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ПАТОФИЗИОЛОГИЧЕСКИЕ ПРЕДПОСЫЛКИ И ТЕРАПЕВТИЧЕСКИЙ ПОТЕНЦИАЛ ТРАНСПЛАНТАЦИИ ФЕКАЛЬНОЙ МИКРОБИОТЫ ПРИ ТЯЖЁЛОМ АЛКОГОЛЬНОМ ГЕПАТИТЕ

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Pathophysiological Prerequisites and Therapeutic Potential of Fecal Microbiota Transplantation in Severe Alcoholic Hepatitis

Резюме

Из-за высокой заболеваемости и смертности проблема тяжёлого алкогольного гепатита до настоящего времени не теряет своей актуальности. При отсутствии специфической терапии, связанная с ним одномесячная выживаемость невелика, а показатели летальности достигают 30-50 %. Хотя назначение кортикостероидов является научно обоснованным лечением первой линии тяжёлого алкогольного гепатита, кратковременный ответ наблюдается примерно у 60 % пациентов, без преимуществ в долгосрочной выживаемости по сравнению с плацебо. Следует также учитывать возникновение неблагоприятных побочных реакций на их применение примерно у 50 % пациентов, а также риск осложнений, в частности, бактериальных и грибковых инфекций. Препараты второй линии, например, пентоксифиллин, этанерцепт, инфликсимаб, N-ацетилцистеин и др. при тяжелом алкогольном гепатите улучшения клинического исхода не показали. В современных руководствах обсуждается целесообразность трансплантации печени у тщательно отобранных, не отвечающих на лечение кортикостероидами больных тяжелым алкогольным гепатитом. Тем не менее, из-за многочисленных противоречий говорить о внедрении данного подхода в клиническую практику ещё рано. В последние годы были достигнуты определённые успехи в понимании патофизиологических механизмов развития алкогольного гепатита, что послужило толчком для новых направлений его патогенетической терапии. Одно из таких направлений — разработка и совершенствование методик, обеспечивающих кишечный эубиоз, в частности, посредством трансплантации фекальной микробиоты. Целью обзора было описать патофизиологические предпосылки и терапевтический потенциал трансплантации фекальной микробиоты от здоровых доноров больным тяжёлым алкогольным гепатитом. Экспериментальные исследования показали положительное влияние трансплантации фекальной микробиоты на микрофлору кишечника, которое приводило к ослаблению индуцированного алкоголем повреждения печени. У пациентов с тяжёлым алкогольным гепатитом данная методика уменьшала выраженность его симптоматики и способствовала увеличению выживаемости по сравнению с получавшими кортикостероиды. Эти предварительные результаты вселяют оптимизм и создают условия для дальнейших клинических испытаний с включением большой когорты больных тяжёлым алкогольным гепатитом для определения групп пациентов, кому трансплантация фекальной микробиоты будет наиболее эффективна с минимальным риском осложнений.

Ключевые слова: *тяжёлый алкогольный гепатит, патогенез, терапия, микробиота кишечника, трансплантация фекальной микробиоты*

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Abstract

Due to the high morbidity and mortality, the problem of severe alcoholic hepatitis has not lost its relevance to date. In the absence of specific therapy, the associated to him one-month survival rate is low, and mortality rates reach 30-50 %. Although the use of corticosteroids is a scientifically proven first-line treatment for severe alcoholic hepatitis, a short-term response is observed in approximately 60 % of patients with no long-term survival benefits compared to placebo. It should also take into account the occurrence of adverse side reactions to their use in about 50 % of patients, as well as the risk of complications, in particular, bacterial and fungal infections. The second-line drugs, for example, pentoxifylline, etanercept, infliximab, N-acetylcysteine, etc. in severe alcoholic hepatitis did not show an improvement in the clinical outcome. The modern guidelines discuss the feasibility of liver transplantation in carefully selected patients who do not respond to corticosteroid treatment with severe alcoholic hepatitis. Nevertheless, due to numerous contradictions, it is too early to talk about the introduction of this approach into clinical practice. In recent years, some progress has been made in understanding the pathophysiological mechanisms of the development of alcoholic hepatitis, which served as an impetus for new directions of its pathogenetic therapy. One of them is the techniques that provide intestinal eubiosis, in particular, through the fecal microbiota transplantation. The purpose of the review was to describe the pathophysiological prerequisites and therapeutic potential of fecal microbiota transplantation from healthy donors to patients with severe alcoholic hepatitis. Experimental studies have shown a positive effect of fecal microbiota transplantation on the intestinal microflora, which led to a weakening of alcohol-induced liver damage. In patients with severe alcoholic hepatitis, it improved the severity of its symptoms and contributed to increased survival compared to those receiving corticosteroids. These preliminary results are encouraging and create conditions for further clinical trials involving a large cohort of patients with severe alcoholic hepatitis, which will allow us to identify those for whom fecal microbiota transplantation will be most effective with minimal risk of complications.

