors such as tumor necrosis factor-α and interleukin-6, and accelerates the progression of MAFLD[18]. The vascular barrier mainly refers to the capillary network of the intestinal tract and the liver sinusoidal endothelium. Damage to the intestinal vascular barrier can lead to translocation of bacteria or bacterial products into the blood circulation, triggering an inflammatory cascade and causing liver injury[19]. In summary, MAFLD is the result of the combined dysfunction of the intestinal mechanical, chemical, biological, immune, and vascular barriers, against the background of dysregulated lipid metabolism, insulin resistance, oxidative stress, inflammatory response, and intestinal microbiota dysbiosis.

Ⅱ. Diagnosis of MAFLD and intestinal microecological imbalance

(Ⅰ) Diagnosis of MAFLD

The diagnosis of MAFLD is based on the following 3 criteria: (1) Fatty liver diagnosed by imaging or vibration-controlled transient elastography (VCTE), and(or) ≥5% macrovesicular steatosis of hepatocytes identified by liver biopsy; (2) Presence of one or more components of metabolic syndrome; (3) Exclusion of other causes that may lead to fatty liver, including excessive alcohol consumption, malnutrition, and Wilson's disease[20].

Recommendation 1: Vibration-controlled transient elastography can be used as the preferred method for the diagnosis of MAFLD, while liver biopsy remains the first recommended criterion for the most accurate diagnosis. (Level of evidence: A; Strength of recommendation: Strong)

(Ⅱ) Diagnosis of intestinal microecological imbalance

The diagnosis of intestinal microecological imbalance can refer to the following indicators[21]: (1) Abnormal cocci/bacilli ratio on fecal microscopy (normal reference value for adults is 1∶3); (2) The logarithmic ratio of DNA copy numbers of Enterobacteriaceae to Bifidobacterium (B/E value)＜1 detected by quantitative polymerase chain reaction; (3) Fecal smear or culture indicates a significant increase or predominance of abnormal flora; (4) Assays such as fecal bacterial fingerprinting indicate alterations in microbiota structure; (5) Abnormal results of metagenomic sequencing analysis. Medical institutions with available technical conditions shall give priority to precise techniques such as fecal bacterial fingerprinting or metagenomic sequencing as the diagnostic basis.

Recommendation 2: For the diagnosis of intestinal microbiota dysbiosis in patients with MAFLD, appropriate methods shall be selected in combination with the own conditions and technical feasibility of the medical institution. At present, metagenomic sequencing is regarded as the preferred detection method due to its advantage of multi-target analysis. (Level of evidence: A; Strength of recommendation: Strong)

Ⅲ. Treatment of MAFLD

(Ⅰ) General treatment

The treatment of MAFLD requires multidisciplinary collaboration. Patients should establish a healthy lifestyle, control caloric intake, and maintain balanced nutrition. Body weight reduction is a critical measure to improve metabolic disorders and liver injury. For patients complicated with obesity, type 2 diabetes mellitus, dyslipidemia, hypertension, or cardiovascular

disease, standardized treatment shall be administered by specialist physicians or general practitioners.

(Ⅱ) Pharmacological treatment

For the treatment of T2DM, hypoglycemic agents with weight loss effects shall be preferentially selected, such as glucagon-like peptide-1 receptor agonists, sodium-glucose co-transporter 2 inhibitors, or metformin. For patients with concomitant hyperlipidemia, statins are the first choice for pharmacological treatment. For patients with concomitant hypertension, angiotensin-converting enzyme inhibitors or angiotensin Ⅱ receptor blockers are the first-line medications, and non-selective β-blockers can be combined in patients with significant portal hypertension. For MAFLD patients with a body mass index (BMI) ≥28 kg/m^2, anti-obesity medications can be used, and bariatric surgery may be considered if the surgical indications for weight loss are met[20].

(Ⅲ) Microecological preparation therapy

At present, a variety of microecological preparations (including probiotics, prebiotics, synbiotics, postbiotics, etc.) have been widely used in clinical practice and have shown favorable therapeutic effects. Engineered probiotic products with targeted colonization function are under development, which are expected to become an important tool for personalized medicine.

1. Probiotics: Refer to live microorganisms that confer a health benefit on the host when administered in adequate amounts, with the effect of reconstructing the intestinal microecology. They have a favorable therapeutic effect on MAFLD patients with mild to moderate intestinal microecological dysbiosis. Currently, Bifidobacterium and Lactobacillus are the most commonly used strains in clinical practice[22].

A meta-analysis of 9 randomized controlled trials conducted by Li et al.[23] showed that Lactobacillus plantarum significantly reduced patients' BMI, along with improvements in abdominal fat and inflammatory markers (such as interleukin-6 and high-sensitivity C-reactive protein). A randomized controlled trial completed by Bai et al.[24] indicated that Bifidobacterium breve BBr60 can safely and effectively regulate BMI, body weight, blood glucose, blood lipids, and liver function parameters, and its mechanism of action may be related to the effect of BBr60 on key intestinal flora.

In the in-depth research on probiotics in the treatment of MAFLD, it has been found that the effect of single strains has certain limitations. A study by Kwon et al.[25] showed that patients in the multi-strain combination treatment group (containing Lactobacillus paracasei BEPC22 and Lactobacillus plantarum BELP53) had significant reductions in body weight, BMI, body fat percentage, and body fat mass compared with the placebo group, while the abundance of Akkermansia was significantly higher than that in the placebo group (all $P<0.05$). A study by AlMalki et al.[26] found that after 12 weeks of treatment with a preparation containing 3 Lactobacillus species and 3 Bifidobacterium species (HEXBIO group), energy intake, body weight, waist circumference, fasting blood glucose, and low-density lipoprotein levels in overweight subjects were significantly improved compared with the control group (all $P<0.05$).

To ensure that probiotic preparations achieve the expected therapeutic effect, the following key points shall be noted in clinical application: First, the administration time has a significant impact on the viability of probiotics. It is recommended to administer them with meals or within 30 to 60 minutes after meals to improve the efficiency of viable bacteria colonization in the intestinal tract. Second, as live bacterial preparations, probiotics should not be used in combination with antibacterial agents in principle to avoid potential interactions. If combination therapy is indeed necessary, increasing the dose of probiotics or adjusting the administration interval can be considered, and an interval of more than 2 hours is usually recommended[27-28].

Recommendation 3: Probiotics treat MAFLD by regulating intestinal microbiota dysbiosis, and multi-strain probiotic preparations have better therapeutic efficacy than single-strain preparations. (Level of evidence: A; Strength of recommendation: Strong) The administration time and method of probiotics can affect the safety and efficacy of probiotics in the treatment of obesity. (Level of evidence: A; Strength of recommendation: Strong)

2. Prebiotics: Refer to a class of organic substances that are neither digested nor absorbed by the host, and can selectively promote the metabolic activity and proliferation of beneficial bacteria in the body, thereby improving the host's health[29]. At present, prebiotics with high-level evidence and widespread recognition almost all belong to carbohydrate polymers, including inulin, galactooligosaccharides (GOS), fructooligosaccharides, and oat β-glucan.

Among numerous prebiotics, inulin-type fructans (ITF) have long been the focus of research, with a regulatory effect on obesity and metabolic disorders[30]. Metabolites produced during ITF fermentation include short-chain fatty acids, propionic acid and butyric acid, which may help regulate appetite and insulin secretion. A study by Hiel et al.[31] found that healthy adults consuming vegetables rich in ITF had enhanced satiety, along with positive changes in the composition and function of the intestinal microbiota. The results of a randomized, single-blind, multicenter, placebo-controlled trial conducted in 150 overweight patients showed that consumption of vegetables rich in natural inulin can reduce energy intake and body weight in overweight populations, with a significant increase in the number of Bifidobacterium[32].

In addition to ITF, GOS also have a weight loss effect. A study by Kong et al.[33] found that GOS can effectively slow down body weight gain in rats with diet-induced obesity without altering energy intake. GOS significantly inhibited the hypertrophy and hyperplasia of white adipose tissue, and markedly reduced the fat-to-body weight ratio. Consistently, GOS significantly improved the levels of serum triglycerides, total cholesterol, and low-density lipoprotein cholesterol. Notably, GOS significantly upregulated the expression levels of browning-related proteins in both WAT and brown adipose tissue, including uncoupling protein 1, PPARγ, and PPARγ coactivator 1α. Chappuis et al.[34] concluded that GOS can improve blood lipid levels and prevent the occurrence of NAFLD through mechanisms independent of body weight management and blood glucose regulation.

It has been reported that conjugated linoleic acid and xylo-oligosaccharides (XOS) have potential therapeutic effects on obesity and diabetes. A meta-analysis showed that CLA combined with exercise intervention can reduce body fat percentage, improve insulin resistance and blood lipid levels[35]. Another study found that XOS can regulate the composition of intestinal microbiota in mice fed a high-fat diet, increase the abundance of beneficial bacteria, alleviate metabolic abnormalities and cognitive dysfunction, and ameliorate the imbalance of lipid composition in the hippocampus[36].

As an emerging dietary supplement, prebiotics have multiple benefits for human health. However, the existing clinical trial data are still insufficient, and further randomized controlled trials targeting the target population are needed to clarify the metabolic health effects of specific prebiotics on patients with MAFLD.

3. Synbiotics: Refer to the compound preparations of prebiotics and probiotics, which combine the biological functions of probiotics and the metabolic regulatory effects of prebiotics, and can synergistically enhance immunity and improve intestinal health.

