

World Journal of *Gastroenterology*

World J Gastroenterol 2023 July 21; 29(27): 4222-4367



REVIEW

- 4222 Rare causes of acute non-variceal upper gastrointestinal bleeding: A comprehensive review
Martino A, Di Serafino M, Orsini L, Giurazza F, Fiorentino R, Crolla E, Campione S, Molino C, Romano L, Lombardi G
- 4236 Sarcopenia in cirrhosis: Prospects for therapy targeted to gut microbiota
Maslennikov R, Alieva A, Poluektova E, Zharikov Y, Suslov A, Letyagina Y, Vasileva E, Levshina A, Kozlov E, Ivashkin V
- 4252 Bile acids and their receptors: Potential therapeutic targets in inflammatory bowel disease
Long XQ, Liu MZ, Liu ZH, Xia LZ, Lu SP, Xu XP, Wu MH
- 4271 Serum resistin and the risk for hepatocellular carcinoma in diabetic patients
Abdalla MMI

ORIGINAL ARTICLE

Basic Study

- 4289 Stomach perforation-induced general occlusion/occlusion-like syndrome and stable gastric pentadecapeptide BPC 157 therapy effect
Kalogjera L, Krezic I, Smoday IM, Vranes H, Zizek H, Yago H, Oroz K, Vukovic V, Kavelj I, Novosel L, Zubcic S, Barisic I, Beketic Oreskovic L, Strbe S, Sever M, Sjekavica I, Skrtic A, Boban Blagaic A, Seiwert S, Sikiric P
- 4317 18 β -glycyrrhetic acid promotes gastric cancer cell autophagy and inhibits proliferation by regulating miR-328-3p/signal transducer and activator of transcription 3
Yang Y, Nan Y, Du YH, Huang SC, Lu DD, Zhang JF, Li X, Chen Y, Zhang L, Yuan L

Observational Study

- 4334 Azathioprine monotherapy withdrawal in inflammatory bowel diseases: A retrospective mono-centric study
Crepaldi M, Maniero D, Massano A, Pavanato M, Barberio B, Savarino EV, Zingone F
- 4344 Predicting portal venous anomalies by left-sided gallbladder or right-sided ligamentum teres hepatis: A large scale, propensity score-matched study
Lin HY, Lee RC, Chai JW, Hsu CY, Chou Y, Hwang HE, Liu CA, Chiu NC, Yen HH

SCIENTOMETRICS

- 4356 Research landscape on COVID-19 and liver dysfunction: A bibliometric analysis
Zyoud SH

ABOUT COVER

Editorial Board Member of *World Journal of Gastroenterology*, Mark C Mattar, AGAF, FACG, MD, Professor of Medicine, Department of Gastroenterology, MedStar Georgetown University Hospital, Washington, DC 20007, United States. mark.c.mattar@medstar.net

AIMS AND SCOPE

The primary aim of *World Journal of Gastroenterology* (WJG, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. WJG mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING

The WJG is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports, Index Medicus, MEDLINE, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 edition of Journal Citation Reports® cites the 2022 impact factor (IF) for WJG as 4.3; IF without journal self cites: 4.1; 5-year IF: 5.3; Journal Citation Indicator: 0.82; Ranking: 33 among 93 journals in gastroenterology and hepatology; and Quartile category: Q2. The WJG's CiteScore for 2021 is 8.3 and Scopus CiteScore rank 2022: Gastroenterology is 22/149.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Yi-Xuan Cai; Production Department Director: Xiang Li; Editorial Office Director: Jia-Ru Fan.

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

EDITORS-IN-CHIEF

Andrzej S Tarnawski

EDITORIAL BOARD MEMBERS

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

PUBLICATION DATE

July 21, 2023

COPYRIGHT

© 2023 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Sarcopenia in cirrhosis: Prospects for therapy targeted to gut microbiota

Roman Maslennikov, Aliya Alieva, Elena Poluektova, Yury Zharikov, Andrey Suslov, Yana Letyagina, Ekaterina Vasileva, Anna Levshina, Evgenii Kozlov, Vladimir Ivashkin

Specialty type: Gastroenterology and hepatology

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C, C, C

Grade D (Fair): D

Grade E (Poor): 0

P-Reviewer: Dai K, China; Li C, China; Zhang Y, China

Received: March 24, 2023

Peer-review started: March 24, 2023

First decision: May 13, 2023

Revised: May 25, 2023

Accepted: June 21, 2023

Article in press: June 21, 2023

Published online: July 21, 2023



Roman Maslennikov, Aliya Alieva, Elena Poluektova, Ekaterina Vasileva, Anna Levshina, Vladimir Ivashkin, Department of Internal Medicine, Gastroenterology and Hepatology, Sechenov University, Moscow 119435, Russia

Roman Maslennikov, Elena Poluektova, Vladimir Ivashkin, The Scientific Community for Human Microbiome Research, Moscow 119435, Russia

Yury Zharikov, Andrey Suslov, Yana Letyagina, Department of Human Anatomy and Histology, Sechenov University, Moscow 119435, Russia

Anna Levshina, Evgenii Kozlov, Laboratory of Immunopathology, Department of Clinical Immunology and Allergy, Sechenov University, Moscow 119991, Russia

Corresponding author: Roman Maslennikov, MD, PhD, Academic Editor, Assistant Professor, Doctor, Professor, Department of Internal Medicine, Gastroenterology and Hepatology, Sechenov University, Pogodinskaya str., 1, bld. 1, Moscow 119435, Russia.

mmmm00@yandex.ru

Abstract

Decreased muscle mass and function, also known as sarcopenia, is common in patients with cirrhosis and is associated with a poor prognosis. Although the pathogenesis of this disorder has not been fully elucidated, a disordered gut-muscle axis probably plays an important role. Decreased barrier function of the gut and liver, gut dysbiosis, and small intestinal bacterial overgrowth (SIBO) can lead to increased blood levels of ammonia, lipopolysaccharides, pro-inflammatory mediators, and myostatin. These factors have complex negative effects on muscle mass and function. Drug interventions that target the gut microbiota (long-term use of rifaximin, lactulose, lactitol, or probiotics) positively affect most links of the compromised gut-muscle axis in patients with cirrhosis by decreasing the levels of hyperammonemia, bacterial translocation, and systemic inflammation and correcting gut dysbiosis and SIBO. However, although these drugs are promising, they have not yet been investigated in randomized controlled trials specifically for the treatment and prevention of sarcopenia in patients with cirrhosis. No data exist on the effects of fecal transplantation on most links of gut-muscle axis in cirrhosis; however, the results of animal experimental studies are promising.

Key Words: Cirrhosis; Muscle; Fragility; Liver; Microbiota; Microbiome

Core Tip: Sarcopenia is common in patients with cirrhosis and is associated with a poor prognosis. Although the pathogenesis of this disorder has not been fully elucidated, a disordered gut-muscle axis probably plays an important role. Drugs that target the gut microbiota positively affect most links of the compromised gut-muscle axis in patients with cirrhosis. However, they have not yet been investigated in randomized controlled trials specifically for the treatment and prevention of sarcopenia in patients with cirrhosis.

Citation: Maslennikov R, Alieva A, Poluektova E, Zharikov Y, Suslov A, Letyagina Y, Vasileva E, Levshina A, Kozlov E, Ivashkin V. Sarcopenia in cirrhosis: Prospects for therapy targeted to gut microbiota. *World J Gastroenterol* 2023; 29(27): 4236-4251

URL: <https://www.wjgnet.com/1007-9327/full/v29/i27/4236.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v29.i27.4236>

INTRODUCTION

Sarcopenia is defined as the loss of muscle mass, strength, and physical function[1]. Sarcopenia has been detected in 14%-55% of patients with cirrhosis[2-6] and attracts the attention of researchers increasingly[7-10]. Sarcopenia was found in 68.5% of patients with cirrhosis who were admitted to the intensive care unit[11]. Recent studies have shown that sarcopenia in patients with cirrhosis is associated with poor short- and long-term prognoses[3,6,11,12]. The decrease in muscle mass in patients with cirrhosis over a year also has an unfavorable prognostic value[13]. A recent meta-analysis of 22 studies confirmed that sarcopenia is an independent predictor of increased mortality in patients with cirrhosis[14].

Sarcopenia in patients with cirrhosis is associated with a decrease in the quality of life[15], increased hepatic venous pressure gradient[12], portal hypertension-related complications (ascites and upper gastrointestinal varices), infections (urinary tract infection and spontaneous peritonitis), hepatic encephalopathy, increased risk of hepatocellular carcinoma, longer hospital stay, higher 30-d readmission rate, lower body mass index and serum albumin levels, longer prothrombin time, higher total bilirubin concentrations, and higher Child-Pugh score[16-20]. In addition, patients with cirrhosis have an increased amount of fat in the muscles (myosteatorsis), which is also an unfavorable prognostic factor[21].

The exact mechanisms underlying the development of sarcopenia in patients with cirrhosis have not yet been established. Among the factors contributing to the development of sarcopenia in cirrhosis, are disorders of the metabolic function of the liver, decreased appetite[22], increased muscle autophagy[2], increased serum myostatin (a protein that blocks muscle growth)[6], catabolic effects of systemic inflammation induced by bacterial translocation from the gut[23-24], and low testosterone levels[25] were found.

GUT-MUSCLE AXIS IN CIRRHOSIS

Gut dysbiosis in patients with cirrhosis

Cirrhosis is associated with a disturbed composition of the gut microbiota, or dysbiosis[26-29]. Despite some inconsistencies, most studies have shown that in patients with cirrhosis, there was an abundance of harmful bacteria of taxa Bacilli, Streptococcaceae, Enterococcaceae, Proteobacteria, and Enterobacteriaceae, and there was a decrease in beneficial gram-positive bacteria of families Ruminococcaceae and Lachnospiraceae[30-42]. The harmful bacteria are facultative anaerobes; therefore, they can survive in oxygenated tissues, penetrate them, and spread throughout the body. This process was termed bacterial translocation and is believed to be an important contributor to the progression of cirrhosis, including the development of a systemic inflammatory response[26-29]. In addition, harmful Enterobacteriaceae of the phylum Proteobacteria, which are abundant in the gut microbiota of patients with cirrhosis, have an active endotoxin [lipopolysaccharide (LPS)]. Since cirrhosis increases the permeability of the intestinal barrier[43-46], LPS can penetrate the body (molecular bacterial translocation), leading to a systemic inflammatory response. The production of short-chain fatty acids (SCFA) by beneficial bacteria also decreases in patients with cirrhosis[30]. These SCFAs are used as a source of energy by intestinal epithelial cells, strengthen the intestinal barrier, and act on specific receptors to regulate human body functions[47]. The metabolism of bile acids, which also affect many human metabolic pathways through their special receptors[48], depends on the gut bacteria and disturbs in cirrhosis[42].

The values of the MELD scale that used to assess the risk of death in patients with cirrhosis are directly correlated with the abundance of harmful gut bacteria from the families Staphylococcaceae, Enterococcaceae, and Enterobacteriaceae, and inversely correlated with the abundance of beneficial bacteria from the families Lachnospiraceae and Ruminococcaceae [36]. Patients with acute-on-chronic liver failure have a lower abundance of beneficial gram-positive bacteria[36]. The Child-Turcotte-Pugh score, used to assess cirrhosis severity, correlates positively with the abundance of Streptococcaceae and negatively with the abundance of Lachnospiraceae[41]. Severe dysbiosis is associated with higher C-reactive protein (CRP) levels, lower serum albumin and cholinesterase levels, and poorer long-term prognosis[40]. The abundance of Lachnospiraceae is negatively correlated with the risk of hospitalization of cirrhosis patients in the intensive care unit

[49]. Abundant Enterobacteriaceae, Enterococcaceae, and Streptococcaceae are associated with hepatic encephalopathy, circulatory failure, and respiratory failure within 30 d of hospitalization of these patients, respectively[49].

Serum LPS levels are positively correlated with the abundance of Enterobacteriaceae and negatively correlated with the abundance of Lachnospiraceae and Ruminococcaceae[36]. Most of the bacterial genetic material found in the blood and ascitic fluid of patients with cirrhosis is from harmful Proteobacteria and Bacilli instead of the beneficial Lachnospiraceae and Ruminococcaceae that are dominant in the gut[50,51]. The serum level of pro-inflammatory cytokine tumor necrosis factor- α (TNF- α) is positively correlated with the serum LPS level and the risk of cirrhosis decompensation, spontaneous bacterial peritonitis, and acute-on-chronic liver failure[52].

Therefore, gut dysbiosis in patients with cirrhosis is associated with bacterial translocation, systemic inflammation, decompensation of liver function, and poor short- and long-term prognoses.

Small intestinal bacterial overgrowth in cirrhosis

Small intestinal bacterial overgrowth (SIBO) is an increase in the content of bacteria in the small intestine[53] and has been detected in almost half of patients with cirrhosis[54]. The prevalence of SIBO increases with increasing severity of cirrhosis[54]. Patients with cirrhosis and SIBO have ascites, minimal and overt hepatic encephalopathy, and spontaneous bacterial peritonitis more often than those without SIBO[54-55]. No relationship has been found between SIBO on the one hand and hypocoagulation, alanine aminotransferase, glutamyl transpeptidase activity, white blood cell, platelet counts, hemoglobin, ascitic fluid albumin levels, and esophageal varices on the other hand in cirrhosis[54]. In patients with cirrhosis, SIBO is associated with the presence of bacterial DNA in peripheral blood[56], higher serum LPS[57] and CRP [58] levels, splanchnic vasodilation, and hyperdynamic circulation[58]. Gut microbiota changes in patients with both cirrhosis and SIBO do not correspond to cirrhosis-associated gut dysbiosis. Therefore, gut dysbiosis and SIBO are most likely separate disorders[59] and SIBO is an independent factor associated with bacterial translocation, systemic inflammation, and the development of several complications in cirrhosis.

Gut-muscle axis in cirrhosis

The pathology of the gut microbiota (gut dysbiosis and SIBO) influences the development of sarcopenia (gut-muscle axis) in patients with cirrhosis.

Bacterial translocation-induced systemic inflammation causes protein catabolism and decreases muscle mass. This is evidenced by the association of sarcopenia with biomarkers of bacterial translocation (LPS) and systemic inflammation (TNF- α) in cirrhosis[23-24]. TNF- α reduced the formation of proteins in muscles[60]. The injection of LPS into the bodies of experimental animals had a similar effect[61].

The second mechanism of harmful effect of the gut microbiota disorders on the muscle tissue in cirrhosis is based on the fact that an excess amount of bacteria in SIBO competes with the human body for nutrients that enter the intestine with food. In support of this mechanism, an association was found between SIBO and malnutrition in cirrhosis[62].