Key words: *severe alcoholic hepatitis, pathogenesis, therapy, gut microbiota, fecal microbiota transplantation*

Conflict of interests

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AH — alcoholic hepatitis, ALT — alanine aminotransferase, AST — aspartate aminotransferase, CTP — Child-Turcotte-Pugh score, DAMPs — damage-associated molecular patterns, FDA — US Food and Drug Administration, FMT — fecal microbiota transplantation, IL — interleukin, LPS — lipopolysaccharides, MDF — modified Maddrey's discriminant function, MELD — model for end-stage liver disease, PAMPs — pathogen-associated molecular patterns, TLR — toll-like receptors

Introduction

Alcoholic hepatitis (AH) is a syndrome characterized by the development of acute-on-chronic liver failure caused by long-lasting and active intake of alcohol. Its specific clinical signs include: the progressive jaundice accompanied by fever (even with no infection), malaise, weight loss and nutritional deficiency, with or without other signs of hepatic decompensation (for example, ascites and/or encephalopathy). Laboratory test results in AH usually reveal neutrophilia, hyperbilirubinemia (>50 mol/L), increased level of aspartate aminotransferase (AST) in blood serum (however, rarely >300 IU/mL), with AST/ALT (alanine aminotransferase) ratio normally exceeding 1.5–2.0. In severe cases, increased prothrombin time, hypoalbuminemia and thrombocytopenia are often observed. Such histological signs as ballooning degeneration of hepatocytes, with amorphous eosinophilic inclusions, termed Mallory-Denk bodies, surrounded by neutrophils, tubular and/or ductal cholestasis, fibrosis, and megamitochondria are considered to be independent predictors for short-term prognosis [1]. Infectious complications that develop in about a half of patients have an adverse effect on AH outcome [2]. The presence of multiple organ failure predicts one-month mortality rate 35-50 %, another 50 % of survivors also die within 12 moths [3].

Generally accepted predictive model for assessing AH severity is Maddrey's discriminant function (DF).

In its modified version (MDF), the threshold value of 32 allows the identification of patients with severe hypertension and usually is a value used to start specific therapy. If not treated, the one-month mortality rate of patients with MDF ≥32 is 30-50 %, while in MDF <32 it is below 10 %. Moreover, it was found that MELD (Model for End-stage Liver Disease) score ≥21 suggests a high risk of 90-day mortality, and patients with MDF ≥32 and Glasgow score ≥9 have a poor prognosis and 84-day survival when treated with corticosteroids. ABIC (Age — Bilirubin — International Normalized Ratio — Creatinine) score allows stratification of patients with AH into the groups of low, medium and high risk of death within 90 days [4, 5].

Corticosteroids are an evidence-based first-line therapy for severe AH, although their effectiveness is disputable [6]. A short-term response to treatment with corticosteroids is observed in about 60 % of patients with no advantages for long-term survival over placebo. The important issues associated with their use include adverse reactions (in about 50 % of patients) and the risk of complications, in particular, of bacterial and fungal infections. Second-line agents, for example, pentoxifylline, etanercept, infliximab, N-acetylcysteine, etc. in severe AH demonstrated no clinical outcome improvement [7]. Current guidelines discuss the advisability of liver transplantation in carefully selected patients with severe AH that are nonresponsive to corticosteroids. Nevertheless, due to many contradictions, it is prematurely to speak of the implementation of this approach in clinical practice [8].

Considering the urgency of this issue, new directions for the management of severe AH have been actively developed in the recent years. In particular, methods are studied that are related to the modulation of gut microbiota that is the first metabolically active site of the interaction of environmental factors with the human body and plays an important role in the development of various diseases, including AH. Hence, the provision of intestinal eubiosis, for example, with probiotics, prebiotics, or with fecal microbiota (FM) transplantation can be a pathogenetically justified method of AH management [9].