Synbiotics regulate the composition of the intestinal microbiota, which can significantly reduce body weight, waist circumference, BMI, body fat percentage, and high-sensitivity C-reactive protein levels, while improving high-density lipoprotein cholesterol levels and enhancing the quality of life related to gastrointestinal health[29]. Bifidobacterium animalis subsp. lactis GCL2505 is a probiotic strain isolated from the feces of healthy adults. A 12-week randomized, double-blind, placebo-controlled, parallel-group comparative trial conducted in Japan showed that compared with the placebo group, the visceral fat area in the GCL2505 group was significantly reduced from baseline at week 8 and week 12, with a significant increase in the total number of Bifidobacterium in feces[37]. Compared with the intake of GCL2505 alone, the intake of GCL2505

combined with inulin in overweight people can effectively reduce abdominal fat accumulation and increase the abundance of intestinal Bifidobacterium[38]. Shi et al.[39] developed a novel synbiotic composed of Lactobacillus plantarum LLY-606 and GOS, which can significantly reduce human visceral fat and waist circumference, alleviate obesity in mice, while improving the structure of intestinal microbiota and increasing serum arginine levels.

The synbiotic composed of Lactobacillus paracasei K56 and GOS or XOS can significantly increase the relative abundance of Lactobacillus, Bifidobacterium, Enterococcus faecalis and Cyanobacteria in the fecal microbiota of overweight individuals, and reduce the abundance of Shigella and Escherichia. These changes are associated with reduced levels of carbon dioxide, methane and hydrogen sulfide, as well as increased concentration of short-chain fatty acids (SCFAs)[40]. Large-scale independent studies have shown that synbiotics prepared with specific strains (such as Lactobacillus gasseri) as dietary supplements have weight loss and anti-inflammatory activities. When combined with galactomannan and (or) inulin fiber, they can enhance the effect of body weight management by synergistically promoting the production of SCFAs and microbiota remodeling[41]. The synbiotic composed of Akkermansia muciniphila and the antioxidant quercetin can improve the pathological process of early-stage obesity and non-alcoholic fatty liver disease by regulating bile acid metabolism and intestinal microbiota. Its mechanisms include promoting bile acid synthesis, enhancing bile acid flux in the enterohepatic circulation, inhibiting hepatic inflammatory state, and regulating adipogenesis and lipid storage in white adipose tissue[42]. This study elaborated a novel mechanism of Akkermansia muciniphila in improving MAFLD, and suggested that the combination of Akkermansia muciniphila and quercetin can be used as a feasible strategy for MAFLD management. The synbiotic MN-Gup-GOS-XOS, composed of Bifidobacterium animalis subsp. lactis MN-Gup, GOS and XOS, can effectively reduce body fat percentage, waist circumference and serum low-density lipoprotein cholesterol levels in obese patients, promote the proliferation of beneficial bacteria, and increase the content of chenodeoxycholic acid, a bile acid substance[43].

Recommendation 4: Synbiotics can treat MAFLD by reshaping the intestinal microbiota through synergistic or complementary effects. (Level of evidence: B; Strength of recommendation: Weak)

Postbiotics: Refer to inactivated probiotics and their metabolites that confer health benefits on the host[44]. A growing number of studies have shown that postbiotics have a significant therapeutic effect on MAFLD, and have gradually become a new focus of research on MAFLD treatment. A study by Plovier et al.[45] found that the protein Amuc_1100 isolated from the outer membrane of Akkermansia muciniphila can interact with Toll-like receptor 2, and significantly improve intestinal barrier function and obesity in mice fed a high-fat diet. In particular, this protein remains stable even at the temperature used for pasteurization. The heat-inactivated form of Bifidobacterium animalis subsp. lactis CECT 8145 (h-k Ba8145) can reduce visceral fat content in individuals with abdominal obesity. Intestinal microbiome analysis showed a significant increase in the abundance of Akkermansia[46]. Targeted delivery of propionate to the colon of obese individuals leads to reduced body weight, decreased intrahepatic lipid content, and improved distribution of intra-abdominal adipose tissue[47]. A study by Zhao et al.[48] found that a combination of postbiotics and prebiotics can promote fecal lipid excretion and effectively ameliorate high-fat diet-induced obesity in mice. The above research results elaborate the potential value of postbiotics in the treatment of obesity, but the specific molecular mechanism of its anti-obesity effect remains to be further studied in depth[49].

Recommendation 5: Postbiotics can be used in the treatment of MAFLD. (Level of evidence: C; Strength of recommendation: Weak)

Recommendation 6: There are numerous types of probiotics, prebiotics, synbiotics and postbiotics, and the clinical use of these preparations shall comply with the specification instructions of each category. (Level of evidence: A; Strength of recommendation: Strong)

(Ⅳ) FMT therapy

FMT is a treatment method that transplants the normal microbiota from the feces of healthy donors into the intestinal tract of patients to reconstruct the imbalanced intestinal microbiota ecosystem, thereby treating intestinal diseases and related extraintestinal diseases[50]. This technology has a significant therapeutic effect on liver cirrhosis and its complications caused by MAFLD. FMT technology covers multiple key links including donor screening and management, preparation of microbiota preparations, assessment of indications and contraindications, selection of transplantation routes, operating procedures, treatment course setting, monitoring and management of adverse reactions, and efficacy evaluation criteria.

1.Donor screening and management: (1) Screening of standard donors: Both related and unrelated donors can be used for microbiota transplantation in patients with MAFLD, but donor conditions must be strictly evaluated, with screening focused on 6 dimensions including physiological status, psychological status, personal and family history, stability, sustainability, and tolerance[51]. The assessment of physiological status is mainly completed through physical examination and laboratory tests, requiring donors aged 18 to 30 years old, with a BMI of 18.5 to 23.9 kg/m^2, and normal results in physical examination, routine blood test, blood biochemical test, and pathogenic indicators. The assessment of psychological status adopts interviews and standardized scales, including the Self-Rating Anxiety Scale, Self-Rating Depression Scale, and Pittsburgh Sleep Quality Index, with all results within the normal range. Personal and family history is obtained through systematic medical history inquiry, and the following conditions must be met: no gastrointestinal discomfort in the past 2 weeks; no use of acid suppressants, antibiotics, or immunosuppressants in the past 3 months; no history of gastrointestinal surgery, acute or chronic infectious diseases, adverse reactions, autoimmune diseases, metabolic diseases, or malignant tumors; no bad habits such as smoking and alcohol consumption; no vaccination, participation in drug trials, or travel to epidemic areas in the past 6 months; no relevant family history, and not in menstrual period or pregnancy. Donor stability is verified by biochemical tests and fecal microbiota sequencing every 2 months. Donors must commit to continuous donation, with specific requirements of at least 2 donations per week, and each fecal sample no less than 50 g. It is recommended to ensure the sustainability of donation by establishing personal files and regular follow-up. Donors shall restrict the intake of intolerance foods (such as dairy products, egg products, etc.) 7 days before transplantation, and undergo food tolerance screening; those with food intolerance shall not participate in this donation. (2) Donor management ① Managed by dedicated personnel, and informed consent form must be signed at the time of enrollment; ② Health questionnaire must be filled out before each donation, and regular physical re-examination shall be conducted every 8 to 12 weeks; ③ Establish personal files and maintain follow-up for donors, timely adjust their lifestyle and diet, and exclude them if necessary; ④ The recommended donation frequency is at least 2 times a week, with no less than 50 g of feces per donation. If the fecal volume is too low, attention should be paid to their gastrointestinal function.

Recommendation 7: When selecting donors, healthy adults aged＜30 years old (optimal 18 to 24 years old) with a BMI of 18.5 to 23.9 kg/m^2 shall be preferentially selected. (Level of evidence: A; Strength of recommendation: Strong)

Recommendation 8: Donor screening criteria shall be established through strict questionnaires, interviews, blood and fecal tests from 6 dimensions including physiology, psychology, personal and family history, sustainability, stability, and tolerance. (Level of evidence: A; Strength of recommendation: Strong)

Recommendation 9: Appropriate management shall be implemented for donors to maintain their stability and sustainability of donation, including regular health re-examination and retention testing of fecal samples. (Level of evidence: A; Strength of recommendation: Strong)

Recommendation 10: Donors shall donate feces regularly, maintain a healthy diet, avoid high-fat, high-protein and irritating foods, and encourage food diversity and moderate exercise at the same time. (Level of evidence: B; Strength of recommendation: Weak)

2. Preparation of microbiota preparations: Microbiota preparations include two types, including fecal bacterial suspensions and fecal microbiota capsules. Despite different dosage forms, they share the same core principle, which is to reconstruct the intestinal microecological balance through transplantation of healthy microbiota[52]. The preparation of fecal bacterial suspension covers key steps including feces collection, bacterial suspension separation, and quality control. Feces collection shall use a dedicated sterile container to collect samples on site, with simultaneous registration of donor information and completion of identification, weighing, and preliminary evaluation, while maintaining anaerobic conditions throughout the process. The prepared bacterial suspension shall be preserved at −80 ℃, with a general shelf life of 6 months. It shall be thawed in a 37 ℃ water bath before use, and the administration shall be completed within 6 hours after thawing[53]. At present, the microfiltration washing method based on an automatic purification system is widely used in clinical practice to prepare bacterial suspension. This method helps reduce FMT-related adverse events, enables quantitative enrichment of microbiota, and maintains the therapeutic effect at the same time[54]. Regarding the optimal feces collection volume, there are differences among different guidelines: the UK guideline recommends 50 g[55], and the European guideline recommends 30 g[56]. Studies have shown that a sample volume less than 50 g may reduce the therapeutic efficacy and increase the risk of recurrence[55]. Domestic experience indicates that a collection volume of no less than 120 g helps ensure the required bacterial count[57]. For bacterial suspension separation, the collected fecal sample is loaded into an automatic purification system with the pipeline connected, and isotonic saline is added at a ratio of 1∶5 to prepare the suspension. After multiple rounds of centrifugation (3 000 to 5 000 r/min, centrifugation radius 10 to 15 cm, 3 min per round), the supernatant is discarded, and washing is repeated 3 times to obtain purified microbiota. In the quality control link, non-contact optical quantitative method is adopted after washing, with 10 mL (approximately 1.0×10^{13} bacteria) as 1 basic unit (U). The bacterial suspension is prepared at a ratio of 2 mL isotonic saline per 1 U of microbiota, which is used for immediate administration, freeze-drying, or low-temperature storage. For cryopreservation, sterile glycerol is added to the bacterial suspension to prepare a bacterial solution containing 10% glycerol, which is stored protected from light[58,59]. The shelf life of the bacterial suspension is 6 months at −80 ℃, and up to 10 years in liquid nitrogen[60]. The final product shall undergo aerobic and anaerobic bacterial testing to ensure the viable bacterial count and safety[61].