A third mechanism linking the pathology of the gut microbiota with sarcopenia in cirrhosis is associated with an increase in the formation of myostatin, a protein that enhances protein catabolism in muscles, and inhibits their growth [63-65]. Serum myostatin levels are elevated in patients with cirrhosis and are correlated with the severity of sarcopenia [6]. Increased myostatin formation in patients with cirrhosis is likely associated with hyperammonemia that led to an increase in the myostatin level as well as a decrease in muscle mass and strength by an NF- κ B-mediated mechanism in experimental animals[66]. However, such effects were not observed in mice with knockout of the myostatin gene[66]. The muscles are normally one of the main sources of ammonia in the body. Therefore, through negative feedback, hyperammonemia may reduce muscle mass to reduce the formation of ammonia by muscles. However, in patients with cirrhosis, the main source of ammonia for systemic circulation is the gut microbiota, which catabolize dietary and mucous proteins. Normally, gut microbiota-derived ammonia is neutralized by the liver; however, in patients with cirrhosis, the detoxifying function of the liver is reduced and portocaval shunts work around it, which leads to a dysfunction of this mechanism for regulating the volume of muscle mass[67-70]. In addition, hyperammonemia may lead to the development of sarcopenia in other ways[69], including increased autophagy[71] and inhibition of muscle protein anabolism[72].

The increased serum TNF- α levels are associated with the increased myostatin gene expression and the decreased muscle mass in experimental cirrhosis, suggesting that systemic inflammation can lead to sarcopenia increasing myostatin production among other mechanisms[24].

Several recent studies have reported changes in the composition of the gut microbiota associated with sarcopenia[73-76]. The abundances of Bacteroidaceae, *Eggerthella*, *Escherichia coli*, *Fusobacterium*, Micrococcaceae, *Rothia*, *Veillonella*, *Weissella*, and other bacteria are associated with a decrease in muscle mass, while the abundances of *Acidaminococcus*, *Akkermansia*, *Anaerotruncus*, *Anaerostipes*, *Barnesiellaceae*, *Bifidobacterium catenulatum*, *Catenibacterium*, *Collinsella*, *Coprococcus*, *Coriobacteriaceae*, *Desulfovibrio*, *Dialister*, *Dorea*, *Erysipelatoclostridiaceae*, *Granulicella*, *Intestinimonas*, *Lachnospiraceae*, *Megasphaera*, *Methanobrevibacter*, *Oscillospira*, *Prevotella*, *Ruminococcus flavefaciens*, *Senegalimassilia*, and other bacteria showed an association with normal muscle mass in patients with cirrhosis. The pronounced heterogeneity of these results were obtained that may be caused by different methods used to assess the muscle mass of patients. Patients with sarcopenia had higher serum levels of CRP, TNF- α , interleukin 1- β , 2 and 6, granulocyte-macrophage-colony-stimulating factor, fibroblast growth factor, and C-X-C motif chemokine ligand 10 than patients without it[73]. Although serum LPS and myostatin levels in this study were higher in patients with sarcopenia than in those without, this increase did not reach the limit of significance[73]. There was no significant difference in zonilin and other cytokines levels and reported manifestations of cirrhosis between patients with and without sarcopenia[73]. Patients with sarcopenia were more likely to have ascites, higher Child-Pugh scores[76], and lower albumin levels[75] than patients with normal muscle mass. No other significant associations were reported in these studies on associations between gut microbiota and muscle mass in cirrhosis.

Disorders of the gut-muscle axis in cirrhosis are shown simplified in [Figure 1](#).

Therefore, it is assumed that the condition of the gut microbiota plays an important role in the development of sarcopenia in patients with cirrhosis and therapy aimed at the gut microbiota (antibiotics, prebiotics, probiotics, and fecal transplantation) may be useful in the treatment and prevention of sarcopenia.

PROSPECTS FOR GUT-MUSCLE AXIS THERAPY IN CIRRHOSIS

Treating gut microbiota in patients with cirrhosis: rifaximin

Rifaximin is a poorly-absorbed antibiotic used against harmful intestinal bacteria. Recent meta-analyses have shown that rifaximin effectively eliminates SIBO[77,78] in patients with irritable bowel syndrome[79-82], cystic fibrosis[83], Crohn's disease[84], diabetes[85], celiac disease[86], acromegaly[87], uncomplicated diverticular disease[88,89], systemic sclerosis[90], rosacea[91], and ulcerative colitis[92]. However, rifaximin was ineffective against SIBO in patients after gastrectomy[93]. The meta-analyses also noted that rifaximin is generally well-tolerated and has a low incidence of side effects[77,78]. Other antibiotics, such as chlortetracycline[94], neomycin, doxycycline, amoxicillin/clavulanate, ciprofloxacin[95], and metronidazole[96] were less effective than rifaximin in eradicating SIBO.

Rifaximin also improved intestinal barrier function (reduced blood levels of diamine oxidase and D-lactic acid), mitigated systemic inflammation (decreased serum CRP level and erythrocyte sedimentation rate)[92], and accelerated orocecal transit[85].

Rifaximin increases the abundance of beneficial bacteria (*Akkermansia*, *Bifidobacterium*, *Faecalibacterium prausnitzii*, and *Ruminococcaceae*) and decreases the number of harmful ones (*Alphaproteobacteria*, *Eggerthella*, *Enterococcus*, and *Streptococcaceae*) in several studies ([Table 1](#))[79,97-106].

Meta-analyses have shown that rifaximin is effective in the primary and secondary prevention of spontaneous bacterial peritonitis, a clinical manifestation of bacterial translocation in patients with cirrhosis; rifaximin was superior to norfloxacin and other antibiotics in this respect[107-110]. Rifaximin also reduces the risk of mortality and need for liver transplantation in patients with cirrhosis[111]. In addition, it is effective in the management of hepatic encephalopathy, which is associated with hyperammonemic conditions such as sarcopenia, and significantly reduces blood ammonium levels in patients with cirrhosis[111-113]. One study reported that rifaximin eradicated SIBO in 76% of patients with cirrhosis-associated minimal hepatic encephalopathy, and this was associated with a more prominent decrease in blood ammonium levels than in patients with cirrhosis without SIBO that were also treated with rifaximin[114].

Rifaximin decreased the blood LPS levels in cirrhosis[115-121], and this was associated with a decrease in serum ammonia levels[118]. Rifaximin also reduces circulating neutrophil expression of TLR-4, which is the main endotoxin receptor[122]. However, the effects of rifaximin on various biomarkers of systemic inflammation in cirrhosis have been inconsistent across studies.

Importantly, rifaximin does not alter the overall resistome[123]; *i.e.*, their intake does not lead to the development of antibacterial resistance. Rifaximin also reduces the rate of all bacterial infections[124] and variceal bleeding in patients with cirrhosis[125-126], prevents the development of hepatorenal syndrome[127-128] and refractory ascites[129-130]. The use of rifaximin in patients with cirrhosis led to a decrease in the abundance of harmful *Streptococcus*, *Eggerthella*, and *Veillonella* ([Table 2](#))[42,117-120,122,130,131].

Overall, the literature suggests that rifaximin does positive affect the main pathogenetic links of the disordered gut-muscle axis in cirrhosis, in particular SIBO, hyperammonemia, and bacterial translocation. Rifaximin also modulates the composition of the gut microbiota reducing the number of bacterial taxa has been associated with muscle loss in patients with cirrhosis. This drug has shown excellent safety and tolerability for long-term use in patients with cirrhosis[127,132,133]. It is very important, since the prevention and treatment of sarcopenia require long-term therapy. This suggests that rifaximin may be effective and safe for these purposes in cirrhosis.

Although other antibiotics have also had positive effects on the prevention of spontaneous bacterial peritonitis, hepatic encephalopathy, and the reduction of bacterial translocation and hyperammonemia in patients with cirrhosis[111,134-136], most of them have poorer safety profiles and fewer number of studies. Thereby, recommendations to investigate their long-term effects on the prevention and treatment of sarcopenia in patients with cirrhosis seem premature. However, this does not exclude their potential use when new data on the efficacy and safety of their long-term use become available.

Rifaximin prevents skeletal muscle atrophy and weakness by decreasing intramuscular myostatin and pro-inflammatory cytokine levels in experimental cirrhosis[24,137]. An uncontrolled study showed that the long-term use of rifaximin in patients with cirrhosis improved nutritional status and allowed patients to maintain a constant amount of muscle mass[138]. Randomized placebo-controlled studies on the effects of long-term rifaximin use on muscle mass, serum myostatin, and other biomarkers of gut-muscle axis disorders in cirrhosis are required to verify this data.

Treating gut microbiota in patients with cirrhosis: prebiotic disaccharides lactulose and lactitol

Lactulose and lactitol are artificial disaccharides that are not broken down by human digestive enzymes and are utilized by the intestinal microbiota. These drugs are primarily used as osmotic laxatives for conditions that involve constipation (including irritable bowel syndrome)[139-141]. They also used for the prevention and treatment of hepatic encephalopathy[142,143], because the abundance of these carbohydrates switches the metabolism of gut bacteria from proteolytic to saccharolytic. This leads to a decrease in the formation of ammonium and other neurotropic metabolites of amino acids[144], and their laxative effects accelerate the removal of these harmful products from the intestine.

Table 1 The effect of rifaximin on the composition of the gut microbiota in various diseases

Disease	Taxa that increase in the abundance after rifaximin	Taxa that decrease in the abundance after rifaximin
Alzheimer's disease [97]	Anaerostipes, Blautia, Erysipelotrichaceae, Erysipelatoclostridium, Faecalitalea, Lactobacillus, and Ruminiclostridium	
Irritable bowel syndrome [79,98-100]	Acidimicrobiales, Acidobacteria, Alteromonas, Arthrobacter, Bacillus, Bacteroidaceae, Butyricimonas, Chloroflexi, Cytophagia, Coprobacillus, Bifidobacterium, Deinococcales, Devosia, Dyella, Faecalibacterium prausnitzii, Frankiales, Gordonibacter, Holdemania, Kocuria, Methylophilales, Micrococcales, Micromonosporales, Nitriliruptorales, Parabacteroides, Prevotellaceae, Propionibacteriales, Rhizobiales, Rhodobacterales, Sphingomonadales, and Streptomyces	Alphaproteobacteria, Anaerotruncus, Blautia luti, Butyricimonas, Cronobacter, Escherichia, Eubacterium ventriosum, Rhodospirillales, Romboutsia, Roseburia inulinivorans, Streptococcaceae, and Tyzzerella
Symptomatic uncomplicated diverticular disease [101-102]	Akkermansia, Bacteroidaceae, Citrobacter, Coprococcus, Dialister Ruminococcaceae, and Veillonellaceae	Anaerotruncus, Anaerostipes, Blautia, Christensenellaceae, Dehalobacteriaceae, Eggerthella lenta, Haemophilus parainfluenzae, Mogibacteriaceae, and Pasteurellaceae
Chronic Kidney Disease [103]	-	Anaerotruncus, Clostridium, and Turicibacter
Gut diseases [104]	Faecalibacterium	Ruminococcus and Roseburia
Ulcerative colitis [105]	Bacteroides and Bifidobacterium	Enterococcus and Lactobacillus
Crohn's disease [106]	Bifidobacterium, Atopobium, and Faecalibacterium prausnitzii	

Table 2 The effect of rifaximin on the composition of the gut microbiota in patients with cirrhosis

Ref.	Taxa that increase in the abundance after rifaximin	Taxa that decrease in the abundance after rifaximin
Bajaj <i>et al</i> [120]	Eubacteriaceae	Veillonellaceae
Kaji <i>et al</i> [117]		Streptococcus, Veillonella
Kaji <i>et al</i> [118]		Streptococcus, Veillonella
Kakiyama <i>et al</i> [42]		Veillonellaceae
Kawaguchi <i>et al</i> [131]		Lactobacillus, Streptococcus, Veillonella
Lv <i>et al</i> [130]	Bacteroides vulgatus	Bacteroides uniformis, Eggerthella lenta, Haemophilus, Prevotella, Roseburia
Patel <i>et al</i> [122]		Akkermansia, Hungatella, Streptococcus, Veillonella
Zeng <i>et al</i> [119]	Bacteroidaceae	Veillonellaceae

Meta-analyses have shown that lactulose and lactitol are effective against hepatic encephalopathy and that they reduce blood ammonia levels. They also decrease the risk of other serious liver-related adverse events, such as liver failure, variceal bleeding, hepatorenal syndrome, spontaneous bacterial peritonitis and other serious infections. These drugs also have excellent safety profiles and have been shown to reduce mortality [111,145-148].

Lactulose and lactitol can be safely taken for six months or more [149-151]. However, they may cause steatorrhea, which can worsen the nutritional status of patients [152].

We were unable to find any data on the effects of these disaccharides on SIBO. Two factors should be considered in this case. First, since these drugs are growth factors for bacteria, they can provoke the development of SIBO. However, SIBO can be eliminated by accelerating intestinal motility caused by these drugs. Further research is required to determine which effect outweighs the other.

The intake of lactitol was accompanied by an increase in the abundance of *Bifidobacterium*, *Lactobacillus*, *Veillonella*, *Enterobacter*, *Sutterella*, *Haemophilus*, and *Aggregatibacter*, and a decrease in the abundance of *Bacteroides*, *Clostridium*, *Eubacterium*, *Klebsiella*, *Pseudoflavonifractor*, and coliform bacteria (Table 3) [153-157]. In addition, there was a decrease in the LPS concentration in the blood of patients with chronic viral hepatitis [158].

The use of lactulose is associated with an increase in the levels of *Bifidobacterium* and *Lactobacillus* and a decrease in the abundance of *Clostridium*, *Eubacterium*, *Enterococcus*, and *Enterobacteriaceae* in patients with cirrhosis (Table 3) [153,154,159,160]. However, other studies have not shown an effect of lactulose on the composition of gut microbiota [161,162]. Several studies demonstrated that the use of lactulose in patients with minimal hepatic encephalopathy led to a decrease in the blood levels of LPS, bacterial DNA, and pro-inflammatory cytokines (TNF- α , IL-6 and IL-18) [160,163,164].