The use of fecal microbiota for medicinal purposes has been known since the ancient times: as early as the in 4th century AD, traditional Chinese medicine practitioners prescribed a suspension of human feces for the management of food poisoning or severe diarrhea. However, the successful use of fecal enemas in patients with severe pseudomembranous enterocolitis was first described in early 1950s. [10]. Since then, an active study of this technique has started. In the last decade, FMT was actively implemented into clinical practice and has already been approved by the US Food and Drug Administration (FDA) for the management of refractory *Clostridium difficile* infection [11]. Currently, good preliminary results of FMT were obtained in patients with gastrointestinal and other systems diseases (Table 1) [12].

Table 1. *Experience of fecal microbiota transplantation in various diseases [12]*

Disease	Level of Evidence	Evidence base of scientific research
Clostridium difficile infection		
Clostridium difficile/		
Recurrent *Clostridium difficile* infection	I	Multiple meta-analyses of RCTs (benefit)
Severe *Clostridium difficile* infection	III-2	Retrospective cohort study (no RCT data)
Primary *Clostridium difficile* infection	II	RCTs (likely equivalence to standard antibiotics)
Inflammatory bowel disease		
Ulcerative colitis induction therapy	I	Multiple meta-analyses of RCTs (benefit)
Ulcerative colitis maintenance therapy	IV	Case reports
Crohn's disease	III-2	Multiple meta-analyses of RCTs (benefit)
Pouch ileitis (pouchitis)	IV	Case series (one negative RCT)
Microscopic colitis	IV	Case series
Functional gastrointestinal disorders		
Irritable bowel syndrome	II	RCTs (mixed results; systematic review negative)
Functional constipation	I	Systematic review of RCTs (heterogeneity)
Multi-drug — resistant microorganisms eradication	III-2	Case control study (RCT negative)
Checkpoint inhibitor colitis	IV	Case series
Augmenting cancer therapeutics	IV	Case series
Metabolic syndrome	IV	Case series (RCTs negative for weight loss)
Neurologic and psychiatric disorders		
Autism	II (abstract)	RCT (abstract form only)
Parkinson's disease	IV	Case series
Schizophrenia, Alzheimer's, multiple sclerosis, anxiety and depression	IV	Case series

Note: The level of evidence is based on criteria developed by the National Health and Medical Research Council of Australia; RCTs — randomized controlled trials

Despite numerous unsolved challenges [13], there are many publications that describe technical and organizational issues related to it [14, 15]. It is assumed that FMT effectiveness is based on the development of a competitive environment in gut due to non-pathogenic microorganisms and their secretion of antimicrobial substances, such as bacteriocins. Furthermore, we should not exclude a positive effect of donor fecal material on the virome and gut microbiota, metabolism of short-chain fatty acids and several bile acids, as well as various immunological mechanisms [16].

The objective of this review was to describe the pathophysiological background and therapeutic potential of FMT from healthy donors to the patients with severe AH.

The role of gut microbiota in human physiology

Gut microbiota is a microecosystem that is often considered as a human "virtual organ". It includes 100 billion bacteria of more than 500 different species. Gut microbiota genome, defined as gut microbiome, contains about 150 times as many genes as the human genome. Microbiota colonizes the gut immediately after the birth of a baby and is present in the human body throughout their life. Its composition varies depending on age, environment, physiological or pathological status [17].

Gut microbiota plays an essential role in human physiology, specifically:

- ferments indigestible food components;
- provides the host with useful metabolites such as short-chain fatty acids that can be a source of energy and have anti-inflammatory effect;
- contributes to the synthesis of several vitamins, including vitamin K and group B vitamins;
- protects intestinal barrier, for example, by enhancing the function of mucous layer;
- regulates immune function, in particular, by stimulating the development of lymphoid structure and increasing the level of involved enzymes and transcription factors;
- prevents the toxic components from entering gastrointestinal tract;
- suppresses some types of pathogenic bacteria [18].

The significance of ethanol-induced changes in intestinal microbiota and increased permeability of intestinal wall in the pathogenesis of alcoholic hepatitis