Recommendation 11: The volume of feces collected for FMT shall be no less than 50 g, and a collection volume ≥ 120 g can ensure sufficient bacterial count obtained at one time. (Level of evidence: A; Strength of recommendation: Strong)

Recommendation 12: It is recommended to use an automatic purification system combined with a microfilter to prepare washed microbiota. (Level of evidence: B; Strength of recommendation: Weak)

Recommendation 13: The therapeutic efficacy of FMT using fecal microbiota prepared from fresh feces is comparable to that using fecal microbiota prepared from frozen feces. (Level of evidence: A; Strength of recommendation: Strong)

Recommendation 14: Donor fecal samples shall be preserved for at least 2 years for safety evidence traceability, and donor screening data and laboratory records shall be preserved for at least 10 years. (Level of evidence: C; Strength of recommendation: Weak)

To overcome the limitations of traditional FMT technology in the preparation and application of bacterial suspension, as well as to simplify the operation and reduce patient discomfort, fecal microbiota capsule transplantation has been developed. This technique is suitable for patients without dysphagia and has the advantages of convenient administration, easy popularization, good tolerability and high safety[62]. Studies have shown that the efficacy of oral fecal microbiota capsules in the prevention of recurrent infections is comparable to that of transplantation via colonoscopy[63]. The preparation of fecal microbiota capsules includes the following steps. (1) Preparation of lyophilized microbiota: Dissolve the intestinal bacteria protectant in sterile isotonic saline, add the washed microbiota, mix well, perform freeze-drying, and store under frozen conditions for no more than 3 months. (2) Capsule preparation: Dispense the lyophilized bacterial powder into capsules, seal the packages, and store at 4 ℃, with a shelf life of no more than 6 months. (3) Quality control: The requirements are consistent with the preparation standards of fecal bacterial suspension.

3. Indications and contraindications of FMT: (1) Indications: Multiple randomized controlled trials have shown that FMT has the potential to improve some metabolic and liver disease indicators in patients with MAFLD, with favorable safety[64,65]. For MAFLD patients with obvious intestinal microecological dysbiosis, FMT intervention may be cautiously explored in clinical research or a strictly standardized medical setting on the premise of fully informed consent and compliance with ethical norms. (2) Contraindications: There are definite contraindications for microbiota transplantation therapy: ① Severe immunodeficiency, such as neutrophil count $<1.5\times10^9$/L or lymphocyte count $<0.5\times10^9$/L; ② Active intestinal injury, including patients with acute fulminant colitis, severe mucosal damage, toxic megacolon, intestinal obstruction, or those receiving enteral nutrition; ③ Severe systemic infection, such as patients with systemic inflammatory response syndrome or extraintestinal organ infection who must receive broad-spectrum antibiotics; ④ Significant nutritional and metabolic disorders, such as BMI <15 kg/m^2, serum albumin level <25 g/L, or fecal and urinary incontinence; ⑤ Recent use of immunosuppressants or cytotoxic drugs, such as treatment with doxorubicin or rituximab, or medium-to-high dose glucocorticoids equivalent to more than 20 mg prednisone per day for more than 4 consecutive weeks; ⑥ During pregnancy or lactation.

Recommendation 15: FMT treatment is recommended for MAFLD patients with intestinal microecological dysbiosis on the basis of weight control and pharmacological treatment. (Level of evidence: A; Strength of recommendation: Strong)

Recommendation 16: The contraindications of FMT include patients with unstable vital signs, severe intestinal injury, severe immunosuppression and pregnant women. (Level of evidence: A; Strength of recommendation: Strong)

4. Routes of FMT: FMT is classified into fecal bacterial suspension transplantation and fecal microbiota capsule transplantation according to the form of microbiota preparations, and the clinical administration route should be selected based on the individual conditions of patients[63]. The administration routes of FMT are mainly divided into upper and lower gastrointestinal tract routes. Upper gastrointestinal administration can be infused via gastroscopy, nasogastric tube, nasojejunal tube, or gastrostomy tube; lower gastrointestinal administration often adopts methods such as colonoscopy, sigmoidoscopy, or retention enema. When clinical conditions permit, transcolonic infusion of the bacterial suspension into the right hemicolon is preferentially recommended. The efficacy rate reported for this route can reach 94.8%, which is superior to the upper gastrointestinal route of administration[66], and its safety is comparable to that of other routes[56]. In contrast, the success rate of single anal enema is usually lower than that of colonoscopy[67], but it is easy to operate and repeated administration helps to improve the therapeutic effect[68].

Recommendation 17: For patients with contraindications to lower gastrointestinal administration due to intestinal obstruction or severe intestinal inflammation, the upper gastrointestinal route can be selected for FMT. (Level of evidence: A; Strength of recommendation: Strong)

Recommendation 18: When administering via the upper gastrointestinal route, the volume of fecal bacterial suspension is recommended to be controlled within 100 mL and no less than 50 mL at minimum. (Level of evidence: A; Strength of recommendation: Strong)

Recommendation 19: For patients with dysphagia, the upper gastrointestinal route for FMT should be avoided. (Level of evidence: A; Strength of recommendation: Strong)

5. Procedures of microbiota transplantation: (1) Preoperative preparation for fecal bacterial suspension transplantation assisted by colonoscopy: ① Informed consent: Explain the operational purpose, expected benefits and potential risks to patients in detail, clarify the preparation process of fecal microbiota, and obtain written informed consent. ② Equipment and supplies preparation: Prepare a colonoscope, dedicated sheath for transendoscopic enteral tubing (TET), 4 to 6 titanium clips, 8 to 10 mL medical liquid paraffin, 3 pieces of disposable dry gauze and 1 piece of "sandwich" dressing. ③ Patient pretreatment: It is recommended to discontinue broad-spectrum antibiotics at least 24 h before FMT[69]. Bowel preparation is performed by oral polyethylene glycol or enema. For intolerant patients, residue-free diet, oral lactulose or fractional enemas can be used 1 to 2 d before operation[70]. Bowel lavage may cause vomiting or aspiration, and should be used cautiously in patients at high risk of aspiration, such as those with dysphagia, intestinal obstruction or long-term bed rest[71]. Painless endoscopy is recommended; non-anesthetic operation can also be considered if intestinal lesions are mild.

(2) Operational procedures of fecal bacterial suspension transplantation assisted by colonoscopy: ① Lubrication and catheterization: Inject 4 to 5 mL of liquid paraffin into the TET extension tube, fully lubricate the guidewire, and insert it completely into the extension tube. ② Colon evaluation: Complete the colon examination and position the endoscope at the ileocecal junction or ascending colon[72]. ③ Biopsy channel lubrication: Inject 3 to 5 mL of liquid paraffin through the biopsy channel to ensure smooth movement of the dedicated sheath for TET within the channel. ④ The dedicated sheath for TET insertion: Advance the TET tube through the biopsy channel to the ileocecal junction; the assistant helps fix the anal canal segment during withdrawal of the endoscope. ⑤ Endoscopic fixation: Reinsert the endoscope to the ileocecal junction, and fix the fixation suture to the intestinal wall with titanium clips (2 clips for the first site, additional clips as appropriate). ⑥ Position adjustment: Withdraw the endoscope slowly and fine-tune the dedicated sheath for TET at the anal end to expose the optimal fixation suture loop. ⑦ Guidewire removal: Expose the guidewire after withdrawing the endoscope, hold the dedicated

sheath for TET gently, and pull out the guidewire slowly. ⑧ External fixation: Connect the one-way valve, fix the dedicated sheath for TET to the perianal skin with adhesive tape (about 2 cm from the anus), and fix the distal end to the ipsilateral buttock without excessive tightness. ⑨ Bacterial suspension infusion: Instruct the patient to lie in the right lateral position, and slowly infuse an appropriate volume of bacterial suspension at a suitable temperature via the dedicated sheath for TET (recommended dose 50 to 150 mL, viable bacteria count$\geqslant 2.5\times10^{12}$ U, flow rate 25 to 50 mL/min). After infusion, maintain the 10 ° Trendelenburg right lateral position for at least 30 min, then turn to the supine position[73]. For repeated infusion, the dedicated sheath for TET can be left to fall off spontaneously; the tube can be removed by applying gentle force slowly. The whole process from preparation to infusion of the bacterial suspension shall be controlled within 2 h. (3) Fecal microbiota capsule transplantation Lyophilized fecal microbiota capsules can be stored at room temperature[74,75]. It has been reported that the efficacy of lyophilized fecal microbiota capsules in the treatment of Clostridioides difficile infection is 78% to 96%[63,76], which is comparable to single FMT via colonoscopy[63]. The capsule formulation can be used without physician assistance, which is more convenient and helps reduce medical costs. No serious adverse reactions have been observed so far. Patients shall take the capsules orally twice daily on an empty stomach for 7 consecutive days. Capsules shall be taken out of the frozen state 2 h before administration and used after rewarming at room temperature.