Table 3 The effect of lactitol and lactulose on the composition of the gut microbiota

Ref.	Disease	Taxa that increase in the abundance after disaccharide	Taxa that decrease in the abundance after disaccharide
Lactitol			
Riggio <i>et al</i> [153]	Cirrhosis	Lactobacilli	Enterobacteria and Enterocicci
Ballongue <i>et al</i> [154]	Healthy persons	Bifidobacterium, <i>Lactobacillus</i> and <i>Streptococcus</i>	Bacteroides, Clostridium, coliforms, and <i>Eubacterium</i>
Li <i>et al</i> [155]	Chronic constipation	Actinobacteria, Bifidobacteriales, Bifidobacteriaceae, <i>Anaerostipes</i> , and <i>Bifidobacterium</i>	-
Tarao <i>et al</i> [156]	Cirrhosis	Bifidobacterium and <i>Lactobacillus</i>	Bacteroides and <i>Clostridium</i>
Lu <i>et al</i> [157]	Cirrhosis	Bifidobacterium, Veillonella, Enterobacter, Sutterella, Haemophilus, <i>Aggregatibacter</i> , <i>Lactobacillus salivarius</i> , <i>L. fermentum</i> , and <i>L. oris</i>	Klebsiella <i>Pseudoflavonifractor</i> , and others
Chen <i>et al</i> [158]	Chronic viral hepatitis	Bifidobacterium and <i>Lactobacillus</i>	Clostridium perfringens
Lactulose			
Riggio <i>et al</i> [153]	Cirrhosis	Lactobacilli	-
Ballongue <i>et al</i> [154]	Healthy persons	Bifidobacterium, <i>Lactobacillus</i> and <i>Streptococcus</i>	Bacteroides, <i>Clostridium</i> , coliforms and <i>Eubacterium</i>
Ziada <i>et al</i> [159]	Minimal hepatic encephalopathy	Bifidobacterium, <i>Lactobacillus</i> , and Bacteroidaceae	Enterobacteriaceae and <i>Enterococcus</i>

The use of lactulose and lactitol has also been associated with a decrease in the amount of bacterial proteolysis products such as cresol, skatol, phenol, and indole in the feces, as well as an increase in the amount of lactate in the feces. Lactate can acidify the feces [154] and convert neutral ammonia to ammonium ions which, unlike ammonia, do not pass through the intestinal barrier because of the presence of an electric charge. Thus, these drugs not only decrease the bacterial catabolism of amino acids with the formation of ammonia, but also decrease ammonia absorption from the intestine. These drugs significantly reduce hyperammonemia after an amino acid load [143].

Thereby, these prebiotic disaccharides reduce the severity of the following adverse factors of the disordered gut-muscle axis in cirrhosis: hyperammonemia, bacterial translocation, and systemic inflammation. Most studies have shown positive effects of these drugs on the composition of the gut microbiota. However, their impact on SIBO is yet to be explored. These drugs are considered safe for long-term use. However, their effects on myostatin levels and muscle mass in patients with cirrhosis and other diseases have not been studied.

Treating gut microbiota in patients with cirrhosis: probiotics

Probiotics are live microorganisms that confer health benefits to the host when administered in adequate amounts [165]. They can be used to treat liver diseases [165-166].

Meta-analyses have shown that probiotics are effective in the prevention and treatment of hepatic encephalopathy and that they decrease the blood levels of LPS and ammonia. However, they do not have a significant effect on mortality or the incidence of spontaneous bacterial peritonitis in patients with cirrhosis [111,167-170]. A meta-analysis did not show that probiotics have a significant effect on the serum level of pro-inflammatory cytokines (TNA-alpha and IL-6) [169]. Another meta-analysis revealed that probiotics do not significantly affect CRP levels, but they lead to a decrease in TNF-α levels [171]. Among the studies not included in these meta-analyses, the following described the effect of probiotics on inflammatory biomarkers in cirrhosis. The probiotic fungus *Saccharomyces boulardii* decreases serum CRP levels and ameliorates hyperdynamic circulation in patients with decompensated cirrhosis [172]. *Escherichia coli* Nissle 1917 reduced the serum levels of IL-6, IL-8, and interferon-γ in patients with hepatic encephalopathy [160]. The probiotics that included *Clostridium butyricum* and *Bifidobacterium infantis* strengthen the intestinal barrier [173].

Probiotics have been shown to be safe when used for six months in patients with cirrhosis [174].

The use of probiotics in cirrhosis leads to an increase in the numbers of *Bifidobacterium*, *Lactobacillus*, Lachnospiraceae, Bacteroidaceae, Clostridiales incertae sedis XIV, *Faecalibacterium prausnitzii*, *Syntrophococcus sucromutans*, *Bacteroides vulgatus*, *Prevotella*, *Alistipes shahii*, *Clostridium* cluster I, *Clostridium coccoides*, and *Eubacterium cylindroides* and a decrease in the numbers of Enterobacteriaceae, *Enterococcus*, *Proteus hauseri*, *Citrobacter* sp., and *Morganella* (Table 4) [159,160,175-178].

Meta-analyses have also shown that probiotics effectively eliminate SIBO [179-180]. This has been observed in patients with cirrhosis [181], chronic liver disease [182], secondary lactase deficiency [183], diarrhea-predominant irritable bowel syndrome [184-186], gastric and colorectal cancer [187], systemic sclerosis [188], and bariatric surgery [189].

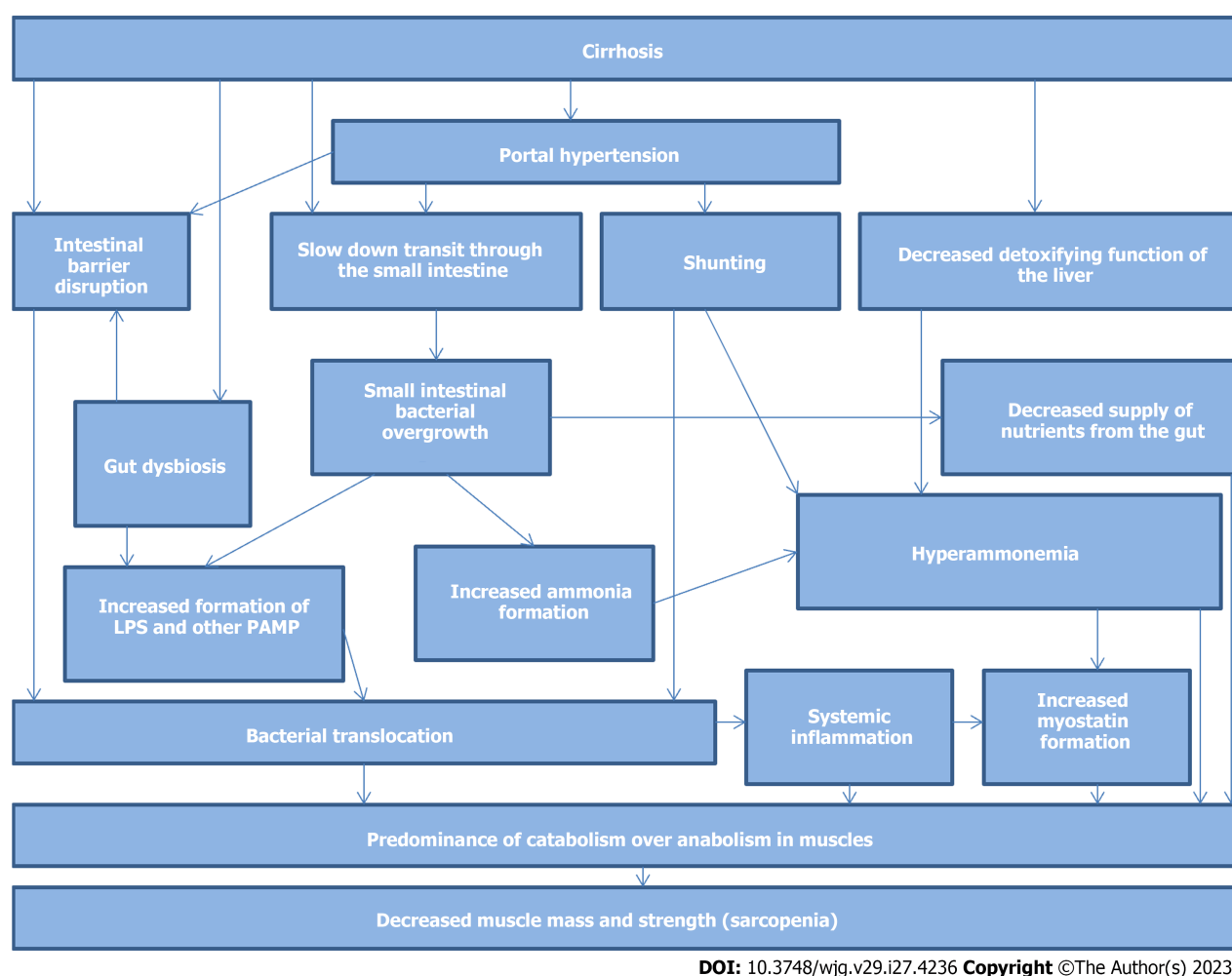


Figure 1 Simplified diagram of gut-muscle axis disorders in patients with cirrhosis. LPS: Lipopolysaccharide; PAMP: Pathogen-associated molecular patterns.

The meta-analysis showed that probiotics enhance both muscle mass and muscle strength in patients with sarcopenia that was not associated with cirrhosis[190]. The probiotic that included *Akkermansia muciniphila* and *Faecalibacterium prausnitzii* decreased myostatin levels in a mouse model of muscular atrophy[191].

Although probiotics have been shown to be effective against several pathological links of the disturbed gut-muscle axis in patients with cirrhosis (SIBO, gut dysbiosis, hyperammonemia, and bacterial translocation), improve muscle function, and increase muscle mass in sarcopenia of another origin, no study has evaluated the effect of probiotics on muscle mass and function in cirrhosis.

Treating gut microbiota in cirrhosis: fecal transplantation

Fecal transplantation involves the transfer of intestinal microbiota from the donor to the intestine of a recipient. This procedure is effective in hepatic encephalopathy[192-194] and leads to an increase in the abundance of Ruminococcaceae and Bifidobacteriaceae and a decrease in the abundance of Streptococcaceae and Veillonellaceae in patients with cirrhosis [193].

No data exist on the effects of this procedure on the severity of hyperammonemia, bacterial translocation, systemic inflammation, myostatin levels, muscle mass and strength, or SIBO in patients with cirrhosis. No human studies have been conducted on the effect of fecal transplantation on muscle mass and strength in patients with sarcopenia of any origin; however, the results of animal experimental studies are promising[195].

CONCLUSION

Drug interventions targeting the gut microbiota positively affect most links of the compromised gut-muscle axis in cirrhosis (Table 5, Figure 2). Therefore, they are promising for the treatment and prevention of sarcopenia in cirrhosis, but have not yet been investigated in randomized controlled trials for these purposes. There are no data on the effect of fecal transplantation on most links of the gut-muscle axis and sarcopenia in cirrhosis, but the results of animal experimental studies are promising.

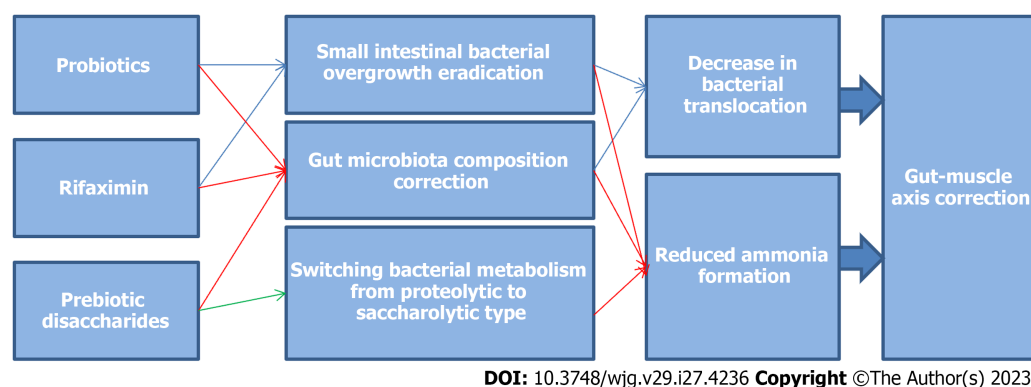
Table 4 The effect of probiotics on the composition of the gut microbiota in cirrhosis

Probiotic	Taxa that increase in the abundance after the probiotic	Taxa that decrease in the abundance after the probiotic
Lactobacillus acidophilus[159]	Bifidobacterium, Lactobacillus, and Bacteroidaceae	Enterobacteriaceae and Enterococcus
Escherichia coli Nissle 1917[160]	Bifidobacterium and Lactobacillus	Pathogenic enterobacteria
Escherichia coli Nissle 1917[175]	Bifidobacterium and Lactobacillus	Proteus hauseri, Citrobacter, and Morganella
Yakult 400[176]	Clostridium coccoides and Eubacterium cylindroides	Enterobacteriaceae
Lactobacillus GG[177]	Clostridiales Incertae Sedis XIV and Lachnospiraceae	Enterobacteriaceae
Bifidobacterium bifidum W23, Bifidobacterium lactis W51, Bifidobacterium lactis W52, Lactobacillus acidophilus W37, Lactobacillus brevis W63, Lactobacillus casei W56, Lactobacillus salivarius W24, Lactococcus lactis W19 and Lactococcus lactis W58[178]	Faecalibacterium prausnitzii, Syntrophococcus sucromutans, Bacteroides vulgatus, Alistipes shahii, and Prevotella	

Table 5 Effects of interventions targeting the gut microbiota on pathogenic factors in the gut-muscle axis in cirrhosis

Intervention	SIBO	Gut dysbiosis	Hyperammonemia	Bacterial translocation	Systemic inflammation
Rifaximin	+	+	+	+	CR
Prebiotic disaccharides	ND	+	+	+	+
Probiotics	+	+	+	+	CR
Fecal transplantation	ND	+	ND	ND	ND

+: A positive effect of this drug on this disorder has been reported; SIBO: Small intestinal bacterial overgrowth; CR: Conflicting results, ND: No data.

**Figure 2** Proposed mechanisms of action of drugs targeting the gut-muscle axis in cirrhosis.

FOOTNOTES

Author contributions: Ivashkin V suggested the idea of the review; All authors contributed to the draft editing; Maslennikov R is the guarantor.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: Russia

ORCID number: Roman Maslennikov 0000-0001-7513-1636; Aliya Alieva 0000-0002-7606-2246; Elena Poluektova 0000-0002-9038-3732; Yury Zharikov 0000-0001-9636-3807; Andrey Suslov 0000-0003-0613-8556; Yana Letyagina 0009-0003-0491-5179; Evgenii Kozlov 0000-0001-6244-1088; Vladimir Ivashkin 0000-0002-6815-6015.