It has been established that liver damage in AH, alongside with the direct effect of ethanol on hepatocytes, can be caused by an inflammatory reaction due to microorganisms, associated molecular structures and products of their metabolism that enter the liver as a result of ethanol-induced changes in gut microbiota and increased permeability of intestinal wall. Actually, acetaldehyde formed during ethanol oxidation, the accumulation of reactive oxygen species and lipid peroxidation cause apoptosis of hepatocytes and the release of extracellular vesicles that, together with interleukin (IL)-1β, affect other types of cells, including polymorphonuclear leukocytes, hepatic stellate cells and sinusoidal endothelial cells, contributing to a necroinflammatory response in liver tissue [19]. At the same time, ethanol suppresses the expression of a wide range of antimicrobial proteins and peptides of the innate immune system contributing to intestinal dysbiosis, bacterial overgrowth and bacterial translocation. As a result, pathogen-associated molecular patterns (PAMPs), in particular, lipopolysaccharides (LPS) of the cell wall of gram-negative bacteria enter the liver through portal vein where, through the LPS-binding protein, they bind to the CD14 receptor located on the membrane of Kupffer cells resulting in the activation of many genes of proinflammatory cytokines and exacerbates liver damage [20] (Fig. 1).

Ethanol-induced changes in gut microbiota are characterized primarily by a decreased number of various species of *Lactobacillus spp.* and *Ruminococcaceae spp.* that attach to epithelial cells and participate in protecting the body from pathogenic and invasive bacteria. Their fermentation products are short-chain fatty acids, in particular, butyrate and propionate that serve as a key energy substrate for both enterocytes and colonocytes [21]. Besides, by producing bacteriocins, *Lactobacillus spp.* suppress microorganisms of *Enterobacteriaceae* family, for example, *Salmonella* or *Shigella* [22]. Moreover, AH-related intestinal dysbiosis is manifested by a decreased level of anti-inflammatory bacteria *Clostridium leptum* and *Faecalibacterium prausnitzii*, as well as by increased level of *Streptococcaceae spp.*, *Bifidobacterium spp., Enterobacter spp., Veillonella spp., Fusobacterium spp., Actinomyces spp.* and *Proteobacteria*; this fact, along with decreased level of *Akkermansia muciniphila*, closely correlates with the liver disease severity [23-26].

Mice that received alcohol for three weeks demonstrated an overgrowth of bacteria in small intestine, dysbiosis in cecum, suppressed expression of genes and proteins of antimicrobial lectins Reg3β and Reg3γ in small intestine, decreased number of *Firmicutes* and increased number of *Bacteroidetes* and *Verrucomicrobia* [27].

The patients with alcohol abuse have a potentially more active pro-inflammatory gut microbiota with significant amounts of endotoxemic contributors *Proteobacteria*, *Clostridium spp.*, *Holdemania spp.* (*Firmicutes*) and *Sutterella spp.* and decreased number of anti-inflammatory bacteria *Faecalibacterium spp*. [28]. Their fecal samples demonstrated about 2,700 times as many *Enterococcus faecalis* as in non-alcoholic subjects. The studies revealed harmful effect of exotoxin cytolysin secreted by these bacteria on ethanol-induced liver