Recommendation 20: It is recommended that patients discontinue antibiotics at least 24 h before FMT. (Level of evidence: A; Strength of recommendation: Strong)

Recommendation 21: It is recommended to perform FMT assisted by painless colonoscopy is preferred. (Level of evidence: B; Strength of recommendation: Weak)

Recommendation 22: Routine bowel preparation shall be performed at least 24 h before FMT, with oral polyethylene glycol combined with a residue-free or low-residue diet. (Level of evidence: A; Strength of recommendation: Strong)

Recommendation 23: The fold-clamping method is strongly recommended to enhance fixation stability. Oblique clamping of titanium clips on the intestinal wall shall be avoided as much as possible, and the fixation area shall be kept away from regions with severe erosion, ulceration or pseudopolyps. (Level of evidence: A; Strength of recommendation: Strong)

Recommendation 24: FMT via the lower gastrointestinal tract is more effective and associated with a lower overall risk than the upper gastrointestinal route. (Level of evidence: A; Strength of recommendation: Strong)

Recommendation 25: It is recommended to infuse the bacterial suspension into the right colon near the ileocecal region via colonoscopy. (Level of evidence: A; Strength of recommendation: Strong)

Recommendation 26: Shortening the interval from feces collection to infusion helps maintain microbiota viability. (Level of evidence: C; Strength of recommendation: Weak)

Recommendation 27: To reduce the risk of aspiration, oral administration of lyophilized fecal microbiota capsules is not recommended for patients at significant risk of reflux. (Level of evidence: A; Strength of recommendation: Weak)

6. Treatment course and cycle of FMT: At present, experts both at home and abroad recommend that the treatment course and cycle of FMT for MAFLD should be individually adjusted according to the patient's response, and multiple transplantations are superior to single transplantation. According to expert opinions and clinical practical experience, it is

recommended to perform FMT for 3 consecutive days per month, once a day, and stable efficacy can be achieved after 3 consecutive months. Maintenance treatment with fecal microbiota capsules can be suspended if there is no improvement. When severe reactions such as fever, severe abdominal pain or severe diarrhea occur, transplantation should be paused or terminated immediately and appropriate management should be provided. When the patient's body temperature exceeds 39 ℃, enterogenic infection should be alerted. Pathogen screening should be carried out immediately, including fecal pathogen detection and blood culture of both donors and recipients, and supportive measures such as anti-infective treatment and fluid replacement should be initiated at the same time. In the event of a life-threatening clinical condition, FMT must be stopped immediately and prompt emergency intervention should be initiated.

Recommendation 28: The treatment course and cycle of FMT should be individually adjusted according to the patient's response. It is recommended for 3 consecutive days per month, once a day, and 3 consecutive months as one treatment course. (Level of evidence: C; Strength of recommendation: Weak)

Recommendation 29: For patients who cannot or are unwilling to receive colonoscopy-assisted FMT, oral lyophilized microbiota capsules can be used instead, 3 times a day, 6 capsules each time, for a total of 2 weeks. (Level of evidence: C; Strength of recommendation: Weak)

Recommendation 30: It is recommended to add one additional standard treatment course on the original basis if any of the following conditions is met: (1) Presence of comorbidities or long-term medications that may significantly interfere with the activity of intestinal microbiota; (2) One additional standard treatment course for every 5-year extension of the disease course; (3) Age ≥ 65 years. (Level of evidence: C; Strength of recommendation: Weak)

Recommendation 31: Patients should be closely monitored for adverse reactions after FMT, including changes of gastrointestinal symptoms, body temperature and vital signs. Timely intervention should be given in case of moderate to severe symptoms. (Level of evidence: C; Strength of recommendation: Weak)

7. Adverse reactions of FMT and their management: After FMT, patients should be closely monitored for adverse reactions, including gastrointestinal symptoms, body temperature, blood pressure, pulse and respiratory rate. Common adverse reactions are mainly limited to the gastrointestinal tract, such as nausea, abdominal pain, abdominal distension or diarrhea. Most symptoms are mild and can resolve spontaneously. The establishment of a standardized adverse event reporting mechanism is recommended. For mild reactions (such as dizziness, slight gastrointestinal discomfort, etc.), close observation is the main approach; if moderate symptoms occur, symptomatic and supportive treatment should be given, and FMT should be

8. Monitoring of FMT: (1) Routine indicator testing includes clinical manifestations, inflammatory markers, immune and biochemical indicators, intestinal barrier function, microbiota analysis, and nutritional absorption assessment. ① Clinical observation: Vital signs and abdominal symptoms (such as abdominal distension, abdominal pain, diarrhea) of patients should be continuously recorded, with attention to defecation frequency, consistency and intestinal peristalsis. If fever occurs (body temperature>38.5 ℃), blood culture should be performed in time, and antibacterial drugs should be selected according to clinical experience and test results. ② Inflammatory markers: Dynamic monitoring of indicators such as C-reactive protein and interleukins helps reflect changes in intestinal inflammatory status and therapeutic response. ③ Intestinal barrier and microbiota status: Intestinal barrier function is evaluated by serum levels of diamine oxidase, D-lactic acid and endotoxin. Meanwhile, the transplantation effect is comprehensively evaluated combined with analysis of microbiota composition and

diversity. ④ Nutritional absorption indicators: BMI, arm muscle circumference, calf circumference, serum albumin, hemoglobin, transferrin and nitrogen balance are monitored to evaluate the recovery of intestinal absorption function. ⑤ Biochemical indicators: Blood glucose, blood lipids, liver and kidney function, and coagulation function are regularly tested to assess systemic metabolic changes. ⑥ Immune-related indicators: The number and activity of immune cells are monitored to evaluate the impact of FMT on host immune regulation. (2) Detection of fecal Bifidobacterium/Enterobacteriaceae ratio (B/E ratio)[77], This ratio can be used as a reference indicator of intestinal microbial colonization resistance. A B/E ratio>1 indicates favorable colonization resistance; a B/E ratio ≤1 indicates decreased colonization resistance. (3) Follow-up and adverse event monitoring, The first follow-up is recommended 3 to 7 days after treatment, focusing on the evaluation of symptom relief and short-term adverse events[78]. The second follow-up is performed around the 4th week to further evaluate the durability of efficacy and recurrence risk[79-81]. There is no unified standard for the long-term follow-up period, which should be individually formulated according to the individual disease progression and safety requirements to accumulate long-term safety data.

9. Efficacy criteria of microecological preparations: The efficacy evaluation of microecological preparations in the treatment of MAFLD should be comprehensively judged based on multi-dimensional indicators. Although there is no global unified "gold standard", domestic and international research and clinical practice mainly conduct evaluation from the following aspects: patient symptoms and signs, liver biochemical indicators, microbial metabolic indicators, controlled attenuation parameter value, liver/spleen density ratio on plain CT scan, magnetic resonance proton density fat fraction, intestinal microbiota structure and liver histological changes. This evaluation system covers three-dimensional evaluation dimensions from micro (microbiota, metabolites) to macro (tissue, imaging, biochemistry, symptoms). In the field of diagnosis, treatment and research of MAFLD, non-invasive quantitative measurement of liver fat content and improvement of metabolic indicators are the most widely used efficacy evaluation criteria in clinical practice and research; while liver biopsy is still an irreplaceable "gold standard" in confirmatory research.

Recommendation 32: The efficacy of microecological preparations in the treatment of MAFLD should be comprehensively evaluated. Non-invasive quantitative measurement of liver fat content and improvement of metabolic indicators are the most widely used efficacy criteria in clinical practice and research. (Level of evidence: A; Strength of recommendation: Strong)

Recommendation 33: All patients receiving FMT should undergo standardized follow-up to evaluate efficacy, recurrence and potential adverse events. (Level of evidence: A; Strength of recommendation: Strong)

Recommendation 34: One week after transplantation is a critical window for observing clinical efficacy and short-term adverse events. (Level of evidence: B; Strength of recommendation: Strong)

Recommendation 35: It is recommended to systematically evaluate the main efficacy indicators at least 4 weeks after transplantation. (Level of evidence: B; Strength of recommendation: Strong)

Ⅳ. Outlook

The technology of microecological preparations in the treatment of MAFLD is developing rapidly. To clarify the optimal dosage, treatment frequency and long-term effect of intestinal microecological preparations and FMT in the treatment of MAFLD, multi-center, large-sample, randomized double-blind placebo-controlled clinical studies still need to be carried out in the future. At the same time, a number of new preparation technologies are emerging, such as artificial intelligence-assisted personalized microbiota transplantation, targeted colonization of microbiota, nanomaterial encapsulation, engineered bacteria preparation and liquid 3D printed capsules, which are expected to further improve the therapeutic effect of FMT.