S-Editor: Li L

L-Editor: A

P-Editor: Cai YX

REFERENCES

- Hari A.** Muscular abnormalities in liver cirrhosis. *World J Gastroenterol* 2021; **27**: 4862-4878 [PMID: 34447231 DOI: 10.3748/wjg.v27.i29.4862]
- Anand A, Nambirajan A, Kumar V, Agarwal S, Sharma S, Mohta S, Gopi S, Kaushal K, Gunjan D, Singh N, Madhusudhan KS, Chauhan SS, Sharma MC, Bansal VK, Saraya A.** Alterations in Autophagy and Mammalian Target of Rapamycin (mTOR) Pathways Mediate Sarcopenia in Patients with Cirrhosis. *J Clin Exp Hepatol* 2022; **12**: 510-518 [PMID: 35535114 DOI: 10.1016/j.jceh.2021.05.004]
- Guo G, Li C, Hui Y, Mao L, Sun M, Li Y, Yang W, Wang X, Yu Z, Fan X, Jiang K, Sun C.** Sarcopenia and frailty combined increases the risk of mortality in patients with decompensated cirrhosis. *Ther Adv Chronic Dis* 2022; **13**: 20406223221109651 [PMID: 35875834 DOI: 10.1177/20406223221109651]
- Hernández-Conde M, Llop E, Gómez-Pimpollo L, Blanco S, Rodríguez L, Fernández Carrillo C, Perelló C, López-Gómez M, Martínez-Porras JL, Fernández-Puga N, Van Den Brule E, Royuela A, Calleja JL.** A nomogram as an indirect method to identify sarcopenia in patients with liver cirrhosis. *Ann Hepatol* 2022; **27**: 100723 [PMID: 35580823 DOI: 10.1016/j.aohep.2022.100723]
- De A, Kumari S, Kaur A, Singh A, Kalra N, Singh V.** Hand-grip strength as a screening tool for sarcopenia in males with decompensated cirrhosis. *Indian J Gastroenterol* 2022; **41**: 284-291 [PMID: 35852763 DOI: 10.1007/s12664-022-01255-2]
- Boga S, Yildirim AE, Ucbilek E, Koksar AR, Sisman ST, Durak I, Sen I, Dogu B, Serin E, Ucbilek AB, Yildirim MO, Erturk SM, Alkim H, Alkim C.** The effect of sarcopenia and serum myokines on prognosis and survival in cirrhotic patients: a multicenter cross-sectional study. *Eur J Gastroenterol Hepatol* 2022; **34**: 1261-1268 [PMID: 36281901 DOI: 10.1097/MEG.0000000000002461]
- Warner I ER, Satapathy SK.** Sarcopenia in the Cirrhotic Patient: Current Knowledge and Future Directions. *J Clin Exp Hepatol* 2023; **13**: 162-177 [PMID: 36647414 DOI: 10.1016/j.jceh.2022.06.005]
- Kuchay MS, Martínez-Montoro JJ, Llamaza-Torres CJ, Fernández-García JC, Ramos-Molina B.** Liver cirrhosis and sarcopenia: a dreadful combination. *Hepatobiliary Surg Nutr* 2022; **11**: 729-731 [PMID: 36268240 DOI: 10.21037/hbsn-22-355]
- Kumar R, Prakash SS, Priyadarshi RN, Anand U.** Sarcopenia in Chronic Liver Disease: A Metabolic Perspective. *J Clin Transl Hepatol* 2022; **10**: 1213-1222 [PMID: 36381104 DOI: 10.14218/JCTH.2022.00239]
- Fox R, Stenning K, Slee A, Macnaughtan J, Davies N.** Sarcopenia in liver cirrhosis: Prevalence, pathophysiology and therapeutic strategies. *Anal Biochem* 2022; **647**: 114581 [PMID: 35134388 DOI: 10.1016/j.ab.2022.114581]
- Khan S, Benjamin J, Maiwall R, Tripathi H, Kapoor PB, Shasthry V, Saluja V, Agrawal P, Thapar S, Kumar G.** Sarcopenia is the independent predictor of mortality in critically ill patients with cirrhosis. *J Clin Transl Res* 2022; **8**: 200-208 [PMID: 35813898]
- Matsui T, Nagai H, Watanabe G, Mouri K, Yoshimine N, Amanuma M, Kobayashi K, Ogino Y, Mukozu T, Matsukiyo Y, Daidou Y, Wakui N, Nakano S, Momiyama K, Matsuda T, Igarashi Y.** Measurement of skeletal muscle volume is useful for predicting prognosis in patients with liver cirrhosis. *Eur J Gastroenterol Hepatol* 2022; **34**: 1151-1157 [PMID: 36170684 DOI: 10.1097/MEG.0000000000002435]
- Kim TH, Jung YK, Yim HJ, Baik JW, Yim SY, Lee YS, Seo YS, Kim JH, Yeon JE, Byun KS.** Impacts of muscle mass dynamics on prognosis of outpatients with cirrhosis. *Clin Mol Hepatol* 2022; **28**: 876-889 [PMID: 36117443 DOI: 10.3350/cmh.2022.0231]
- Tantai X, Liu Y, Yeo YH, Praktiknjo M, Mauro E, Hamaguchi Y, Engelmann C, Zhang P, Jeong JY, van Vugt JLA, Xiao H, Deng H, Gao X, Ye Q, Zhang J, Yang L, Cai Y, Liu N, Li Z, Han T, Kaido T, Sohn JH, Strassburg C, Berg T, Trebicka J, Hsu YC, IJzermans JNM, Wang J, Su GL, Ji F, Nguyen MH.** Effect of sarcopenia on survival in patients with cirrhosis: A meta-analysis. *J Hepatol* 2022; **76**: 588-599 [PMID: 34785325 DOI: 10.1016/j.jhep.2021.11.006]
- Shanavas N, Devadas K, Nahaz N, Varghese J, Cyriac R, Mathew D.** Association of Sarcopenia with Health Related Quality of Life in Cirrhotics. *J Assoc Physicians India* 2021; **69**: 11-12 [PMID: 34781614]
- Topan MM, Sporea I, Dănilă M, Popescu A, Ghiuchici AM, Lupuşoru R, Şirli R.** Impact of Sarcopenia on Survival and Clinical Outcomes in Patients With Liver Cirrhosis. *Front Nutr* 2021; **8**: 766451 [PMID: 34746216 DOI: 10.3389/fnut.2021.766451]
- Zeng X, Shi ZW, Yu JJ, Wang LF, Luo YY, Jin SM, Zhang LY, Tan W, Shi PM, Yu H, Zhang CQ, Xie WF.** Sarcopenia as a prognostic predictor of liver cirrhosis: a multicentre study in China. *J Cachexia Sarcopenia Muscle* 2021; **12**: 1948-1958 [PMID: 34520115 DOI: 10.1002/jcsm.12797]
- Nardelli S, Riggio O, Gioia S, Merli M, Spagnoli A, di Martino M, Pelle G, Ridola L.** Risk factors for hepatic encephalopathy and mortality in cirrhosis: The role of cognitive impairment, muscle alterations and shunts. *Dig Liver Dis* 2022; **54**: 1060-1065 [PMID: 35058135 DOI: 10.1016/j.dld.2021.12.015]
- Miwa T, Hanai T, Nishimura K, Maeda T, Ogiso Y, Imai K, Suetsugu A, Takai K, Shiraki M, Shimizu M.** Handgrip strength stratifies the risk of covert and overt hepatic encephalopathy in patients with cirrhosis. *JPEN J Parenter Enteral Nutr* 2022; **46**: 858-866 [PMID: 34287991 DOI: 10.1002/jpen.2222]
- Dajti E, Renzulli M, Ravaioli F, Marasco G, Vara G, Brandi N, Rossini B, Colecchia L, Alemanni LV, Ferrarese A, Vestito A, Tamè M, Azzaroli F, Festi D, Golfieri R, Colecchia A.** The interplay between sarcopenia and portal hypertension predicts ascites and mortality in cirrhosis. *Dig Liver Dis* 2023; **55**: 637-643 [PMID: 36470723 DOI: 10.1016/j.dld.2022.11.011]
- Ebadi M, Tsien C, Bhanji RA, Dunichand-Hoedl AR, Rider E, Motamedrad M, Mazurak VC, Baracos V, Montano-Loza AJ.** Skeletal Muscle Pathological Fat Infiltration (Myosteatosis) Is Associated with Higher Mortality in Patients with Cirrhosis. *Cells* 2022; **11** [PMID: 35456024 DOI: 10.3390/cells11081345]
- Ishizu Y, Ishigami M, Honda T, Imai N, Ito T, Yamamoto K, Yokoyama S, Ishikawa T, Kawashima H.** Decreased appetite is associated with the presence of sarcopenia in patients with cirrhosis. *Nutrition* 2022; **103-104**: 111807 [PMID: 36029694 DOI: 10.1016/j.nut.2022.111807]

- 23 **Sato S**, Namisaki T, Murata K, Fujimoto Y, Takeda S, Enomoto M, Shibamoto A, Ishida K, Ogawa H, Takagi H, Tsuji Y, Kaya D, Fujinaga Y, Furukawa M, Inoue T, Sawada Y, Nishimura N, Kitagawa K, Ozutsumi T, Takaya H, Kaji K, Shimozato N, Kawaratani H, Moriya K, Akahane T, Mitoro A, Yoshiji H. The association between sarcopenia and endotoxin in patients with alcoholic cirrhosis. *Medicine (Baltimore)* 2021; **100**: e27212 [PMID: [34516526](#) DOI: [10.1097/MD.00000000000027212](#)]
- 24 **Han JW**, Kim DI, Nam HC, Chang UI, Yang JM, Song DS. Association between serum tumor necrosis factor- α and sarcopenia in liver cirrhosis. *Clin Mol Hepatol* 2022; **28**: 219-231 [PMID: [34281295](#) DOI: [10.3350/cmh.2021.0082](#)]
- 25 **Sinclair M**, Grossmann M, Angus PW, Hoermann R, Hey P, Scodellaro T, Gow PJ. Low testosterone as a better predictor of mortality than sarcopenia in men with advanced liver disease. *J Gastroenterol Hepatol* 2016; **31**: 661-667 [PMID: [26414812](#) DOI: [10.1111/jgh.13182](#)]
- 26 **Maslennikov R**, Ivashkin V, Efremova I, Poluektova E, Shirokova E. Gut-liver axis in cirrhosis: Are hemodynamic changes a missing link? *World J Clin Cases* 2021; **9**: 9320-9332 [PMID: [34877269](#) DOI: [10.12998/wjcc.v9.i31.9320](#)]
- 27 **Giannelli V**, Di Gregorio V, Iebba V, Giusto M, Schippa S, Merli M, Thalheimer U. Microbiota and the gut-liver axis: bacterial translocation, inflammation and infection in cirrhosis. *World J Gastroenterol* 2014; **20**: 16795-16810 [PMID: [25492994](#) DOI: [10.3748/wjg.v20.i45.16795](#)]
- 28 **Arab JP**, Martin-Mateos RM, Shah VH. Gut-liver axis, cirrhosis and portal hypertension: the chicken and the egg. *Hepatol Int* 2018; **12**: 24-33 [PMID: [28550391](#) DOI: [10.1007/s12072-017-9798-x](#)]
- 29 **Gómez-Hurtado I**, Such J, Sanz Y, Francés R. Gut microbiota-related complications in cirrhosis. *World J Gastroenterol* 2014; **20**: 15624-15631 [PMID: [25400446](#) DOI: [10.3748/wjg.v20.i42.15624](#)]
- 30 **Jin M**, Kalainy S, Baskota N, Chiang D, Deehan EC, McDougall C, Tandon P, Martínez I, Cervera C, Walter J, Abalde JG. Faecal microbiota from patients with cirrhosis has a low capacity to ferment non-digestible carbohydrates into short-chain fatty acids. *Liver Int* 2019; **39**: 1437-1447 [PMID: [30919578](#) DOI: [10.1111/liv.14106](#)]
- 31 **Zeng Y**, Chen S, Fu Y, Wu W, Chen T, Chen J, Yang B, Ou Q. Gut microbiota dysbiosis in patients with hepatitis B virus-induced chronic liver disease covering chronic hepatitis, liver cirrhosis and hepatocellular carcinoma. *J Viral Hepat* 2020; **27**: 143-155 [PMID: [31600845](#) DOI: [10.1111/jvh.13216](#)]
- 32 **Kajihara M**, Koido S, Kanai T, Ito Z, Matsumoto Y, Takakura K, Saruta M, Kato K, Odamaki T, Xiao JZ, Sato N, Ohkusa T. Characterisation of blood microbiota in patients with liver cirrhosis. *Eur J Gastroenterol Hepatol* 2019; **31**: 1577-1583 [PMID: [31441799](#) DOI: [10.1097/MEG.0000000000001494](#)]
- 33 **Chen Z**, Xie Y, Zhou F, Zhang B, Wu J, Yang L, Xu S, Stedtfeld R, Chen Q, Liu J, Zhang X, Xu H, Ren J. Featured Gut Microbiomes Associated With the Progression of Chronic Hepatitis B Disease. *Front Microbiol* 2020; **11**: 383 [PMID: [32265857](#) DOI: [10.3389/fmicb.2020.00383](#)]
- 34 **Zheng R**, Wang G, Pang Z, Ran N, Gu Y, Guan X, Yuan Y, Zuo X, Pan H, Zheng J, Wang F. Liver cirrhosis contributes to the disorder of gut microbiota in patients with hepatocellular carcinoma. *Cancer Med* 2020; **9**: 4232-4250 [PMID: [32281295](#) DOI: [10.1002/cam4.3045](#)]
- 35 **Lapidot Y**, Amir A, Nosenko R, Uzan-Yulzari A, Veitsman E, Cohen-Ezra O, Davidov Y, Weiss P, Bradichevski T, Segev S, Koren O, Safran M, Ben-Ari Z. Alterations in the Gut Microbiome in the Progression of Cirrhosis to Hepatocellular Carcinoma. *mSystems* 2020; **5** [PMID: [32546668](#) DOI: [10.1128/mSystems.00153-20](#)]
- 36 **Bajaj JS**, Heuman DM, Hylemon PB, Sanyal AJ, White MB, Monteith P, Noble NA, Unser AB, Daita K, Fisher AR, Sikaroodi M, Gillevet PM. Altered profile of human gut microbiome is associated with cirrhosis and its complications. *J Hepatol* 2014; **60**: 940-947 [PMID: [24374295](#) DOI: [10.1016/j.jhep.2013.12.019](#)]
- 37 **Ahluwalia V**, Betrapally NS, Hylemon PB, White MB, Gillevet PM, Unser AB, Fagan A, Daita K, Heuman DM, Zhou H, Sikaroodi M, Bajaj JS. Impaired Gut-Liver-Brain Axis in Patients with Cirrhosis. *Sci Rep* 2016; **6**: 26800 [PMID: [27225869](#) DOI: [10.1038/srep26800](#)]
- 38 **Liu Y**, Jin Y, Li J, Zhao L, Li Z, Xu J, Zhao F, Feng J, Chen H, Fang C, Shilpakar R, Wei Y. Small Bowel Transit and Altered Gut Microbiota in Patients With Liver Cirrhosis. *Front Physiol* 2018; **9**: 470 [PMID: [29780327](#) DOI: [10.3389/fphys.2018.00470](#)]
- 39 **Inoue T**, Nakayama J, Moriya K, Kawaratani H, Momoda R, Ito K, Iio E, Nojiri S, Fujiwara K, Yoneda M, Yoshiji H, Tanaka Y. Gut Dysbiosis Associated With Hepatitis C Virus Infection. *Clin Infect Dis* 2018; **67**: 869-877 [PMID: [29718124](#) DOI: [10.1093/cid/ciy205](#)]
- 40 **Maslennikov R**, Ivashkin V, Efremova I, Alieva A, Kashuh E, Tsvetaeva E, Poluektova E, Shirokova E, Ivashkin K. Gut dysbiosis is associated with poorer long-term prognosis in cirrhosis. *World J Hepatol* 2021; **13**: 557-570 [PMID: [34131470](#) DOI: [10.4254/wjh.v13.i5.557](#)]
- 41 **Chen Y**, Yang F, Lu H, Wang B, Chen Y, Lei D, Wang Y, Zhu B, Li L. Characterization of fecal microbial communities in patients with liver cirrhosis. *Hepatology* 2011; **54**: 562-572 [PMID: [21574172](#) DOI: [10.1002/hep.24423](#)]
- 42 **Kakiyama G**, Pandak WM, Gillevet PM, Hylemon PB, Heuman DM, Daita K, Takei H, Muto A, Nittono H, Ridlon JM, White MB, Noble NA, Monteith P, Fuchs M, Thacker LR, Sikaroodi M, Bajaj JS. Modulation of the fecal bile acid profile by gut microbiota in cirrhosis. *J Hepatol* 2013; **58**: 949-955 [PMID: [23333527](#) DOI: [10.1016/j.jhep.2013.01.003](#)]
- 43 **Nicoletti A**, Ponzianni FR, Biolato M, Valenza V, Marrone G, Sganga G, Gasbarrini A, Miele L, Grieco A. Intestinal permeability in the pathogenesis of liver damage: From non-alcoholic fatty liver disease to liver transplantation. *World J Gastroenterol* 2019; **25**: 4814-4834 [PMID: [31543676](#) DOI: [10.3748/wjg.v25.i33.4814](#)]
- 44 **Lian XX**, Sun YP, Guo XX. [Correlation between intestinal mucosal permeability and prognosis in patients with liver cirrhosis]. *Zhonghua Gan Zang Bing Za Zhi* 2020; **28**: 58-63 [PMID: [32023701](#) DOI: [10.3760/cma.j.issn.1007-3418.2020.01.014](#)]
- 45 **Choi Y**, Jeon WK, Hwang SJ, Kim BI, Sohn CI, Park DI, Cho YK, Kim HJ, Park JH. The role of the gut barrier function in the pathophysiology of viral liver cirrhosis. *Hepatogastroenterology* 2011; **58**: 1244-1247 [PMID: [21937387](#) DOI: [10.5754/hge10338](#)]
- 46 **Assimakopoulos SF**, Tsamandas AC, Tsiaoussis GI, Karatzas E, Triantos C, Vagianos CE, Spiliopoulou I, Kaltezioti V, Charonis A, Nikolopoulou VN, Scopa CD, Thomopoulos KC. Altered intestinal tight junctions' expression in patients with liver cirrhosis: a pathogenetic mechanism of intestinal hyperpermeability. *Eur J Clin Invest* 2012; **42**: 439-446 [PMID: [22023490](#) DOI: [10.1111/j.1365-2362.2011.02609.x](#)]
- 47 **Bach Knudsen KE**, Lærke HN, Hedemann MS, Nielsen TS, Ingerslev AK, Gundelund Nielsen DS, Theil PK, Purup S, Hald S, Schioldan AG, Marco ML, Gregersen S, Hermansen K. Impact of Diet-Modulated Butyrate Production on Intestinal Barrier Function and Inflammation. *Nutrients* 2018; **10** [PMID: [30322146](#) DOI: [10.3390/nu10101499](#)]
- 48 **Shulpekova Y**, Zharkova M, Tkachenko P, Tikhonov I, Stepanov A, Synitsyna A, Izotov A, Butkova T, Shulpekova N, Lapina N, Nechaev V, Kardasheva S, Okhlobystin A, Ivashkin V. The Role of Bile Acids in the Human Body and in the Development of Diseases. *Molecules* 2022; **27** [PMID: [35684337](#) DOI: [10.3390/molecules27113401](#)]
- 49 **Bajaj JS**, Vargas HE, Reddy KR, Lai JC, O'Leary JG, Tandon P, Wong F, Mitrani R, White MB, Kelly M, Fagan A, Patil R, Sait S, Sikaroodi M, Thacker LR, Gillevet PM. Association Between Intestinal Microbiota Collected at Hospital Admission and Outcomes of Patients With Cirrhosis. *Clin Gastroenterol Hepatol* 2019; **17**: 756-765.e3 [PMID: [30036646](#) DOI: [10.1016/j.cgh.2018.07.022](#)]