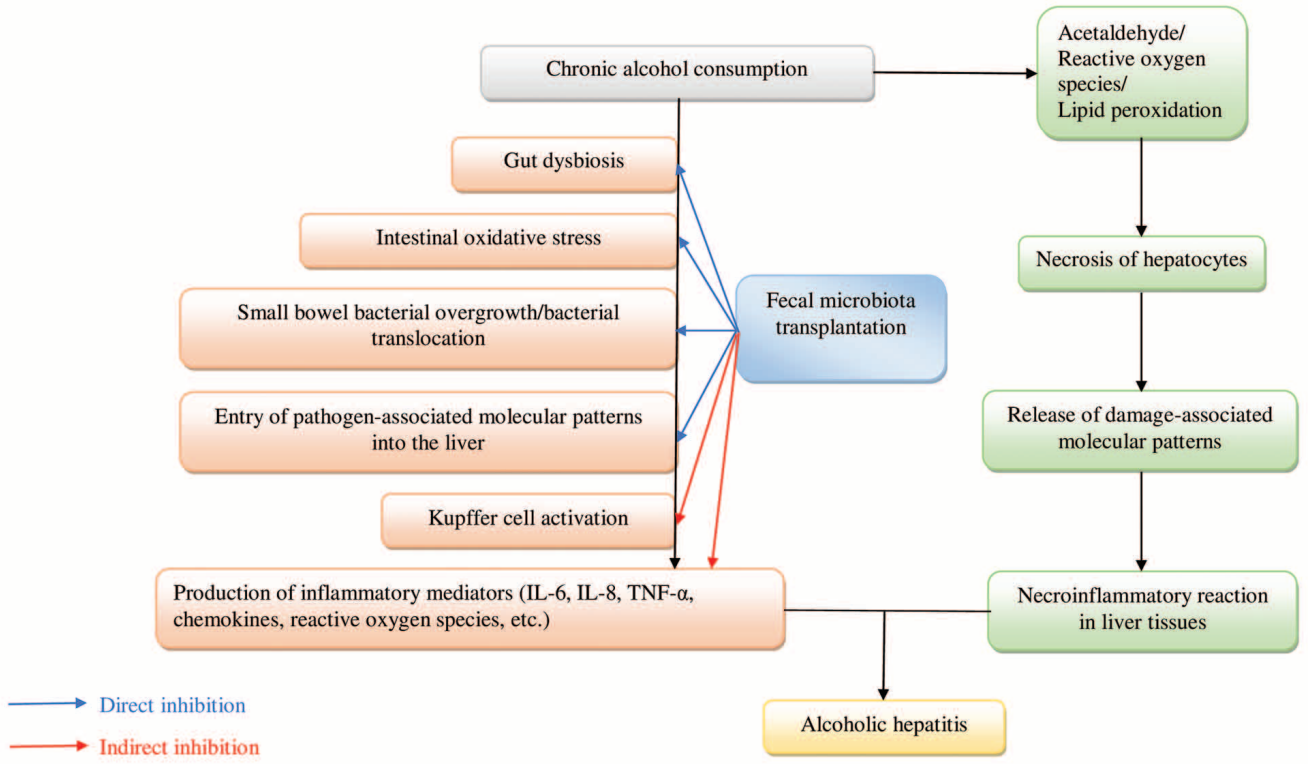

Figure 1. *Potential mechanisms of the positive effect of fecal microbiota transplantation on key links in the pathogenesis of alcoholic hepatitis. IL-6 — interleukin-6; IL-8 — interleukin-8; TNF-α — tumor necrosis factor-alpha*

diseases, and found a correlation between the number of these microorganisms and the severity of AH and mortality of patients suffeting with it [29].

In the study performed by Sundaram V. et al. (2014) [30], the patients with AH and *Clostridium difficile* infection had higher hospital mortality (adjusted odds ratio (OR) 1.75; P = 0.04), longer predicted hospital stay (10.63 vs 5.75 days; P <0.001) and higher predicted treatment costs ($ 36,924.30 vs $ 29,136.58; P <0.001) compared to the patients without it.

Currently, the cause of bacterial overgrowth in alcoholics is not established. It can be due to their specific weakened peristalsis, as well as to the suppression of their innate and adaptive immune response. In healthy subjects, a wide range of antimicrobial proteins and peptides of innate immunity system secreted by intestinal epithelial cells not destroys pathogenic microorganisms and participates in the maintenance of normal gut microflora. Alcohol-induced suppression of its expression causes intestinal dysbiosis and overgrowth of bacteria which contributes to the disturbance of tryptophan metabolism and decreased indole production. Some indole derivatives are ligands for the aryl hydrocarbon receptor that, in turn, are involved in antimicrobial protection through the induction of IL-22. IL-22 increases the expression of antimicrobial Reg3 lectins derived from regenerating intestinal islets that can maintain low bacterial colonization of mucous membrane [31]. At the same time, Reg3γ deficient mice had increased bacterial colonization of the mucous membrane and the surface of epithelial cells, as well as more expressed translocation of bacteria to mesenteric lymph nodes and liver that resulted in its more pronounced ethanol-induced damage. Moreover, long-time intragastric alcohol administration to mice reduced the intestinal expression of Reg3β and Reg3γ mRNAs contributing to intestinal dysbiosis, bacterial overgrowth, and bacterial translocation [32].

Bacterial translocation is a physiological process that occurs in 5 % of healthy population and plays an important role in maintaining host immune function by delivering a small number of bacteria and their components to the reticuloendothelial system of liver. Different pathological conditions result in the steady increase in the rate and/or degree of bacterial translocation [33]. An important physical barrier that prevents the translocation is the intestinal epithelial cells closely connected with each other by tight junction proteins, primarily of claudin family. Under oxidative stress, ethanol and its metabolites can increase the permeability of intestinal wall having a direct harmful effect on adhesion junctions and on the integrity of tight junction proteins, in particular, ZO-1 (Zonula Occludens 1) [34]. Moreover, by disrupting the glycosylation of mucosal proteins, they can cause mucosa erosion and ulceration, and, possibly, change the number and composition of enteroadhesive bacterial species [35]. Dysbiosis-induced subclinical inflammation and tumor necrosis factor receptor (TNFR)1 signaling

in enterocytes may mediate the disruption of intestinal barrier and increase intestinal wall permeability [36]. Alcohol-induced modification of microbial metabolites, in particular, of short-chain fatty acids (butyrate, acetate, and propionate) is another contributive factor [37]. Thus, the decreased number of butyrate-producing bacteria weakens the strong connection between intestinal epithelial cells due to decreased expression of tight junction proteins and mucins [38]. Tight junction proteins, including ZO-1, may be adversely affected by increased intestinal expression of several microRNAs, such as miR-122 and miR-212 [39]. Finally, deoxycholic acid can also impair intestinal barrier function, while ursodeoxycholic acid prevents it [40].