代谢相关脂肪性肝病(metabolic associated fatty liver disease,MAFLD)是一种由肝脏脂质过量沉积引发的慢性进展性疾病[1],发病率超过30%,部分患者可进展为脂肪性肝炎、肝硬化甚至肝细胞癌,造成重大社会负担[2]。研究表明,"肠-肝轴"功能失调是MAFLD进展的核心环节,但其炎症与免疫之间相互作用机制尚不明确,且存在早期预警困难、有效治疗药物及方法匮乏等关键瓶颈问题。

近年研究发现,肠道菌群紊乱不仅削弱肠道机械与生物屏障,还会改变免疫化学屏障,从而加速MAFLD的进展[3]。菌群失衡后,色氨酸、脂肪酸及次级胆汁酸等关键代谢产物水平显著下降,而支链氨基酸水平则升高。肠道屏障一旦受损时,内毒素及其他微生物产物可通过门静脉进入肝脏,以激活模式识别受体,进而驱动巨噬细胞、树突状细胞和自然杀伤细胞等天然免疫细胞的炎症级联反应[4]。这为肠道微生态治疗MAFLD奠定了理论基础。目前,微生态调控作为MAFLD的治疗策略,其机制与临床研究已获得较多进展,但目前对于益生菌的具体选择、剂量范围、给药路径及效果评估等关键环节,仍缺乏统一标准。

为促进微生态疗法在MAFLD临床实践中的规范化应用,提升治疗效果并保障患者安全,由中国研究型医院学会肝病(中西医结合)专业委员会牵头,联合相关领域专家共同制定了本指南。以非酒精性脂肪性肝病(non-alcoholic fatty liver disease,NAFLD)、MAFLD或代谢功能障碍相关脂肪性肝病与粪菌移植(fecal microbiota transplantation,FMT)、肠菌移植、肠道微生物移植、肠道微生态、微生态制剂为关键词,系统检索中国知网、维普资讯、万方数据、中国科技论文在线及PubMed、ScienceDirect等数据库在2015年10月—2025年10月发表的相关文献,经筛选、评估后,最终采纳81篇作为参考文献。指南严格遵循PICO原则,以临床问题为核心、循证证据为基础,重点明确了微生态疗法应用于MAFLD的适用人群与临床价值。本指南由肝病学、微生态学及循证医学等多领域专家共同编订,经多次审议与讨论,针对存在分歧的观点通过集体表决形成最终推荐意见。

本指南旨在为临床医师应用微生态疗法干预MAFLD提供临床参考,不作为强制性规范。鉴于该领域仍在不断发展,本指南无法涵盖所有临床问题。在实际诊疗中,医师应结合患者具体情况、个人意愿及可用医疗资源,并依据现有最佳证据、专业经验与适应证,制定个体化方案。文中证据质量按高(A)、中(B)、低(C)三级划分,推荐强度分为强推荐与弱推荐两级,见表1。

一、肠-肝轴紊乱与MAFLD的发病机制

MAFLD的形成与脂质代谢失衡、氧化应激、胰岛素抵抗、炎症反应及肠道菌群失调等因素相关。肠道微生态是人体肠道内由数万亿微生物(包括细菌、真菌、病毒等)构成的复杂生态系统,与人体健康密切相关[5]。研究表明,MAFLD患者普遍存在肠道菌群失调[6,7],这种失衡会削弱肠道屏障完整性,使内毒素等有害微生物产物通过"泄漏"的肠道经门静脉到达肝脏后激活免疫细胞,引发炎症[8]。反之,肝脏功能的改变也会影响菌群形成和肠道环境,从而形成恶性循环,促使MAFLD进展[9]。因此,肠道微生态已成为MAFLD发生、发展的关键参与者,也是极具潜力的治疗新靶点。

肠道屏障是隔绝肠道内有害物质进入全身循环的关键防线,通过机械、化学、生物、免疫及血管屏障的协同作用实现[10]。机械屏障主要由肠上皮细胞间的紧密连接构成。菌群失调产生的内毒素可导致紧密连接蛋白表达下调或结构破坏,使得原本被限制在肠腔内的毒素得以穿过肠上皮,进入门静脉系统,直接攻击肝脏[11]。化学屏障指分泌的黏液、胆汁、糖蛋白、黏多糖、消化酶、溶菌酶等化学物质,可破坏食物中的抗原,抵御微生物侵入血液循环[12]。肠壁黏液层含抗菌肽,可阻止细菌进入门静脉。而代谢相关脂肪性肝炎小鼠的抗菌肽表达下

表1　推荐意见的推荐强度和证据等级

分级	说明
证据质量	
高质量(A)	证据来源于至少一项设计合理的多中心随机对照试验,后续研究对当前评估结果改变的可能性较小
中质量(B)	证据来源于至少一项设计良好的非随机临床试验、队列研究或病例对照研究,后续研究有可能影响当前的评估结果
低质量(C)	证据来源于临床经验、描述性案例研究、专家委员会的报告、权威组织机构意见,后续研究很有可能改变当前的评估结果
推荐强度	
强推荐	充分考虑证据质量、潜在疗效及预后,具有较高的成本-获益比,强烈支持推荐使用
弱推荐	证据价值参差不齐,推荐意见存在不确定性,或推荐意见成本-获益比不高,对推荐意见持保守态度

调,会导致肠道内毒素易位、肝脏炎症和纤维化[13]。此外,胆汁酸通过激活法尼醇X受体[14],负向调节固醇调节元件结合蛋白1c的表达,降低脂肪相关基因的表达,从而减少MAFLD的发生[15]。生物屏障指肠道内正常的共生微生物群落,其产生的代谢物与MAFLD的发病机制和进展密切相关,如丁酸通过增加肠道紧密连接蛋白抑制MAFLD发展[16]。肠道菌群中的酵母和某些细菌(如大肠杆菌、金黄色葡萄球菌和肺炎克雷伯菌)产生的内源性乙醇可诱发小鼠严重肝损伤、炎症、纤维化,从而加速MAFLD[17]。免疫屏障由淋巴细胞和浆细胞分泌的免疫球蛋白A(secretory immunoglobulin A, sIgA)组成[10]。由于sIgA对肠道内的革兰氏阴性菌有特殊抑制作用,当肠黏膜受损时,sIgA功能明显受到抑制,从而促进肠道内细菌移位,刺激肿瘤坏死因子-α、白细胞介素-6等炎症因子的产生,加快MAFLD的进展[18]。血管屏障主要指肠道的毛细血管网和肝脏的肝窦内皮。肠血管屏障损伤会导致细菌或细菌产物易位进入血液循环,引发炎症级联反应,损伤肝脏[19]。总之,MAFLD是在脂质代谢紊乱、胰岛素抵抗、氧化应激与炎症反应及肠道菌群失衡的背景下,肠道机械、化学、生物、免疫及血管屏障综合作用的结果。

二、MAFLD诊断与肠道微生态失衡诊断

(一)MAFLD诊断

诊断MAFLD基于以下3个标准:(1)影像或振动控制瞬时弹性成像诊断脂肪肝和(或)肝活检发现≥5%肝细胞大泡性脂肪变性;(2)存在1项及以上代谢综合征组分;(3)排除过量饮酒、营养不良、肝豆状核变性等可能导致脂肪肝的其他原因[20]。

推荐意见1:振动控制瞬时弹性成像诊断技术可以作为诊断MAFLD的首选方法,最精确的诊断标准仍首推肝活检。(证据等级:A;推荐强度:强)

(二)肠道微生态失衡诊断

肠道微生态失衡的诊断可参考以下指标[21]:(1)粪便镜检球杆菌比例异常(成人正常参考值为1∶3);(2)定量PCR检测显示肠杆菌与双歧杆菌DNA拷贝数的对数比(B/E值)<1;(3)粪便涂片或培养提示非正常菌群显著增多或占主导;(4)粪便细菌指纹图谱等检测提示菌群结构改变;(5)宏基因组测序分析结果异常。有条件的医疗机构应优先采用粪便指纹图谱或宏基因测序等精准技术作为诊断依据。

推荐意见2:在诊断MAFLD患者的肠道菌群失调时,应结合医疗机构自身条件与技术可行性选用适当方法。当前,宏基因测序因其多靶点分析优势,已被视为优先选择的检测手段。(证据等级:A;推荐强度:强)

三、MAFLD的治疗

(一)一般治疗

MAFLD的治疗需多学科协作,患者应建立健康生活方式,控制热量摄入,保持营养均衡。减轻体重是改善代谢紊乱和肝损伤的重要措施,对于合并肥胖、2型糖尿病、血脂紊乱、高血压或心血管病的患者,应由专科医师或全科医师进行规范治疗。

(二)药物治疗

治疗2型糖尿病时,应优先选择具有减重作用的降糖药物,如胰高血糖素样肽-1受体激动剂、钠-葡萄糖协同转运蛋白2抑制剂或二甲双胍等;伴有高血脂时,药物治疗首选他汀类药物;伴有高血压时,用药首选血管紧张素转化酶抑制剂或血管紧张素Ⅱ受体阻滞剂,合并显著门静脉高压时可联用非选择性β受体阻滞剂;对于BMI≥28 kg/m^{2}的MAFLD患者,可应用减重药物,符合减重手术指征可考虑减重手术治疗[20]。

(三)微生态制剂治疗

目前,多种微生态制剂(如益生菌、益生元、合生元、后生元等)已在临床广泛应用,并显示出良好效果。具有靶向定植功能的工程化益生菌产品正在研发中,有望成为个性化医疗的重要工具。