- 50 **Bruns T**, Reuken PA, Stengel S, Gerber L, Appenrodt B, Schade JH, Lammert F, Zeuzem S, Stallmach A. The prognostic significance of bacterial DNA in patients with decompensated cirrhosis and suspected infection. *Liver Int* 2016; **36**: 1133-1142 [PMID: 26901072 DOI: 10.1111/liv.13095]
- 51 **Alvarez-Silva C**, Schierwagen R, Pohlmann A, Magdaleno F, Uschner FE, Ryan P, Vehreschild MJGT, Claria J, Latz E, Lelouvier B, Arumugam M, Trebicka J. Compartmentalization of Immune Response and Microbial Translocation in Decompensated Cirrhosis. *Front Immunol* 2019; **10**: 69 [PMID: 30800122 DOI: 10.3389/fimmu.2019.00069]
- 52 **Wang Z**, Wang A, Gong Z, Biviano I, Liu H, Hu J. Plasma claudin-3 is associated with tumor necrosis factor- α -induced intestinal endotoxemia in liver disease. *Clin Res Hepatol Gastroenterol* 2019; **43**: 410-416 [PMID: 31053499 DOI: 10.1016/j.clinre.2018.11.014]
- 53 **Ivashkin VT**, Maev IV, Abduganieva DI, Alekseeva OP, Alekseenko SA, Zolnikova OYu, Korochanskaya NV, Medvedev OS, Poluektova EA, Simanenkova VI, Trukhmanov AS, Khlynov IB, Tsukanov VV, Shifrin OS, Ivashkin KV, Lapina TL, Maslennikov RV, Fadeeva MV, Ulyanin AI. Practical Recommendation of the Scientific Community for Human Microbiome Research (CHMR) and the Russian Gastroenterological Association (RGA) on Small Intestinal Bacterial Overgrowth in Adults. *Russian Journal of Gastroenterology, Hepatology, Coloproctology* 2022; **32**: 68-85 [DOI: 10.22416/1382-4376-2022-32-3-68-85]
- 54 **Maslennikov R**, Pavlov C, Ivashkin V. Small intestinal bacterial overgrowth in cirrhosis: systematic review and meta-analysis. *Hepatol Int* 2018; **12**: 567-576 [PMID: 30284684 DOI: 10.1007/s12072-018-9898-2]
- 55 **Feng X**, Li X, Zhang X, Chen W, Tian Y, Yang Q, Yang Y, Pan H, Jiang Z. Hepatic Encephalopathy in Cirrhotic Patients and Risk of Small Intestinal Bacterial Overgrowth: A Systematic Review and Meta-Analysis. *Biomed Res Int* 2022; **2022**: 2469513 [PMID: 36303585 DOI: 10.1155/2022/2469513]
- 56 **Jun DW**, Kim KT, Lee OY, Chae JD, Son BK, Kim SH, Jo YJ, Park YS. Association between small intestinal bacterial overgrowth and peripheral bacterial DNA in cirrhotic patients. *Dig Dis Sci* 2010; **55**: 1465-1471 [PMID: 19517230 DOI: 10.1007/s10620-009-0870-9]
- 57 **Wang J**, Chen M, Sun G, Et Al. Small bowel bacterial overgrowth and endotoxemia in cirrhosis. *Zhonghua Nei Ke Za Zhi* 2002; **41**: 459-461 [PMID: 12189115]
- 58 **Maslennikov R**, Pavlov C, Ivashkin V. Is small intestinal bacterial overgrowth a cause of hyperdynamic circulation in cirrhosis? *Turk J Gastroenterol* 2019; **30**: 964-975 [PMID: 31767551 DOI: 10.5152/tjg.2019.18551]
- 59 **Maslennikov R**, Ivashkin V, Efremova I, Poluektova E, Kudryavtseva A, Krasnov G. Gut dysbiosis and small intestinal bacterial overgrowth as independent forms of gut microbiota disorders in cirrhosis. *World J Gastroenterol* 2022; **28**: 1067-1077 [PMID: 35431497 DOI: 10.3748/wjg.v28.i10.1067]
- 60 **Lang CH**, Frost RA, Nairn AC, MacLean DA, Vary TC. TNF- α impairs heart and skeletal muscle protein synthesis by altering translation initiation. *Am J Physiol Endocrinol Metab* 2002; **282**: E336-E347 [PMID: 11788365 DOI: 10.1152/ajpendo.00366.2001]
- 61 **Lang CH**, Frost RA, Jefferson LS, Kimball SR, Vary TC. Endotoxin-induced decrease in muscle protein synthesis is associated with changes in eIF2B, eIF4E, and IGF-I. *Am J Physiol Endocrinol Metab* 2000; **278**: E1133-E1143 [PMID: 10827017 DOI: 10.1152/ajpendo.2000.278.6.E1133]
- 62 **Yao J**, Chang L, Yuan L, Duan Z. Nutrition status and small intestinal bacterial overgrowth in patients with virus-related cirrhosis. *Asia Pac J Clin Nutr* 2016; **25**: 283-291 [PMID: 27222411 DOI: 10.6133/apjcn.2016.25.2.06]
- 63 **Esposito P**, Picciotto D, Battaglia Y, Costigliolo F, Viazzi F, Verzola D. Myostatin: Basic biology to clinical application. *Adv Clin Chem* 2022; **106**: 181-234 [PMID: 35152972 DOI: 10.1016/bs.acc.2021.09.006]
- 64 **Sharma M**, McFarlane C, Kambadur R, Kukreti H, Bonala S, Srinivasan S. Myostatin: expanding horizons. *IUBMB Life* 2015; **67**: 589-600 [PMID: 26305594 DOI: 10.1002/iub.1392]
- 65 **Dschietzig TB**. Myostatin - From the Mighty Mouse to cardiovascular disease and cachexia. *Clin Chim Acta* 2014; **433**: 216-224 [PMID: 24680839 DOI: 10.1016/j.cca.2014.03.021]
- 66 **Qiu J**, Thapaliya S, Runkana A, Yang Y, Tsien C, Mohan ML, Narayanan A, Egtesad B, Mozdzia PE, McDonald C, Stark GR, Welle S, Naga Prasad SV, Dasarathy S. Hyperammonemia in cirrhosis induces transcriptional regulation of myostatin by an NF- κ B-mediated mechanism. *Proc Natl Acad Sci U S A* 2013; **110**: 18162-18167 [PMID: 24145431 DOI: 10.1073/pnas.1317049110]
- 67 **Richardson AJ**, McKain N, Wallace RJ. Ammonia production by human faecal bacteria, and the enumeration, isolation and characterization of bacteria capable of growth on peptides and amino acids. *BMC Microbiol* 2013; **13**: 6 [PMID: 23312016 DOI: 10.1186/1471-2180-13-6]
- 68 **Walker V**. Ammonia metabolism and hyperammonemic disorders. *Adv Clin Chem* 2014; **67**: 73-150 [PMID: 25735860 DOI: 10.1016/bs.acc.2014.09.002]
- 69 **Jindal A**, Jagdish RK. Sarcopenia: Ammonia metabolism and hepatic encephalopathy. *Clin Mol Hepatol* 2019; **25**: 270-279 [PMID: 31006226 DOI: 10.3350/cmh.2019.0015]
- 70 **Wright G**, Noiret L, Olde Damink SW, Jalan R. Interorgan ammonia metabolism in liver failure: the basis of current and future therapies. *Liver Int* 2011; **31**: 163-175 [PMID: 20673233 DOI: 10.1111/j.1478-3231.2010.02302.x]
- 71 **Qiu J**, Tsien C, Thapaliya S, Narayanan A, Weihl CC, Ching JK, Egtesad B, Singh K, Fu X, Dubyak G, McDonald C, Almasan A, Hazen SL, Naga Prasad SV, Dasarathy S. Hyperammonemia-mediated autophagy in skeletal muscle contributes to sarcopenia of cirrhosis. *Am J Physiol Endocrinol Metab* 2012; **303**: E983-E993 [PMID: 22895779 DOI: 10.1152/ajpendo.00183.2012]
- 72 **Davuluri G**, Krokowski D, Guan BJ, Kumar A, Thapaliya S, Singh D, Hatzoglou M, Dasarathy S. Metabolic adaptation of skeletal muscle to hyperammonemia drives the beneficial effects of l-leucine in cirrhosis. *J Hepatol* 2016; **65**: 929-937 [PMID: 27318325 DOI: 10.1016/j.jhep.2016.06.004]
- 73 **Ponziani FR**, Picca A, Marzetti E, Calvani R, Conta G, Del Chierico F, Capuani G, Faccia M, Fianchi F, Funaro B, Josè Coelho-Junior H, Petito V, Rinninella E, Paroni Sterbini F, Reddel S, Vernocchi P, Cristina Mele M, Miccheli A, Putignani L, Sanguinetti M, Pompili M, Gasbarrini A; GuLiver study group. Characterization of the gut-liver-muscle axis in cirrhotic patients with sarcopenia. *Liver Int* 2021; **41**: 1320-1334 [PMID: 33713524 DOI: 10.1111/liv.14876]
- 74 **Ren X**, Hao S, Yang C, Yuan L, Zhou X, Zhao H, Yao J. Alterations of intestinal microbiota in liver cirrhosis with muscle wasting. *Nutrition* 2021; **83**: 111081 [PMID: 33348106 DOI: 10.1016/j.nut.2020.111081]
- 75 **Maslennikov R**, Ivashkin V, Alieva A, Poluektova E, Kudryavtseva A, Krasnov G, Zharkova M, Zharikov Y. Gut dysbiosis and body composition in cirrhosis. *World J Hepatol* 2022; **14**: 1210-1225 [PMID: 35978666 DOI: 10.4254/wjh.v14.i6.1210]
- 76 **Lee PC**, Lee KC, Yang TC, Lu HS, Cheng TY, Chen YJ, Chiou JJ, Huang CW, Yang UC, Chia-Hui Tan E, Chou SH, Kuo YL, Schnabl B, Huang YH, Hou MC. Sarcopenia-related gut microbial changes are associated with the risk of complications in people with cirrhosis. *JHEP Rep* 2023; **5**: 100619 [PMID: 36536957 DOI: 10.1016/j.jhepr.2022.100619]
- 77 **Wang J**, Zhang L, Hou X. Efficacy of rifaximin in treating with small intestine bacterial overgrowth: a systematic review and meta-analysis.