Increased permeability of intestinal wall results in the situation when microorganisms, their associated molecular structures (LPS, bacterial DNA, peptidoglycans and lipopeptides), as well as the products of their metabolism cannot be adequately neutralized by local mesenteric lymph nodes and in large quantities enter the liver via mesenteric and portal circulation [41]. Here they are specifically recognized and bound by a family of Toll-like receptors (TLR) that start their clearance mechanisms and trigger the inflammatory signaling cascade. Here, TLR4 and TLR9 are the receptors of two most immunogenic bacterial products LPS and bacterial DNA, respectively [42].

TLR4 located on Kupffer cells are activated by LPS via NF-kB (nuclear factor kB) molecular signaling pathway that stimulates the expression of NLRP3 inflammasome mRNA, adapter protein ASC (apoptosis-associated speck-like protein containing a CARD), cleaved caspase 1, caspase 1, pro-IL-1β, and pro-IL-18 [43]. Morevove, with the involvement of the TIR domain-containing adapter inducing interferon-beta (TRIF) and independently of ATP/P2X7R signaling pathway, LPS stimulates NLRP3-induced caspase 1 activation and secretion of IL-1β [44]. IL-1/IL-1R signaling pathway also plays an essential role in LPS-associated liver injury [45].

TLR9 is localized in the endoplasmic reticulum of dendritic cells, macrophages, endothelial cells, and hepatocytes and mainly recognizes unmethylated CpG sequences in bacterial DNA [46].

The interaction of bacteria and their metabolic products with TLR stimulates intracellular molecular pathways contributing to the activation of NF-κB and the expression of inflammatory cytokines TNF-α, IL-1β, IL-6, IL-12, IL-18, chemokines CXCL1, CXCL2, CCL2, CCL5 , CCL3, CCL4, vasoactive substances NO, and reactive oxygen species. This local inflammatory storm results in the recruitment of systemic leukocytes such as neutrophils, CD4(+) T cells, and monocytes which contributes to liver damage [47].

Thus, ethanol-induced liver damage causes the release of damage-associated molecular patterns (DAMPs). DAMPs, in turn, activate macrophages contributing to their transdifferentiation into a pro-inflammatory phenotype and the subsequent typical inflammatory response with apoptosis and necrosis of hepatocytes as a final result. On the other hand, ethanol alters intestinal microbiota, and the associated increased permeability of intestinal wall results in the delivery of bacterial products through the portal vein to the liver with the development of a classic PAMPs-mediated inflammatory response associated with the activation of macrophages.

The main cause of death in patients with severe AH is the multiple organ failure that usually associated with underlying systemic inflammatory response syndrome. It can be caused by infectious complications, first of all, sepsis due to bacteremia as a result of bacterial translocation [48], or have a non-infectious nature due to ethanol-induced liver damage caused by PAMPs and DAMPs [49].

Excessively significant compensatory anti-inflammatory response due to corticosteroids causes immune paralysis that is characterized by decreased expression of HLA-DR antigen on the surface of macrophages, increased expression of immune inhibition markers, such as PD1 (programmed cell death 1), TIM-3 (T-cell immunoglobulin and mucin domain 3), and decreased phagocytic activity of neutrophils and monocytes which forms the basis for the susceptibility to infections [50]. Alongside with many other types of immune cells with impaired function due to severe AH, an insufficient antibacterial cytokine/cytotoxic response of MAIT cells (mucosal associated invariant T-cells) was recently revealed [51].

The study of fecal microbiota transplantation effectiveness in severe alcoholic hepatitis

Results of preclinical experimental studies demonstrated that FMT reduced alcohol-induced liver damages, for example, those resulting from restoration of intestinal goblet cells. Mucin produced by them covers the epithelial lining of the mucous membrane surface and crypts and is the first barrier that prevents bacteria from contacting the epithelium. Moreover, FMT increased the levels of Reg3β and Reg3γ mRNA in colon which prevented intestinal dysbiosis, bacterial overgrowth and bacterial translocation, as well as reversed changes in the metabolism of some bile acids, in particular, deoxycholic acid [52].