1.益生菌:是指对宿主健康有益的活微生物,具有重建肠道微生态的作用。对存在肠道微生态轻度、中度紊乱的MAFLD患者具有较好治疗作用。目前临床应用以双歧杆菌和乳杆菌为主[22]。

Li等[23]对9项随机对照试验的荟萃分析显示,植物乳杆菌可显著减轻患者BMI,同时观察到腹部脂肪及炎症标志物(如白细胞介素-6和高敏C反应蛋白)的改善。Bai等[24]完成的随机对照试验表明,短双歧杆菌BBr60能够安全有效地调节BMI、体重、血糖、血脂及肝功能指标,其作用机制可能与BBr60对关键肠道菌群的影响有关。

在深入研究益生菌治疗MAFLD的过程中,发

现单一菌株的作用存在一定局限性。Kwon 等[25]研究显示,多菌株组合治疗组(含副干酪乳杆菌 BEPC22 和植物乳杆菌 BELP53)患者体重、BMI、体脂百分比及体脂肪量较安慰剂组显著下降,而阿克曼菌属丰度较安慰剂组显著升高(P 均<0.05)。AlMalki 等[26]研究发现,超重受试者接受含 3 种乳杆菌属和 3 种双歧杆菌属(HEXBIO 组)治疗 12 周后,其能量摄入量、体重、腰围、空腹血糖和低密度脂蛋白水平较对照组明显提高(P 均<0.05)。

为确保益生菌制剂达到预期效果,临床应用时需注意以下关键点:首先,服药时间对益生菌活性有显著影响,建议随餐或餐后 30～60 min 内使用,以提高活菌定植肠道的效率;其次,益生菌作为活菌制剂,原则上不宜与抗菌药物联用,以免发生相互作用。若确需联合用药,可考虑增加益生菌剂量或调整给药时间,通常建议间隔 2 h 以上[27, 28]。

推荐意见 3:益生菌通过调节肠道菌群失衡治疗 MAFLD,多菌株益生菌制剂疗效优于单一菌株制剂(证据等级:A;推荐强度:强)。益生菌的使用时间与方法可影响其治疗肥胖症的安全性和有效性。(证据等级:A;推荐强度:强)

2. 益生元:是一类有机物质,既不会被宿主消化吸收,又能选择性地促进体内有益菌的代谢活动与增殖生长,进而改善宿主的健康[29]。目前证据等级较高且公认的益生元几乎均属于碳水化合物聚合物,包括菊粉、低聚半乳糖(galactooligosaccharide, GOS)、低聚果糖和燕麦 β-葡聚糖等。

在众多益生元中,菊粉型果聚糖(inulin-type fructan, ITF)一直是研究焦点,其对肥胖和代谢紊乱具有调节作用[30]。ITF 发酵过程中产生的代谢物包括短链脂肪酸、丙酸和丁酸,可能有助于调节食欲和胰岛素分泌。Hiel 等[31]研究发现,食用富含 ITF 蔬菜的健康成年人饱腹感增强,同时肠道菌群组成与功能发生积极转变。一项在 150 例超重患者中开展的随机、单盲、多中心、安慰剂对照试验结果表明,食用富含天然菊粉的蔬菜可使超重人群摄入减少、体重减轻,且双歧杆菌的数量显著增多[32]。

除 ITF 外,GOS 亦具有减重作用。Kong 等[33]研究发现,GOS 在不改变能量摄入的情况下,可有效减缓饮食诱导肥胖大鼠的体重增加。GOS 显著抑制了白色脂肪组织的肥大与增生,并明显降低了脂肪/体重比值。与之相符的是,GOS 显著改善了血清甘油三酯、总胆固醇和低密度脂蛋白胆固醇水平。值得注意的是,GOS 在白色和棕色脂肪组织中均显著提高了褐变相关蛋白的表达水平,包括解偶联蛋白 1、过氧化物酶体增殖物激活受体 γ 和 PPARγ 辅激活因子 1α。Chappuis 等[34]认为,GOS 可通过独立于体重管理和血糖调控的机制改善血脂水平,并预防 NAFLD 的发生。

据报道,共轭亚油酸和低聚木糖(xylo-oligosaccharide, XOS)对肥胖和糖尿病具有潜在治疗作用。一项荟萃分析显示,共轭亚油酸联合运动干预可降低体脂率、改善胰岛素抵抗及血脂水平[35]。另一项研究发现,XOS 可调节高脂饮食小鼠的肠道菌群组成,增加有益菌丰度,缓解代谢异常和认知功能障碍,改善海马体中的脂质组成失衡[36]。

益生元作为新兴膳食补充剂,对人体健康具有多方面益处,但现有临床试验数据尚不充分,需进一步开展针对目标人群的随机对照试验研究,以明确特定益生元对 MAFLD 患者的代谢健康效应。

3. 合生元:是益生元和益生菌的复合制剂,兼具益生菌的生物功能与益生元的代谢调节作用,可协同增强免疫力并改善肠道健康。

合生元调节肠道菌群组成,可显著降低体重、腰围、BMI、体脂率、高敏 C 反应蛋白水平,同时改善高密度脂蛋白胆固醇,并提高胃肠道健康相关生活质量[29]。动物双歧杆菌乳酸亚种 GCL2505 是从健康成人粪便中分离的益生菌菌株,日本一项为期 12 周的随机双盲、安慰剂对照、平行组比较试验显示,与安慰剂组相比,GCL2505 组在第 8 周和第 12 周时内脏脂肪面积较基线显著降低,粪便中双歧杆菌总数显著增加[37]。与单独摄入 GCL2505 相比,超重人群摄入 GCL2505 联合菊粉可有效减少腹部脂肪堆积,增加肠道双歧杆菌丰度[38]。Shi 等[39]开发了一种由植物乳杆菌 LLY-606 和 GOS 组成的新型合生元,可显著降低人体内脏脂肪及腰围,减轻小鼠肥胖程度,同时改善肠道菌群结构并提升血清精氨酸水平。

副干酪乳杆菌 K56 与 GOS 或 XOS 组成的合生元,可显著提高超重个体粪便微生物群中乳杆菌属、双歧杆菌属、粪肠球菌和蓝藻菌的相对丰度,并降低志贺菌与埃希菌丰度,这些变化与二氧化碳、甲烷及硫化氢水平降低及短链脂肪酸浓度增加有关[40]。大型独立研究表明,采用特定菌株(如加氏

乳杆菌)制备的合生元作为膳食补充剂,具有减重和抗炎活性,其与半乳甘露聚糖和(或)菊粉纤维联合使用时,可通过协同作用促进短链脂肪酸生成及微生物群"重组",增强体重管理效果[41]。嗜黏蛋白阿克曼菌和抗氧化剂槲皮素构成的合生元,可通过调节胆汁酸代谢和肠道菌群,改善早期肥胖和NAFLD的病理进程,其机制包括促进胆汁酸合成、增强肠-肝循环中胆汁酸通量、抑制肝脏炎症状态、调节白色脂肪组织生成和储存[42]。该研究阐述了嗜黏蛋白阿克曼菌改善MAFLD的新机制,认为嗜黏蛋白阿克曼菌与槲皮素联合使用可作为MAFLD管理的可行策略。由动物双歧杆菌乳酸亚种MN-Gup、GOS和XOS构成的合生元MN- Gup-GOS-XOS,可有效降低肥胖患者体脂率、腰围和血清低密度脂蛋白胆固醇水平,促进有益菌群增殖,并增加胆酸类物质鹅去氧胆酸含量[43]。

推荐意见4:合生元可通过协同或互补作用重塑肠道微生物群以治疗MAFLD。(证据等级:B;推荐强度:弱)

4.后生元:是指经过灭活处理的益生菌及其代谢产物,对宿主健康有益[44]。越来越多的研究表明,后生元对MAFLD具有显著治疗作用,逐渐成为MAFLD治疗研究的新焦点。Plovier等[45]研究发现,从黏液嗜酸杆菌外膜分离的蛋白Amuc_1100可与Toll样受体2相互作用,显著改善肠道屏障功能和高脂饮食小鼠的肥胖,尤其该蛋白经巴氏杀菌温度仍保持稳定。动物双歧杆菌乳酸亚种CECT 8145的热灭活形式(h-k Ba8145)可减轻腹型肥胖者的内脏脂肪含量。肠道微生物组分析显示,阿克曼菌属显著增加[46]。将丙酸盐靶向输送至肥胖者结肠,其体重减轻、肝内脂质含量减少,腹腔内脂肪组织分布好转[47]。Zhao等[48]研究发现,后生元和益生元的组合物可促进粪便脂质排泄,有效改善高脂饮食诱导的小鼠肥胖。上述研究结果阐述了后生元在肥胖症治疗中的潜在价值,但其治疗肥胖症的具体分子机制有待进一步深入研究[49]。

推荐意见5:后生元可用于治疗MAFLD。(证据等级:C;推荐强度:弱)

推荐意见6:益生菌、益生元、合生元及后生元品类较多,应遵循不同品类的说明书使用。(证据等级:A;推荐强度:强)

(四)FMT治疗

FMT是一种通过将健康供体粪便中的正常菌群移植至患者肠道内,以重建其失衡的肠道菌群生态,进而治疗肠道疾病及相关肠外疾病的方法[50]。该技术对MAFLD导致的肝硬化及其并发症具有显著疗效。FMT技术涵盖供体筛选与管理、菌群制剂制备、适应证与禁忌证评估、移植途径选择、操作步骤、疗程设定、不良反应监测与处理以及疗效评价标准等多个关键环节。