- Expert Rev Gastroenterol Hepatol* 2021; **15**: 1385-1399 [PMID: 34767484 DOI: 10.1080/17474124.2021.2005579]
- 78 **Gatta L**, Scarpignato C. Systematic review with meta-analysis: rifaximin is effective and safe for the treatment of small intestine bacterial overgrowth. *Aliment Pharmacol Ther* 2017; **45**: 604-616 [PMID: 28078798 DOI: 10.1111/apt.13928]
 - 79 **Zhuang X**, Tian Z, Li L, Zeng Z, Chen M, Xiong L. Fecal Microbiota Alterations Associated With Diarrhea-Predominant Irritable Bowel Syndrome. *Front Microbiol* 2018; **9**: 1600 [PMID: 30090090 DOI: 10.3389/fmicb.2018.01600]
 - 80 **Liu ZJ**, Wei H, Duan LP, Zhu SW, Zhang L, Wang K. [Clinical features of irritable bowel syndrome with small intestinal bacterial overgrowth and a preliminary study of effectiveness of Rifaximin]. *Zhonghua Yi Xue Za Zhi* 2016; **96**: 1896-1902 [PMID: 27373356 DOI: 10.3760/cma.j.issn.0376-2491.2016.24.005]
 - 81 **Bae S**, Lee KJ, Kim YS, Kim KN. Determination of rifaximin treatment period according to lactulose breath test values in nonconstipated irritable bowel syndrome subjects. *J Korean Med Sci* 2015; **30**: 757-762 [PMID: 26028929 DOI: 10.3346/jkms.2015.30.6.757]
 - 82 **Peralta S**, Cottone C, Doveri T, Almasio PL, Craxi A. Small intestine bacterial overgrowth and irritable bowel syndrome-related symptoms: experience with Rifaximin. *World J Gastroenterol* 2009; **15**: 2628-2631 [PMID: 19496193 DOI: 10.3748/wjg.15.2628]
 - 83 **Furnari M**, De Alessandri A, Cresta F, Haupt M, Bassi M, Calvi A, Haupt R, Bodini G, Ahmed I, Bagnasco F, Giannini EG, Casciaro R. The role of small intestinal bacterial overgrowth in cystic fibrosis: a randomized case-controlled clinical trial with rifaximin. *J Gastroenterol* 2019; **54**: 261-270 [PMID: 30232597 DOI: 10.1007/s00535-018-1509-4]
 - 84 **Biancone L**, Vernia P, Agostini D, Ferrieri A, Pallone F. Effect of rifaximin on intestinal bacterial overgrowth in Crohn's disease as assessed by the H₂-Glucose Breath Test. *Curr Med Res Opin* 2000; **16**: 14-20 [PMID: 16422030 DOI: 10.1185/0300799009117003]
 - 85 **Cuoco L**, Montalto M, Jorizzo RA, Santarelli L, Arancio F, Cammarota G, Gasbarrini G. Eradication of small intestinal bacterial overgrowth and oro-cecal transit in diabetics. *Hepatogastroenterology* 2002; **49**: 1582-1586 [PMID: 12397741]
 - 86 **Tursi A**, Brandimarte G, Giorgetti G. High prevalence of small intestinal bacterial overgrowth in celiac patients with persistence of gastrointestinal symptoms after gluten withdrawal. *Am J Gastroenterol* 2003; **98**: 839-843 [PMID: 12738465 DOI: 10.1111/j.1572-0241.2003.07379.x]
 - 87 **Resmini E**, Parodi A, Savarino V, Greco A, Rebora A, Minuto F, Ferone D. Evidence of prolonged oro-cecal transit time and small intestinal bacterial overgrowth in acromegalic patients. *J Clin Endocrinol Metab* 2007; **92**: 2119-2124 [PMID: 17405840 DOI: 10.1210/jc.2006-2509]
 - 88 **Tursi A**, Brandimarte G, Giorgetti GM, Elisei W. Assessment of small intestinal bacterial overgrowth in uncomplicated acute diverticulitis of the colon. *World J Gastroenterol* 2005; **11**: 2773-2776 [PMID: 15884120 DOI: 10.3748/wjg.v11.i18.2773]
 - 89 **D'Inca R**, Pomerri F, Vettorato MG, Dal Pont E, Di Leo V, Ferronato A, Medici V, Sturmiolo GC. Interaction between rifaximin and dietary fibre in patients with diverticular disease. *Aliment Pharmacol Ther* 2007; **25**: 771-779 [PMID: 17373915 DOI: 10.1111/j.1365-2036.2007.03266.x]
 - 90 **Parodi A**, Sessarego M, Greco A, Bazzica M, Filaci G, Setti M, Savarino E, Indiveri F, Savarino V, Ghio M. Small intestinal bacterial overgrowth in patients suffering from scleroderma: clinical effectiveness of its eradication. *Am J Gastroenterol* 2008; **103**: 1257-1262 [PMID: 18422815 DOI: 10.1111/j.1572-0241.2007.01758.x]
 - 91 **Parodi A**, Paolino S, Greco A, Drago F, Mansi C, Rebora A, Parodi A, Savarino V. Small intestinal bacterial overgrowth in rosacea: clinical effectiveness of its eradication. *Clin Gastroenterol Hepatol* 2008; **6**: 759-764 [PMID: 18456568 DOI: 10.1016/j.cgh.2008.02.054]
 - 92 **Yang C**, Zhang X, Wang S, Huo X, Wang J. Small intestinal bacterial overgrowth and evaluation of intestinal barrier function in patients with ulcerative colitis. *Am J Transl Res* 2021; **13**: 6605-6610 [PMID: 34306403]
 - 93 **Pérez Aisa A**, García Gavilán MC, Alcaide García J, Méndez Sánchez IM, Rivera Irigoien R, Fernández Cano F, Pereda Salguero T, Rivas Ruiz F. Small intestinal bacterial overgrowth is common after gastrectomy but with little impact on nutritional status. *Gastroenterol Hepatol* 2019; **42**: 1-10 [PMID: 30197248 DOI: 10.1016/j.gastrohep.2018.07.001]
 - 94 **Di Stefano M**, Malservisi S, Veneto G, Ferrieri A, Corazza GR. Rifaximin versus chlortetracycline in the short-term treatment of small intestinal bacterial overgrowth. *Aliment Pharmacol Ther* 2000; **14**: 551-556 [PMID: 10792117 DOI: 10.1046/j.1365-2036.2000.00751.x]
 - 95 **Yang J**, Lee HR, Low K, Chatterjee S, Pimentel M. Rifaximin versus other antibiotics in the primary treatment and retreatment of bacterial overgrowth in IBS. *Dig Dis Sci* 2008; **53**: 169-174 [PMID: 17520365 DOI: 10.1007/s10620-007-9839-8]
 - 96 **Lauritano EC**, Gabrielli M, Scarpellini E, Ojetti V, Roccarina D, Villita A, Fiore E, Flore R, Santoliquido A, Tondi P, Gasbarrini G, Ghirlanda G, Gasbarrini A. Antibiotic therapy in small intestinal bacterial overgrowth: rifaximin versus metronidazole. *Eur Rev Med Pharmacol Sci* 2009; **13**: 111-116 [PMID: 19499846]
 - 97 **Suhocki PV**, Ronald JS, Diehl AME, Murdoch DM, Doraiswamy PM. Probing gut-brain links in Alzheimer's disease with rifaximin. *Alzheimers Dement (NY)* 2022; **8**: e12225 [PMID: 35128026 DOI: 10.1002/trc2.12225]
 - 98 **Liu Z**, Zhu S, He M, Li M, Wei H, Zhang L, Sun Q, Jia Q, Hu N, Fang Y, Song L, Zhou C, Tao H, Kao JY, Zhu H, Owyang C, Duan L. Patients with breath test positive are necessary to be identified from irritable bowel syndrome: a clinical trial based on microbiomics and rifaximin sensitivity. *Chin Med J (Engl)* 2022; **135**: 1716-1727 [PMID: 36070467 DOI: 10.1097/CM9.0000000000002294]
 - 99 **Li Y**, Hong G, Yang M, Li G, Jin Y, Xiong H, Qian W, Hou X. Fecal bacteria can predict the efficacy of rifaximin in patients with diarrhea-predominant irritable bowel syndrome. *Pharmacol Res* 2020; **159**: 104936 [PMID: 32470562 DOI: 10.1016/j.phrs.2020.104936]
 - 100 **Soldi S**, Vasileiadis S, Uggeri F, Campanale M, Morelli L, Fogli MV, Calanni F, Grimaldi M, Gasbarrini A. Modulation of the gut microbiota composition by rifaximin in non-constipated irritable bowel syndrome patients: a molecular approach. *Clin Exp Gastroenterol* 2015; **8**: 309-325 [PMID: 26673000 DOI: 10.2147/CEG.S89999]
 - 101 **De Vincentis A**, Santonico M, Del Chierico F, Altomare A, Marigliano B, Laudisio A, Reddel S, Grasso S, Zompanti A, Pennazza G, Putignani L, Guarino MPL, Cicala M, Antonelli Incalzi R. Gut Microbiota and Related Electronic Multisensorial System Changes in Subjects With Symptomatic Uncomplicated Diverticular Disease Undergoing Rifaximin Therapy. *Front Med (Lausanne)* 2021; **8**: 655474 [PMID: 34350192 DOI: 10.3389/fmed.2021.655474]
 - 102 **Ivashkin V**, Shifrin O, Maslennikov R, Poluektova E, Korolev A, Kudryavtseva A, Krasnov G, Benuni N, Barbara G. Eubiotic effect of rifaximin is associated with decreasing abdominal pain in symptomatic uncomplicated diverticular disease: results from an observational cohort study. *BMC Gastroenterol* 2023; **23**: 82 [PMID: 36959568 DOI: 10.1186/s12876-023-02690-x]
 - 103 **Kimber C**, Zhang S, Johnson C, West RE 3rd, Prokopienko AJ, Mahnken JD, Yu AS, Hoofnagle AN, Ir D, Robertson CE, Miyazaki M, Chonchol M, Jovanovich A, Kestenbaum B, Frank DN, Nolin TD, Stubbs JR. Randomized, Placebo-Controlled Trial of Rifaximin Therapy for Lowering Gut-Derived Cardiovascular Toxins and Inflammation in CKD. *Kidney360* 2020; **1**: 1206-1216 [PMID: 34322673 DOI: 10.34067/kid.0003942020]
 - 104 **Ponziani FR**, Scaldaferri F, De Siena M, Mangiola F, Matteo MV, Pecere S, Petito V, Sterbini FP, Lopetuso LR, Masucci L, Cammarota G,