At present, the effectiveness of FMT in severe AH was studied only in small clinical trials involving a limited number of subjects. In the first pilot study, eight patients with severe AH and contraindications to corticosteroids (MELD mean score 31 ± 5.6; MELD-Na score 33.6 ± 4.3; Child-Turcotte-Pugh (CTP) score 14 ± 0,8; serum AST level 137 ± 57 IU/mL) received the injection of 30 g of fecal material from carefully selected healthy donors, daily, for 7 days, through a nasoduodenal tube. As early as in the course of treatment, a significant improvement was observed in the severity of disease in comparison with the control group patients

who received routine treatment. The positive effect persisted all over the follow-up period (mean 355 days; range 220–368 days), with ascites resolved in 5 (57.1 %) patients and hepatic encephalopathy — in 6 (71.4 %) patients. Mean serum bilirubin level decreased from 20.5 ± 7.6 mg/dL to 2.86 ± 0.69 mg/dL (P = 0.001). CTP, MELD and MELD-Na scores decreased from 14.5 ± 0.8 to 7.7 ± 1.2, from 31.0 ± 5.6 to 12.3 ± 3.7, and from 33.6 ± 4.3 to 13.7 ± 4.6 (P <0.001), respectively. Survival rate was significantly higher in those who underwent FMT compared with the control group (87.5 % vs 33.3 %; P = 0.018). Half of them had excessive flatulence. Microbiota test one year after FMT demonstrated the dominance of *Firmicutes* species, decreased *Proteobacteria*, and increased *Actinobacteria* levels. The change in the relative number of both several pathogenic species, in particular, *Klebsiella pneumonia* (from 10 % to <1 % after 1 year) and non-pathogenic species, for example, *Enterococcus villorum* (9-23 % after 6 months), *Bifidobacterium longum* (6-50 % after 6 months), and *Megasphaera elsdenii* (10-60 % after 1 year) worth mentioning. Initially increased levels of methane metabolism, degradation of 4-fluorobenzoic acid (mediated by *Pseudomonas* and *Escherichia coli* groups), and bacterial invasion of epithelial cells decreased one year after FMT. At the same time, the initially decreased levels of bile secretion, carotenoid biosynthesis, and pantothenate biosynthesis improved almost to normal values [53].

Later, the staff of the same clinic conducted a study involving 61 patients with severe AH where the long term effectiveness of FMT (n = 35) was compared with the treatment with corticosteroids (n = 26). Ascites, hepatic encephalopathy, infectious complications and cases of long-term hospitalizations were observed more often in those who received corticosteroids (P <0.05), while a return to alcohol intake was less common (28.6 % vs 53.8 %), and the period of time associated with it was longer in those who underwent TFM (P = 0.04). Three-year survival rate was higher after FMT (65.7 % vs 38.5 %, P = 0.052), and mortality due to sepsis was significantly higher in those who received corticosteroids (N = 13/16, 81.2 %; P = 0.008). Intestinal microbiota test revealed significant increases during one to two years in relative abundance of *Bifidobacterium spp.* as well as the decrease in relative abundance of *Acinetobacter spp.* and *Porphyromonas spp.* in patients who received FMT compared with those who received corticosteroids [54].

A study performed by Dhiman R. et al. (2020) [55], included 33 patients with severe AH; 13 of them underwent FMT, while 20 received corticosteroids. The mean age (39.6 vs 40.7 years), CTP (11.5 vs 12.1) and MELD (25.2 versus 25.6) baseline scores, as well as DF (87.0 vs 83.6) demonstrated almost no differences between the groups. FMT was carried out after a five-day oral intake of antibiotics by a single injection of 30 g of freshly prepared fecal material from carefully selected healthy donors using nasojejunal tube. The patients who underwent FMT had better 1- and 3-month survival rates, as well as better resolution rate of hepatic encephalopathy and ascites, compared with those who received corticosteroids. Spontaneous bacterial peritonitis and bleeding from upper gastrointestinal tract were equally common in both groups. The most common FMT-related side effects were excessive flatulence (100 %), gastroesophageal reflux (53.8 %) and nausea (23.1 %).

Preliminary results from one of the currently ongoing randomized clinical trials (NCT03091010) involving a total of 82 patients with severe AH also showed better survival after FMT than after treatment with corticosteroids [56].