1.供体的筛选与管理:(1)标准供体的筛选,亲属或非亲属供体均可用于MAFLD患者菌群移植,但需严格评估供体条件,重点从生理状态、心理状态、个人及家族史、稳定性、持续性及耐受性等6个维度进行筛选[51]。生理状态评估主要通过体格检查及实验室检测完成,要求供体年龄18~30岁,BMI 18.5~23.9 kg/m^2,且体格检查、血常规、血生化及病原学指标均正常;心理状态评估采用访谈与标准化量表(包括焦虑自评量表、抑郁自评量表及匹兹堡睡眠质量量表),结果均正常。个人及家族史通过系统病史询问获取,需满足以下条件:近2周无胃肠不适;近3个月未使用抑酸剂、抗生素或免疫抑制剂;无消化道手术史、急慢性传染病、不良反应、自身免疫性疾病、代谢性疾病及恶性肿瘤史;无吸烟、饮酒等不良习惯;近6个月未接种疫苗、未参加药物试验或前往疫区;无相关家族病史,非经期及孕期。供体稳定性通过每2个月1次的生物化学检测及粪菌测序验证。供体需承诺持续捐赠,具体要求为每周至少捐赠2次,每次粪便量不低于50 g。建议通过建立个人档案及定期随访确保捐赠持续性。供体需在移植前7 d限制摄入不耐受的食品(如乳制品、蛋类等),并进行食物耐受性筛查,若存在不耐受则不得参与本次捐赠。(2)供体管理,①由专人负责管理,入选时须签署知情同意书;②每次捐献前需填写健康问卷,并定期(每8~12周)复查体检;③为供体建立个人档案并保持随访,及时调整其生活方式与饮食,必要时予以剔除;④捐献频率建议每周至少2次,每次不少于50 g,若粪便量过少需关注其胃肠功能。

推荐意见7:选择供体时,应优先选择年龄<30岁(最佳为18~24岁),BMI 18.5~23.9 kg/m^{2}的健康成年人。(证据等级:A;推荐强度:强)

推荐意见8:应从生理、心理、个人及家族史、持续性、稳定性及耐受性6个维度,通过严格问卷、访谈及血液、粪便检查等方式建立供体筛选标准。(证据等级:A;推荐强度:强)

推荐意见9:供体应进行适当管理以维持其稳定性和持续性,包括定期健康复查及粪便样本留存检测。(证据等级:A;推荐强度:强)

推荐意见10:供体应定期捐赠粪便,并保持健康饮食,避免高脂、高蛋白及刺激性食品,同时鼓励食物多样化和适量运动。(证据等级:B;推荐强度:弱)

2.菌群制剂的制备:菌群制剂包括粪菌悬液和粪菌胶囊两种类型,其剂型不同但核心原理一致,均通过移植健康菌群重建肠道微生态平衡[52]。粪菌悬液的制备包括粪便采集、菌液分离和质量控制等关键步骤。粪便采集需使用专用无菌容器现场收取样本,同步登记供体信息并完成鉴定、称重与初步评估,全程维持厌氧条件。菌液制备后于-80 ℃保存,保存期一般为6个月,使用前需经37 ℃水浴解冻,解冻后6 h内需完成使用[53]。当前临床多采用基于自动纯化系统的微过滤洗涤方法制备菌液,该方法有助于减少FMT相关不良事件,并可实现定量菌群富集,同时保持治疗效果[54]。关于粪便最佳采集量,不同指南存在差异:英国指南建议50 g[55],欧洲指南推荐30 g[56]。研究显示,若样本量低于50 g,可能降低疗效并增加复发风险[55]。国内经验表明,采集量不低于120 g有助于保障所需菌量[57]。菌液分离时,将采集的粪便样本装入自动纯化系统,连接管路,按1∶5比例加入等渗盐水制备悬液,经多次离心(3 000～5 000 r/min,离心半径10～15 cm,3 min/次)后弃去上清,重复洗涤3次以获取纯净菌群。质量控制环节,洗涤后采用非接触式光学定量法,以10 mL(约1.0×10^{13}个细菌)为1个基本计量单位(U),按1 U菌群加入2 mL等渗盐水的比例制备菌悬液,用于即时使用、冷冻干燥或低温保存。冻存时,在菌悬液中加入无菌甘油,配制成含10%甘油的菌液,避光保存[58,59]。菌液在-80 ℃下保存期限为6个月,液氮中可达10年[60]。最终产物需经需氧菌与厌氧菌检测,以保证活菌数量及安全性[61]。

推荐意见11:FMT供体粪便采集量应不少于50 g,若采集量≥120 g,可确保一次性获得充足菌量。(证据等级:A;推荐强度:强)

推荐意见12:建议采用自动纯化系统联合微过滤器制备洗涤菌群。(证据等级:B;推荐强度:弱)

推荐意见13:采用新鲜粪便制备的粪菌进行FMT,其疗效与采用冷冻粪便制备的粪菌相当。(证据等级:A;推荐强度:强)

推荐意见14:供体粪便样本至少保存2年以备安全证据溯源,供体筛选资料及实验室记录应至少保存10年。(证据等级:C;推荐强度:弱)

为克服传统FMT技术在菌液制备与应用环节的局限性,并简化操作、减轻患者不适,粪菌胶囊移植技术应运而生。该技术适用于无吞咽障碍患者,具有使用便捷、易于推广、耐受性好且安全性高等优势[62]。研究显示,口服粪菌胶囊在预防复发性感染方面的疗效与经结肠镜移植相当[63]。粪菌胶囊制备包括以下步骤。(1)配制冻干菌群:将肠菌保护剂溶于无菌等渗盐水中,加入洗涤后的菌群,混匀后进行冷冻干燥,并于冷冻条件下保存不超过3个月。(2)胶囊制备:将冻干菌粉分装入胶囊,密封包装后置于4 ℃冷藏,保质期在6个月以内。(3)质量控制:要求与粪菌悬液制备标准一致。

3.FMT的适应证与禁忌证:(1)适应证,多项随机对照试验表明,FMT在MAFLD患者中具有改善部分代谢与肝病指标的潜力,且安全性良好[64,65]。对于合并明显肠道微生态紊乱的MAFLD患者,在充分知情同意并符合伦理规范的前提下,可考虑在临床研究或严格规范的医疗环境中审慎探索FMT干预。(2)禁忌证,菌群移植治疗存在明确禁忌情况:①免疫功能严重低下,如中性粒细胞计数<1.5×10^9/L或淋巴细胞计数<0.5×10^9/L;②肠道存在活动性损伤,包括急性暴发性结肠炎、重度黏膜受损、中毒性巨结肠、肠梗阻或正在实施肠内营养的患者;③处于全身性严重感染状态,如出现系统性炎症反应综合征或伴有肠外器官感染,且必须接受广谱抗生素治疗者;④存在显著营养代谢问题,如BMI<15 kg/m^2、人血清白蛋白水平<25 g/L,或

伴有大小便控制障碍;⑤近期曾使用免疫抑制剂或细胞毒性药物,如接受过阿霉素、利妥昔单抗治疗,或连续4周以上每日使用相当于泼尼松20 mg以上的中高剂量糖皮质激素;⑥处于妊娠期或哺乳阶段。

推荐意见15:对存在肠道微生态紊乱的MAFLD患者,在控制体重及实施药物治疗的基础上,均建议开展FMT治疗。(证据等级:A;推荐强度:强)

推荐意见16:FMT的禁忌证包括生命体征不稳定者、存在严重肠道损伤者、严重免疫抑制状态患者及妊娠期女性。(证据等级:A;推荐强度:强)

4.FMT途径:FMT根据菌群制剂形式可分为粪菌悬液移植与粪菌胶囊移植,临床给药途径需结合患者个体情况选择[63]。FMT给药途径主要分为上消化道和下消化道两类。上消化道给药可通过胃镜、鼻胃管、鼻空肠管或胃造口管进行输注;下消化道给药则常采用结肠镜、乙状结肠镜或保留灌肠等方式。在临床条件允许时,优先推荐经结肠镜将菌液输送至右半结肠,该途径报告的有效率可达94.8%,优于上消化道给药途径[66],且安全性与其他途径相当[56]。相比之下,单次肛门灌肠的成功率通常低于结肠镜[67],但其操作简便,重复实施有助于提高治疗效果[68]。

推荐意见17:对于存在肠梗阻或严重肠道炎症等存在下消化道给药禁忌证的患者,可选用上消化道途径进行FMT。(证据等级:A;推荐强度:强)

推荐意见18:经上消化道途径给药时,粪菌悬浮液建议控制在100 mL以内,最低不少于50 mL。(证据等级:A;推荐强度:强)

推荐意见19:存在吞咽困难者,应避免采用上消化道途径进行FMT。(证据等级:A;推荐强度:强)