- Sanguinetti M, Gasbarrini A. Increased Faecalibacterium abundance is associated with clinical improvement in patients receiving rifaximin treatment. *Benef Microbes* 2020; **11**: 519-525 [PMID: 32885687 DOI: 10.3920/BM2019.0171]
- 105 **Brigidi P**, Swennen E, Rizzello F, Bozzolascio M, Matteuzzi D. Effects of rifaximin administration on the intestinal microbiota in patients with ulcerative colitis. *J Chemother* 2002; **14**: 290-295 [PMID: 12120885 DOI: 10.1179/joc.2002.14.3.290]
- 106 **Maccaferri S**, Vitali B, Klinder A, Kolida S, Ndagijimana M, Laghi L, Calanni F, Brigidi P, Gibson GR, Costabile A. Rifaximin modulates the colonic microbiota of patients with Crohn's disease: an in vitro approach using a continuous culture colonic model system. *J Antimicrob Chemother* 2010; **65**: 2556-2565 [PMID: 20852272 DOI: 10.1093/jac/dkq345]
- 107 **Pimentel R**, Gregório C, Figueiredo P. Antibiotic prophylaxis for prevention of spontaneous bacterial peritonitis in liver cirrhosis: systematic review. *Acta Gastroenterol Belg* 2021; **84**: 333-342 [PMID: 34217185 DOI: 10.51821/84.2.333]
- 108 **Faust N**, Yamada A, Haider H, Komaki Y, Komaki F, Micic D, Sakuraba A. Systemic review and network meta-analysis: Prophylactic antibiotic therapy for spontaneous bacterial peritonitis. *World J Hepatol* 2020; **12**: 239-252 [PMID: 32547691 DOI: 10.4254/wjh.v12.i5.239]
- 109 **Soni H**, Kumar-M P, Sharma V, Bellam BL, Mishra S, Mahendru D, Mandavdhare HS, Medhi B, Dutta U, Singh V. Antibiotics for prophylaxis of spontaneous bacterial peritonitis: systematic review & Bayesian network meta-analysis. *Hepatol Int* 2020; **14**: 399-413 [PMID: 32266675 DOI: 10.1007/s12072-020-10025-1]
- 110 **Kamal F**, Khan MA, Khan Z, Cholankeril G, Hammad TA, Lee WM, Ahmed A, Waters B, Howden CW, Nair S, Satapathy SK. Rifaximin for the prevention of spontaneous bacterial peritonitis and hepatorenal syndrome in cirrhosis: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol* 2017; **29**: 1109-1117 [PMID: 28763340 DOI: 10.1097/MEG.0000000000000940]
- 111 **Dhiman RK**, Thumburu KK, Verma N, Chopra M, Rath S, Dutta U, Singal AK, Taneja S, Duseja A, Singh M. Comparative Efficacy of Treatment Options for Minimal Hepatic Encephalopathy: A Systematic Review and Network Meta-Analysis. *Clin Gastroenterol Hepatol* 2020; **18**: 800-812.e25 [PMID: 31476436 DOI: 10.1016/j.cgh.2019.08.047]
- 112 **Eltawil KM**, Laryea M, Peltekian K, Molinari M. Rifaximin vs. conventional oral therapy for hepatic encephalopathy: a meta-analysis. *World J Gastroenterol* 2012; **18**: 767-777 [PMID: 22371636 DOI: 10.3748/wjg.v18.i8.767]
- 113 **Zhu GQ**, Shi KQ, Huang S, Wang LR, Lin YQ, Huang GQ, Chen YP, Braddock M, Zheng MH. Systematic review with network meta-analysis: the comparative effectiveness and safety of interventions in patients with overt hepatic encephalopathy. *Aliment Pharmacol Ther* 2015; **41**: 624-635 [PMID: 25684317 DOI: 10.1111/apt.13122]
- 114 **Zhang Y**, Feng Y, Cao B, Tian Q. Effects of SIBO and rifaximin therapy on MHE caused by hepatic cirrhosis. *Int J Clin Exp Med* 2015; **8**: 2954-2957 [PMID: 25932262]
- 115 **Vlachogiannakos J**, Saveriadis AS, Viazis N, Theodoropoulos I, Foudoulis K, Manolakopoulos S, Raptis S, Karamanolis DG. Intestinal decontamination improves liver haemodynamics in patients with alcohol-related decompensated cirrhosis. *Aliment Pharmacol Ther* 2009; **29**: 992-999 [PMID: 19210289 DOI: 10.1111/j.1365-2036.2009.03958.x]
- 116 **Takaya H**, Namisaki T, Sato S, Kaji K, Tsuji Y, Kaya D, Fujinaga Y, Sawada Y, Shimozato N, Kawaratani H, Moriya K, Akahane T, Mitoro A, Yoshiji H. Increased Endotoxin Activity Is Associated with the Risk of Developing Acute-on-Chronic Liver Failure. *J Clin Med* 2020; **9** [PMID: 32422875 DOI: 10.3390/jcm9051467]
- 117 **Kaji K**, Saikawa S, Takaya H, Fujinaga Y, Furukawa M, Kitagawa K, Ozutsumi T, Kaya D, Tsuji Y, Sawada Y, Kawaratani H, Moriya K, Namisaki T, Akahane T, Mitoro A, Yoshiji H. Rifaximin Alleviates Endotoxemia with Decreased Serum Levels of Soluble CD163 and Mannose Receptor and Partial Modification of Gut Microbiota in Cirrhotic Patients. *Antibiotics (Basel)* 2020; **9** [PMID: 32235367 DOI: 10.3390/antibiotics9040145]
- 118 **Kaji K**, Takaya H, Saikawa S, Furukawa M, Sato S, Kawaratani H, Kitade M, Moriya K, Namisaki T, Akahane T, Mitoro A, Yoshiji H. Rifaximin ameliorates hepatic encephalopathy and endotoxemia without affecting the gut microbiome diversity. *World J Gastroenterol* 2017; **23**: 8355-8366 [PMID: 29307995 DOI: 10.3748/wjg.v23.i47.8355]
- 119 **Zeng X**, Tang XJ, Sheng X, Ni W, Xin HG, Chen WZ, Jiang CF, Lin Y, Shi J, Shi B, Chen YX, Yuan ZL, Xie WF. Does low-dose rifaximin ameliorate endotoxemia in patients with liver cirrhosis: a prospective study. *J Dig Dis* 2015; **16**: 665-674 [PMID: 26474237 DOI: 10.1111/1751-2980.12294]
- 120 **Bajaj JS**, Heuman DM, Sanyal AJ, Hylemon PB, Sterling RK, Stravitz RT, Fuchs M, Ridlon JM, Daita K, Monteith P, Noble NA, White MB, Fisher A, Sikaroodi M, Rangwala H, Gillevet PM. Modulation of the metabiome by rifaximin in patients with cirrhosis and minimal hepatic encephalopathy. *PLoS One* 2013; **8**: e60042 [PMID: 23565181 DOI: 10.1371/journal.pone.0060042]
- 121 **Kalambokis GN**, Mouzaki A, Rodi M, Tsianos EV. Rifaximin improves thrombocytopenia in patients with alcoholic cirrhosis in association with reduction of endotoxaemia. *Liver Int* 2012; **32**: 467-475 [PMID: 22098272 DOI: 10.1111/j.1478-3231.2011.02650.x]
- 122 **Patel VC**, Lee S, McPhail MJW, Da Silva K, Guilly S, Zamalloa A, Witherden E, Støy S, Manakkat Vijay GK, Pons N, Galleron N, Huang X, Gencer S, Coen M, Tranah TH, Wendon JA, Bruce KD, Le Chatelier E, Ehrlich SD, Edwards LA, Shoaie S, Shawcross DL. Rifaximin- α reduces gut-derived inflammation and mucin degradation in cirrhosis and encephalopathy: RIFSYS randomised controlled trial. *J Hepatol* 2022; **76**: 332-342 [PMID: 34571050 DOI: 10.1016/j.jhep.2021.09.010]
- 123 **Yu X**, Jin Y, Zhou W, Xiao T, Wu Z, Su J, Gao H, Shen P, Zheng B, Luo Q, Li L, Xiao Y. Rifaximin Modulates the Gut Microbiota to Prevent Hepatic Encephalopathy in Liver Cirrhosis Without Impacting the Resistome. *Front Cell Infect Microbiol* 2021; **11**: 761192 [PMID: 35118004 DOI: 10.3389/fcimb.2021.761192]
- 124 **Mariani M**, Zuccaro V, Patruno SF, Scudeller L, Sacchi P, Lombardi A, Vecchia M, Columpsi P, Marone P, Filice G, Bruno R. The impact of rifaximin in the prevention of bacterial infections in cirrhosis. *Eur Rev Med Pharmacol Sci* 2017; **21**: 1151-1158 [PMID: 28338174]
- 125 **Zeng X**, Sheng X, Wang PQ, Xin HG, Guo YB, Lin Y, Zhong JW, He CZ, Yin J, Liu TT, Ma WJ, Xiao X, Shi PM, Yuan ZL, Yang L, Ma X, Xu JM, Shen XZ, Yang CQ, Zhu X, Lv NH, Xie WF. Low-dose rifaximin prevents complications and improves survival in patients with decompensated liver cirrhosis. *Hepatol Int* 2021; **15**: 155-165 [PMID: 33385299 DOI: 10.1007/s12072-020-10117-y]
- 126 **Flamm SL**, Mullen KD, Heimanson Z, Sanyal AJ. Rifaximin has the potential to prevent complications of cirrhosis. *Therap Adv Gastroenterol* 2018; **11**: 1756284818800307 [PMID: 30283499 DOI: 10.1177/1756284818800307]
- 127 **Ibrahim ES**, Alsebaey A, Zaghla H, Moawad Abdelmageed S, Gameel K, Abdelsameea E. Long-term rifaximin therapy as a primary prevention of hepatorenal syndrome. *Eur J Gastroenterol Hepatol* 2017; **29**: 1247-1250 [PMID: 28902040 DOI: 10.1097/MEG.0000000000000967]
- 128 **Dong T**, Aronsohn A, Gautham Reddy K, Te HS. Rifaximin Decreases the Incidence and Severity of Acute Kidney Injury and Hepatorenal Syndrome in Cirrhosis. *Dig Dis Sci* 2016; **61**: 3621-3626 [PMID: 27655104 DOI: 10.1007/s10620-016-4313-0]
- 129 **Wang Z**, Hou W, Zhang W, Wu HX, Zheng SJ, Hu ZJ. [Rifaximin improves clinical symptoms and short-term survival in cirrhotic patients

with refractory type ascites]. *Zhonghua Gan Zang Bing Za Zhi* 2022; **30**: 1170-1174 [PMID: 36891693 DOI: 10.3760/cma.j.cn501113-20210918-00475]

- 130 **Lv XY**, Ding HG, Zheng JF, Fan CL, Li L. Rifaximin improves survival in cirrhotic patients with refractory ascites: A real-world study. *World J Gastroenterol* 2020; **26**: 199-218 [PMID: 31988585 DOI: 10.3748/wjg.v26.i2.199]
- 131 **Kawaguchi T**, Suzuki F, Imamura M, Murashima N, Yanase M, Mine T, Fujisawa M, Sato I, Yoshiji H, Okita K, Suzuki K. Rifaximin-altered gut microbiota components associated with liver/neuropsychological functions in patients with hepatic encephalopathy: An exploratory data analysis of phase II/III clinical trials. *Hepatol Res* 2019; **49**: 404-418 [PMID: 30589492 DOI: 10.1111/hepr.13300]
- 132 **Yokoyama K**, Fukuda H, Yamauchi R, Higashi M, Miyayama T, Higashi T, Uchida Y, Shibata K, Tsuchiya N, Fukunaga A, Umeda K, Takata K, Tanaka T, Shakado S, Sakisaka S, Hirai F. Long-Term Effects of Rifaximin on Patients with Hepatic Encephalopathy: Its Possible Effects on the Improvement in the Blood Ammonia Concentration Levels, Hepatic Spare Ability and Refractory Ascites. *Medicina (Kaunas)* 2022; **58** [PMID: 36143954 DOI: 10.3390/medicina58091276]
- 133 **Kawaratani H**, Kondo Y, Tatsumi R, Kawabe N, Tanabe N, Sakamaki A, Okumoto K, Uchida Y, Endo K, Kawaguchi T, Oikawa T, Ishizu Y, Hige S, Takami T, Terai S, Ueno Y, Mochida S, Takikawa Y, Torimura T, Matsuura T, Ishigami M, Koike K, Yoshiji H. Long-Term Efficacy and Safety of Rifaximin in Japanese Patients with Hepatic Encephalopathy: A Multicenter Retrospective Study. *J Clin Med* 2022; **11** [PMID: 35329897 DOI: 10.3390/jcm11061571]
- 134 **Glal KAM**, Abd-El salam SM, Mostafa TM. Nitazoxanide versus rifaximin in preventing the recurrence of hepatic encephalopathy: A randomized double-blind controlled trial. *J Hepatobiliary Pancreat Sci* 2021; **28**: 812-824 [PMID: 33768619 DOI: 10.1002/jhbp.947]
- 135 **Gómez-Hurtado I**, Gimenez P, García I, Zapater P, Francés R, González-Navajas JM, Manichanh C, Ramos JM, Bellot P, Guarner F, Such J. Norfloxacin is more effective than Rifaximin in avoiding bacterial translocation in an animal model of cirrhosis. *Liver Int* 2018; **38**: 295-302 [PMID: 28834270 DOI: 10.1111/liv.13551]
- 136 **Pedretti G**, Calzetti C, Missale G, Fiaccadori F. Rifaximin versus neomycin on hyperammonemia in chronic portal systemic encephalopathy of cirrhotics. A double-blind, randomized trial. *Ital J Gastroenterol* 1991; **23**: 175-178 [PMID: 1751811]
- 137 **Murata K**, Kaji K, Nishimura N, Enomoto M, Fujimoto Y, Takeda S, Tsuji Y, Fujinaga Y, Takaya H, Kawaratani H, Namisaki T, Akahane T, Yoshiji H. Rifaximin enhances the L-carnitinemediated preventive effects on skeletal muscle atrophy in cirrhotic rats by modulating the gutlivermuscle axis. *Int J Mol Med* 2022; **50** [PMID: 35686541 DOI: 10.3892/ijmm.2022.5157]
- 138 **Ishikawa T**, Endo S, Imai M, Azumi M, Nozawa Y, Sano T, Iwanaga A, Honma T, Yoshida T. Changes in the Body Composition and Nutritional Status after Long-term Rifaximin Therapy for Hyperammonemia in Japanese Patients with Hepatic Encephalopathy. *Intern Med* 2020; **59**: 2465-2469 [PMID: 33055469 DOI: 10.2169/internalmedicine.5094-20]
- 139 **Miller LE**, Tennilä J, Ouweland AC. Efficacy and tolerance of lactitol supplementation for adult constipation: a systematic review and meta-analysis. *Clin Exp Gastroenterol* 2014; **7**: 241-248 [PMID: 25050074 DOI: 10.2147/CEG.S58952]
- 140 **Maev IV**, Kazyulin AN, Kucheryavy YuA, Cheryomushkin SV, Goncharenko AYU, Gilyuk AV. Diagnosis of Functional Gastrointestinal Disorders and Choice of Treatment Regimen in Constipation Patients. *Russian Journal of Gastroenterology, Hepatology, Coloproctology* 2021; **31**: 7-16 [DOI: 10.22416/1382-4376-2021-31-3-7-16]
- 141 **Ivashkin VT**, Maev IV, Shelygin YuA, Baranskaya EK, Belous SS, Belousova EA, Beniashvili AG, Vasilyev SV, Veselov AV, Grigoryev EG, Kostenko NV, Kashnikov VN, Kulikovskiy VF, Loranskaya ID, Lyashenko OS, Poluektova EA, Rumyantsev VG, Timerbulatov VM, Fomenko OYu, Khubezov DA, Chashkova EYu, Chibisov GI, Shapina MV, Sheptulin AA, Shifrin OS, Trukhmanov AS, Alekseeva OP, Alekseenko SA, Baranovsky AYU, Zolnikova OYu, Korochanskaya NV, Mammayev SN, Khlynov IB, Tsukanov VV. Diagnosis and Treatment of Irritable Bowel Syndrome: Clinical Recommendations of the Russian Gastroenterological Association and Association of Coloproctologists of Russia. *Russian Journal of Gastroenterology, Hepatology, Coloproctology* 2021; **31**: 74-95 [DOI: 10.22416/1382-4376-2021-31-5-74-95]
- 142 **Morgan MY**. Current state of knowledge of hepatic encephalopathy (part III): non-absorbable disaccharides. *Metab Brain Dis* 2016; **31**: 1361-1364 [PMID: 27638474 DOI: 10.1007/s11011-016-9910-2]
- 143 **Sharma P**, Sharma BC. Disaccharides in the treatment of hepatic encephalopathy. *Metab Brain Dis* 2013; **28**: 313-320 [PMID: 23456517 DOI: 10.1007/s11011-013-9392-4]
- 144 **Masini A**, Efrati C, Merli M, Attili AF, Amodio P, Ceccanti M, Riggio O. Effect of lactitol on blood ammonia response to oral glutamine challenge in cirrhotic patients: evidence for an effect of nonabsorbable disaccharides on small intestine ammonia generation. *Am J Gastroenterol* 1999; **94**: 3323-3327 [PMID: 10566738 DOI: 10.1111/j.1572-0241.1999.01546.x]
- 145 **Blanc P**, Daures JP, Rouillon JM, Peray P, Pierrugues R, Larrey D, Gremy F, Michel H. Lactitol or lactulose in the treatment of chronic hepatic encephalopathy: results of a meta-analysis. *Hepatology* 1992; **15**: 222-228 [PMID: 1531204 DOI: 10.1002/hep.1840150209]
- 146 **Gluud LL**, Vilstrup H, Morgan MY. Nonabsorbable disaccharides for hepatic encephalopathy: A systematic review and meta-analysis. *Hepatology* 2016; **64**: 908-922 [PMID: 27081787 DOI: 10.1002/hep.28598]
- 147 **Gluud LL**, Vilstrup H, Morgan MY. Non-absorbable disaccharides versus placebo/no intervention and lactulose versus lactitol for the prevention and treatment of hepatic encephalopathy in people with cirrhosis. *Cochrane Database Syst Rev* 2016; **2016**: CD003044 [PMID: 27153247 DOI: 10.1002/14651858.CD003044.pub4]
- 148 **Sharma P**, Sharma BC, Agrawal A, Sarin SK. Primary prophylaxis of overt hepatic encephalopathy in patients with cirrhosis: an open labeled randomized controlled trial of lactulose versus no lactulose. *J Gastroenterol Hepatol* 2012; **27**: 1329-1335 [PMID: 22606978 DOI: 10.1111/j.1440-1746.2012.07186.x]
- 149 **Agrawal A**, Sharma BC, Sharma P, Sarin SK. Secondary prophylaxis of hepatic encephalopathy in cirrhosis: an open-label, randomized controlled trial of lactulose, probiotics, and no therapy. *Am J Gastroenterol* 2012; **107**: 1043-1050 [PMID: 22710579 DOI: 10.1038/ajg.2012.113]
- 150 **Riggio O**, Balducci G, Ariosto F, Merli M, Tremiteira S, Ziparo V, Capocaccia L. Lactitol in the treatment of chronic hepatic encephalopathy--a randomized cross-over comparison with lactulose. *Hepatogastroenterology* 1990; **37**: 524-527 [PMID: 2253931]
- 151 **Riggio O**, Balducci G, Ariosto F, Merli M, Picche U, Pinto G, Tremiteira S, Ziparo V, Capocaccia L. Lactitol in prevention of recurrent episodes of hepatic encephalopathy in cirrhotic patients with portal-systemic shunt. *Dig Dis Sci* 1989; **34**: 823-829 [PMID: 2656134 DOI: 10.1007/BF01540265]
- 152 **Merli M**, Caschera M, Piat C, Pinto G, Diofebi M, Riggio O. The effect of lactulose and lactitol administration on fecal fat excretion in patients with liver cirrhosis. *J Clin Gastroenterol* 1992; **15**: 125-127 [PMID: 1401823 DOI: 10.1097/00004836-199209000-00009]
- 153 **Riggio O**, Variale M, Testore GP, Di Rosa R, Di Rosa E, Merli M, Romiti A, Candiani C, Capocaccia L. Effect of lactitol and lactulose administration on the fecal flora in cirrhotic patients. *J Clin Gastroenterol* 1990; **12**: 433-436 [PMID: 2398251 DOI: 10.1007/BF01540265]