Potential complications and risks associated with fecal microbiota

Despite the fact that FMT is a technically simple procedure, one should consider the possibility of a number of complications during its performance. For example, it is not recommended to inject large volumes of fecal material through nasoenteral tube or through upper endoscopy [57] due to the risk of aspiration; sedation should be avoided, and if appropriate, antiemetics should be used [58]. The experience has shown that FMT via LGI is safer, although there are reports on the superficial rupture of colonic mucosa when using colonoscopy [59].

A recent systematic review and meta-analysis of 61 clinical trials, including a total of 5,099 patients with *Clostridium difficile* infection, demonstrated FMT-associated severe side effects in less than 1 % of cases [60]. Some patients after FMT may develop fever, as well as transient gastrointestinal disorders, in particular, belching, nausea, vomiting, diarrhea, constipation, discomfort, stomach cramps, stomach gurgling, flatulence [61]. These are more common in young adults or in patients with previously diagnosed irritable bowel syndrome or inflammatory bowel disease [62]. There were reports on the individual cases of diverticulitis, acute appendicitis, and peritonitis, although they could be associated with both FMT and comorbidities [63]. FMT was expected to exacerbate previous inflammatory bowel diseases [64]. However, in a prospective multicenter study (NCT03106844) of 50 patients with such diseases who underwent FMT for recurrent *Clostridium difficile* infection, these concerns proved true in only 2 % of cases [65].

An important problem of FMT is the risk of the transmission of severe infection which is particularly relevant for vulnerable patients with impaired immune function [66]. For example, there were reports on two cases of cytomegalovirus infection in patients with ulcerative colitis. One of them developed it after self-administration of fecal material from the stool of the patient's child [67], and another one — after autologous FMT [68].

American authors reported on two patients with bacteremia after FMT caused by extended-spectrum beta-lactamase-producing *Escherichia coli* that was found in donor's feces using genomic sequencing [69]. It should be mentioned that faecal material was transplanted to them without testing for microorganisms with multidrug resistance, such as bacteria producing extended spectrum beta-lactamases, methicillin-resistant *Staphylococcus aureus,*carbapenem-resistant *Enterobacteriaceae,* etc., although control over their presence is a routine practice in the US state databank (OpenBiome, Cambridge, Massachusetts) since 2016 [70]. In 2019, FDA published a list of minimum requirements for screening and testing the feces donors for the presence of multidrug-resistant organisms [71].

Zellmer C. et al. (2021) [72] described four patients with self-limiting diarrhea that developed after FMT; it is associated with shiga toxin-producing *Escherichia coli*. Feces donor was found shiga toxin-negative by enzyme immunoassay, however, subsequently a more sensitive nucleic acid amplification test of fecal samples produces positive result.

Infections caused by enteropathogenic *Escherichia coli* were also reported, however, it is still unknown whether they were pathogenic or could be a part of normal gut microbiota. According to current guidelines, it is unnecessary to screen donors of fecal material for enteropathogenic *Escherichia coli* [73], however, FDA requirements stipulate the need for appropriate testing together with examination of donors, along with the examination, for shiga toxin-producing *Escherichia coli* in order to better identify these pathogens and prevent their possible transmission, especially in immunocompromised individuals [74].

COVID-19 pandemic raises concerns over potential transmission of SARS-CoV-2 coronavirus with FMT. Although the genetic material of SARS-CoV-2, including live virus, was found in the feces of individuals after a novel coronavirus infection even after the respiratory symptoms resolution [75], no actual cases of infection through donor fecal material were reported. Performing of SARS-CoV-2 RT-PCR test on fecal samples is currently not widely available. However, experts stand for screening donors for symptoms of novel coronavirus infection with quarantine of their stool and further monitoring of the disease [76].

Conclusion

Severe AH is often associated with the development of multiple organ failure which determines an unfavorable prognosis and is accompanied by high mortality rate. In accordance with current guidelines, corticosteroids are the first-line treatment for severe AH, however, their effectiveness is not observed in every patient. Moreover, none of the second-line therapeutic approaches demonstrated reduced one-month mortality. Considering this challenging issue, a number of high-potential methods are currently undergoing clinical trials; one of them is FMT. The preliminary results of its use produce optimism and create conditions for further studies with the inclusion of a large cohort of patients with severe AH in order to determine the groups of patients to enjoy the maximal effectiveness of FMT and suffer the minimal risk of complications.

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