5.菌群移植操作步骤:(1)结肠镜辅助下粪菌悬液移植术前准备,①知情同意:向患者详细说明操作目标、预期获益及潜在风险,解释粪菌制备流程,获取书面知情同意;②器械与物品准备:备齐肠镜、经内镜肠道植管术(transendoscopic enteral tubing, TET)专用套管、钛夹4~6枚、医用液状石蜡8~10 mL、一次性干纱布3块及“三明治”敷料1份;③患者预处理:建议在FMT前至少24 h停用广谱抗生素[69],采用口服聚乙二醇清洁肠道或灌肠准备。对于不耐受者,可改为术前1~2 d无渣饮食、口服乳果糖或分次灌肠[70]。肠道灌洗可能引发呕吐或误吸,对存在吞咽困难、肠梗阻或长期卧床等高误吸风险患者应谨慎使用[71]。推荐使用无痛内镜操作,若肠道病变较轻也可考虑非麻醉下操作。(2)结肠镜辅助下粪菌悬液移植操作步骤,①润滑与置管:向TET延长管注入4~5 mL液状石蜡,充分润滑导丝并全部送入延长管内;②结肠评估:完成结肠检查,使内镜停留于回盲部或升结肠[72];③钳道润滑:经钳道孔注入3~5 mL液状石蜡,确保TET专用套管在钳道内顺畅移动;④置入TET专用套管:将TET专用套管经钳道送入回盲部,退镜过程中助手协助固定肛管段;⑤内镜固定:再次进镜至回盲部,用钛夹将固定线固定于肠壁(首站使用2枚,后续酌情使用);⑥调整位置:缓慢退镜并配合肛门端TET专用套管的微调,以显露最佳固定线环;⑦移除导丝:退镜后暴露导丝,轻持TET专用套管并缓慢拔出导丝;⑧体外固定:连接单向阀门,将TET专用套管以胶布固定于肛旁皮肤(距肛门约2 cm),远端固定于同侧臀部,避免过紧;⑨菌液输注:嘱患者右侧卧位,经TET专用套管缓慢注入适量温度适宜的菌液(推荐剂量50~150 mL,活菌量≥2.5×10^{12} U,流率25~50 mL/min)。输注后保持头低脚高(10°)右侧卧位至少30 min,后可转为仰卧位[73]。若需重复输注,可待TET专用套管自行脱落;拔管时缓慢加力即可。菌液制备至输注全程应控制在2 h内。(3)粪菌胶囊移植,冻干粪菌胶囊可实现室温储存[74,75]。据报道,冻干粪菌胶囊治疗艰难梭菌感染的有效率达78%~96%[63,76],其疗效与经结肠镜的单次FMT相当[63]。该胶囊制剂可在无医师协助的情况下使用,操作更为便捷且有助于降低医疗成本。目前尚未观察到严重不良反应。患者需连续7 d每日2次空腹口服该制剂。胶囊应在服用前2 h从冷冻状态取出,置于室温复温后使用。

推荐意见20:建议患者在行FMT前至少提前24 h停用抗生素。(证据等级:A;推荐强度:强)

推荐意见21:推荐使用无痛结肠镜辅助下行FMT。(证据等级:B;推荐强度:弱)

推荐意见 22:在进行 FMT 前至少 24 h 进行常规肠道准备。口服聚乙二醇,配合无渣或少渣饮食。(证据等级:A;推荐强度:强)

推荐意见 23:强烈推荐采用皱襞夹持法以增强固定牢固性,应尽量避免钛夹与肠壁斜面夹持,同时钛夹固定区需避开重度糜烂、溃疡或假息肉区域。(证据等级:A;推荐强度:强)

推荐意见 24:下消化道途径进行 FMT 较上消化道疗效更优,且总体风险更低。(证据等级:A;推荐强度:强)

推荐意见 25:推荐经结肠镜将菌液输注至右结肠,接近回盲部。(证据等级:A;推荐强度:强)

推荐意见 26:缩短粪便采集至输注的时间有助于保持菌群活性。(证据等级:C;推荐强度:弱)

推荐意见 27:为降低误吸风险,不建议存在显著反流风险的患者口服冻干型粪菌胶囊。(证据等级:A;推荐强度:弱)

6.FMT 疗程与治疗周期:目前,国内外专家均建议 FMT 治疗 MAFLD 的疗程和周期应根据患者应答情况个体化调整,多次移植效果优于单次移植。根据专家意见及临床实践经验,推荐每月连续 3 d 进行 FMT,每天 1 次,连续 3 个月可取得稳定疗效。后续可采用粪菌胶囊维持治疗。

推荐意见 28:FMT 的疗程和周期应根据患者应答情况个体化调整,推荐以每月连续 3 d、每天 1 次,连续 3 个月为 1 个疗程。(证据等级:C;推荐强度:弱)

推荐意见 29:对于无法或不愿接受结肠镜辅助 FMT 的患者,可改用口服冻干菌群胶囊治疗,建议 3 次/d、6 粒/次,疗程共 2 周。(证据等级:C;推荐强度:弱)

推荐意见 30:符合下列任一情况时,建议在原有基础上追加 1 个标准疗程:(1)存在可能显著干扰肠道菌群活性的合并疾病或长期用药;(2)患病时间每延长 5 年追加 1 个标准疗程;(3)年龄≥65 岁。(证据等级:C;推荐强度:弱)

7.FMT 不良反应及其处理:FMT 后应密切监测患者的不良反应,包括消化道症状、体温、血压、脉搏及呼吸频率等。常见不良反应主要局限于消化道,如恶心、腹痛、腹胀或腹泻等,多数症状程度较轻,可自行缓解。建议建立标准化的不良事件报告机制。对于轻度反应(如头晕、轻微胃肠不适等),以密切观察为主;若出现中度症状,应给予对症支持治疗,若未见改善则需暂停 FMT。当发生发热、剧烈腹痛或严重腹泻等严重反应时,应立即暂停或终止移植,并进行相应处理。患者体温超过 39 ℃时,需警惕肠源性感染,应立即开展病原排查,包括供体与受体的粪便病原体检测及血培养,同时启动抗感染治疗和补液等支持措施。如出现危及生命的临床状况,必须立即停止 FMT,并迅速采取急救干预。

推荐意见 31:FMT 后应密切监测患者不良反应,包括消化道症状、体温及生命体征变化,若出现中重度症状应及时干预。(证据等级:C;推荐强度:弱)

8.FMT 的监测:(1)一般指标检测涵盖临床表现、炎症标志物、免疫与生化指标、肠屏障功能及菌群分析、营养吸收评估等。①临床观察:需持续记录患者的生命体征及腹部症状(如腹胀、腹痛、腹泻),关注排便频率、性状及肠蠕动情况。若出现发热(体温>38.5 ℃),应及时进行血培养,并依据临床经验及检测结果选用抗菌药物;②炎症标志物:动态监测 C 反应蛋白、白细胞介素等指标,有助于反映肠道炎症状态的变化和治疗反应;③肠屏障与菌群状态:通过血清二胺氧化酶、D-乳酸及内毒素水平评估肠屏障功能,同时结合菌群组成与多样性分析,综合评估移植效果;④营养吸收指标:监测 BMI、上臂肌围、腓肠肌围、人血清白蛋白、血红蛋白、转铁蛋白及氮平衡等,以评估肠道吸收功能的恢复情况;⑤生化指标:定期检测血糖、血脂、肝肾功能及凝血功能等,用于评估全身代谢变化;⑥免疫相关指标:监测免疫细胞数量及其活性变化,评估 FMT 对宿主免疫调节的影响。(2)粪便双歧杆菌/肠杆菌比值(B/E 值)检测[77],该比值可作为肠道微生物定植抗力的参考指标。B/E 值>1 提示定植抗力良好;若 B/E 值≤1,则提示定植抗力下降。(3)随访与不良事件监测,建议在治疗后 3～7 d 进行首次随访,重点评估症状缓解情况与短期不良事件[78];

第 4 周左右进行第 2 次随访,进一步评价疗效持久性与复发风险[79-81]。长期随访周期尚无统一标准,应根据个体病情发展和安全性需求个体化制定,以积累远期安全性数据。

9. 微生态制剂的疗效判断标准:微生态制剂治疗 MAFLD 的疗效评估需基于多维度指标进行综合判断。目前虽无全球统一的"金标准",但国内外研究及临床实践主要从以下层面展开评估:患者症状体征、肝脏生化学指标、微生物代谢指标、受控衰减参数值、CT 平扫肝/脾密度比值、磁共振质子密度脂肪分数、肠道菌群结构及肝组织学改变等。该评估体系涵盖从微观(菌群、代谢物)到宏观(组织、影像、生化、症状)的立体评价维度。在 MAFLD 的诊疗与研究领域,肝脏脂肪含量的无创定量测量与代谢指标的改善,是临床实践和研究中应用最广泛的疗效评判依据;而肝活检依然是确证性研究中不可替代的"金标准"。

推荐意见 32:应综合评估微生态制剂治疗 MAFLD 的疗效。肝脏脂肪含量的无创定量测量和代谢指标的改善是临床实践和研究中应用最为广泛的疗效判断标准。(证据等级:A;推荐强度:强)

推荐意见 33:所有接受 FMT 的患者均应接受规范随访,以评估疗效、复发情况及潜在不良事件。(证据等级:A;推荐强度:强)

推荐意见 34:移植后 1 周是观察临床起效与短期不良事件的关键窗口期。(证据等级:B;推荐强度:强)

推荐意见 35:主要疗效指标建议在移植后至少 4 周进行系统评估。(证据等级:B;推荐强度:强)

四、展望

微生态制剂治疗 MAFLD 技术正迅速发展。为明确肠道微生态制剂及 FMT 治疗 MAFLD 的最佳剂量、治疗频率及远期效果,未来仍需开展多中心、大样本、随机双盲安慰剂对照临床研究。同时,多项新型制剂技术不断涌现,如人工智能辅助的个性化菌群移植、菌群靶向定植、纳米材料包裹、工程菌制备及液体 3D 打印胶囊等,这些技术有望进一步提高 FMT 的治疗效果。

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