- 10.1097/00004836-199008000-00016]
- 154 **Ballongue J**, Schumann C, Quignon P. Effects of lactulose and lactitol on colonic microflora and enzymatic activity. *Scand J Gastroenterol Suppl* 1997; **222**: 41-44 [PMID: 9145445 DOI: 10.1080/00365521.1997.11720716]
 - 155 **Li XQ**, Zhang XM, Wu X, Lan Y, Xu L, Meng XC, Li JN. Beneficial effects of lactitol on the composition of gut microbiota in constipated patients. *J Dig Dis* 2020; **21**: 445-453 [PMID: 32483935 DOI: 10.1111/1751-2980.12912]
 - 156 **Tarao K**, Tamai S, Ito Y, Okawa S, Hayashi M. [Effects of lactitol on fecal bacterial flora in patients with liver cirrhosis and hepatic encephalopathy]. *Nihon Shokakibyo Gakkai Zasshi* 1995; **92**: 1037-1050 [PMID: 7643458]
 - 157 **Lu H**, Chen L, Pan X, Yao Y, Zhang H, Zhu X, Lou X, Zhu C, Wang J, Li L, Wu Z. Lactitol Supplementation Modulates Intestinal Microbiome in Liver Cirrhotic Patients. *Front Med (Lausanne)* 2021; **8**: 762930 [PMID: 34722597 DOI: 10.3389/fmed.2021.762930]
 - 158 **Chen C**, Li L, Wu Z, Chen H, Fu S. Effects of lactitol on intestinal microflora and plasma endotoxin in patients with chronic viral hepatitis. *J Infect* 2007; **54**: 98-102 [PMID: 17049992 DOI: 10.1016/j.jinf.2005.11.013]
 - 159 **Ziada DH**, Soliman HH, El Yamany SA, Hamisa MF, Hasan AM. Can Lactobacillus acidophilus improve minimal hepatic encephalopathy? A neurometabolite study using magnetic resonance spectroscopy. *Arab J Gastroenterol* 2013; **14**: 116-122 [PMID: 24206740 DOI: 10.1016/j.ajg.2013.08.002]
 - 160 **Manzhalii E**, Moysenchenko V, Kondratiuk V, Molochek N, Falalyeyeva T, Kobylak N. Effect of a specific Escherichia coli Nissle 1917 strain on minimal/mild hepatic encephalopathy treatment. *World J Hepatol* 2022; **14**: 634-646 [PMID: 35582294 DOI: 10.4254/wjh.v14.i3.634]
 - 161 **Sarangi AN**, Goel A, Singh A, Sasi A, Aggarwal R. Faecal bacterial microbiota in patients with cirrhosis and the effect of lactulose administration. *BMC Gastroenterol* 2017; **17**: 125 [PMID: 29179682 DOI: 10.1186/s12876-017-0683-9]
 - 162 **Wang JY**, Bajaj JS, Wang JB, Shang J, Zhou XM, Guo XL, Zhu X, Meng LN, Jiang HX, Mi YQ, Xu JM, Yang JH, Wang BS, Zhang NP. Lactulose improves cognition, quality of life, and gut microbiota in minimal hepatic encephalopathy: A multicenter, randomized controlled trial. *J Dig Dis* 2019; **20**: 547-556 [PMID: 31448533 DOI: 10.1111/1751-2980.12816]
 - 163 **Jain L**, Sharma BC, Srivastava S, Puri SK, Sharma P, Sarin S. Serum endotoxin, inflammatory mediators, and magnetic resonance spectroscopy before and after treatment in patients with minimal hepatic encephalopathy. *J Gastroenterol Hepatol* 2013; **28**: 1187-1193 [PMID: 23425082 DOI: 10.1111/jgh.12160]
 - 164 **Moratalla A**, Ampuero J, Bellot P, Gallego-Durán R, Zapater P, Roger M, Figueruela B, Martínez-Moreno B, González-Navajas JM, Such J, Romero-Gómez M, Francés R. Lactulose reduces bacterial DNA translocation, which worsens neurocognitive shape in cirrhotic patients with minimal hepatic encephalopathy. *Liver Int* 2017; **37**: 212-223 [PMID: 27388776 DOI: 10.1111/liv.13200]
 - 165 **Ivashkin VT**, Maev IV, Abdulganieva DI, Alekseenko SA, Gorelov AV, Zakharova IN, Zolnikova OYu, Ivashkina NYu, Korochanskaya NV, Mammayev SN, Poluektova EA, Trukhmanov AS, Usenko DV, Uspensky YuP, Tsukanov VV, Shifrin OS, Berezhnaya IV, Ivashkin KV, Lapina TL, Maslennikov RV, Nikolaeva SV, Sugyan NG, Ulyanin AI. Practical Recommendations of Scientific Society for the Study of Human Microbiome and the Russian Gastroenterological Association on Use of Probiotics, Prebiotics, Synbiotics and Functional Foods in Treatment and Prevention of Gastroenterological Diseases in Children and Adults. *Russian Journal of Gastroenterology, Hepatology, Coloproctology* 2021; **31**: 65-91 [DOI: 10.22416/1382-4376-2021-31-2-65-91]
 - 166 **Maslennikov R**, Ivashkin V, Efremova I, Poluektova E, Shirokova E. Probiotics in hepatology: An update. *World J Hepatol* 2021; **13**: 1154-1166 [PMID: 34630882 DOI: 10.4254/wjh.v13.i9.1154]
 - 167 **Cao Q**, Yu CB, Yang SG, Cao HC, Chen P, Deng M, Li LJ. Effect of probiotic treatment on cirrhotic patients with minimal hepatic encephalopathy: A meta-analysis. *Hepatobiliary Pancreat Dis Int* 2018; **17**: 9-16 [PMID: 29428113 DOI: 10.1016/j.hbpd.2018.01.005]
 - 168 **Viramontes Hörner D**, Avery A, Stow R. The Effects of Probiotics and Synbiotics on Risk Factors for Hepatic Encephalopathy: A Systematic Review. *J Clin Gastroenterol* 2017; **51**: 312-323 [PMID: 28059938 DOI: 10.1097/MCG.0000000000000789]
 - 169 **Huang L**, Yu Q, Peng H, Zhen Z. Alterations of gut microbiome and effects of probiotic therapy in patients with liver cirrhosis: A systematic review and meta-analysis. *Medicine (Baltimore)* 2022; **101**: e32335 [PMID: 36595801 DOI: 10.1097/MD.00000000000032335]
 - 170 **Dalal R**, McGee RG, Riordan SM, Webster AC. Probiotics for people with hepatic encephalopathy. *Cochrane Database Syst Rev* 2017; **2**: CD008716 [PMID: 28230908 DOI: 10.1002/14651858.CD008716.pub3]
 - 171 **Kazemi A**, Soltani S, Ghorabi S, Keshkar A, Daneshzad E, Nasri F, Mazloomi SM. Effect of probiotic and synbiotic supplementation on inflammatory markers in health and disease status: A systematic review and meta-analysis of clinical trials. *Clin Nutr* 2020; **39**: 789-819 [PMID: 31060892 DOI: 10.1016/j.clnu.2019.04.004]
 - 172 **Maslennikov R**, Efremova I, Ivashkin V, Zharkova M, Poluektova E, Shirokova E, Ivashkin K. Effect of probiotics on hemodynamic changes and complications associated with cirrhosis: A pilot randomized controlled trial. *World J Hepatol* 2022; **14**: 1667-1677 [PMID: 36157871 DOI: 10.4254/wjh.v14.i8.1667]
 - 173 **Xia X**, Chen J, Xia J, Wang B, Liu H, Yang L, Wang Y, Ling Z. Role of probiotics in the treatment of minimal hepatic encephalopathy in patients with HBV-induced liver cirrhosis. *J Int Med Res* 2018; **46**: 3596-3604 [PMID: 29806520 DOI: 10.1177/0300060518776064]
 - 174 **Dhiman RK**, Rana B, Agrawal S, Garg A, Chopra M, Thumburu KK, Khattri A, Malhotra S, Duseja A, Chawla YK. Probiotic VSL#3 reduces liver disease severity and hospitalization in patients with cirrhosis: a randomized, controlled trial. *Gastroenterology* 2014; **147**: 1327-37.e3 [PMID: 25450083 DOI: 10.1053/j.gastro.2014.08.031]
 - 175 **Lata J**, Novotný I, Příbramská V, Juránková J, Fric P, Kroupa R, Stibůrek O. The effect of probiotics on gut flora, level of endotoxin and Child-Pugh score in cirrhotic patients: results of a double-blind randomized study. *Eur J Gastroenterol Hepatol* 2007; **19**: 1111-1113 [PMID: 17998837 DOI: 10.1097/MEG.0b013e3282efa40e]
 - 176 **Koga H**, Tamiya Y, Mitsuyama K, Ishibashi M, Matsumoto S, Imaoka A, Hara T, Nakano M, Oeda K, Umezaki Y, Sata M. Probiotics promote rapid-turnover protein production by restoring gut flora in patients with alcoholic liver cirrhosis. *Hepatol Int* 2013; **7**: 767-774 [PMID: 26201812 DOI: 10.1007/s12072-012-9408-x]
 - 177 **Bajaj JS**, Heuman DM, Hylemon PB, Sanyal AJ, Puri P, Sterling RK, Luketic V, Stravitz RT, Siddiqui MS, Fuchs M, Thacker LR, Wade JB, Daita K, Sistrun S, White MB, Noble NA, Thorpe C, Kakiyama G, Pandak WM, Sikaroodi M, Gillevet PM. Randomised clinical trial: Lactobacillus GG modulates gut microbiome, metabolome and endotoxemia in patients with cirrhosis. *Aliment Pharmacol Ther* 2014; **39**: 1113-1125 [PMID: 24628464 DOI: 10.1111/apt.12695]
 - 178 **Horvath A**, Durdevic M, Leber B, di Vora K, Rainer F, Kronen E, Douschan P, Spindelboeck W, Durchschein F, Zollner G, Stauber RE, Fickert P, Stiegler P, Stadlbauer V. Changes in the Intestinal Microbiome during a Multispecies Probiotic Intervention in Compensated Cirrhosis. *Nutrients* 2020; **12** [PMID: 32585997 DOI: 10.3390/nu12061874]
 - 179 **Zhong C**, Qu C, Wang B, Liang S, Zeng B. Probiotics for Preventing and Treating Small Intestinal Bacterial Overgrowth: A Meta-Analysis

and Systematic Review of Current Evidence. *J Clin Gastroenterol* 2017; **51**: 300-311 [PMID: 28267052 DOI: 10.1097/MCG.0000000000000814]

- 180 Nickles MA, Hasan A, Shakhbazova A, Wright S, Chambers CJ, Sivamani RK. Alternative Treatment Approaches to Small Intestinal Bacterial Overgrowth: A Systematic Review. *J Altern Complement Med* 2021; **27**: 108-119 [PMID: 33074705 DOI: 10.1089/acm.2020.0275]
- 181 Lunia MK, Sharma BC, Sharma P, Sachdeva S, Srivastava S. Probiotics prevent hepatic encephalopathy in patients with cirrhosis: a randomized controlled trial. *Clin Gastroenterol Hepatol* 2014; **12**: 1003-8.e1 [PMID: 24246768 DOI: 10.1016/j.cgh.2013.11.006]
- 182 Kwak DS, Jun DW, Seo JG, Chung WS, Park SE, Lee KN, Khalid-Saeed W, Lee HL, Lee OY, Yoon BC, Choi HS. Short-term probiotic therapy alleviates small intestinal bacterial overgrowth, but does not improve intestinal permeability in chronic liver disease. *Eur J Gastroenterol Hepatol* 2014; **26**: 1353-1359 [PMID: 25244414 DOI: 10.1097/MEG.0000000000000214]
- 183 Ruchkina IN, Fadeeva NA. [The role of a combined probiotic in the treatment of lactase deficiency]. *Ter Arkh* 2021; **93**: 431-434 [PMID: 36286777 DOI: 10.26442/00403660.2021.04.200808]
- 184 Luo M, Liu Q, Xiao L, Xiong LS. Golden bifid might improve diarrhea-predominant irritable bowel syndrome via microbiota modulation. *J Health Popul Nutr* 2022; **41**: 21 [PMID: 35578355 DOI: 10.1186/s41043-022-00302-0]
- 185 Bustos Fernández LM, Man F, Lasa JS. "Impact of *Saccharomyces boulardii* CNCM I-745 on bacterial overgrowth and composition of intestinal microbiota in IBS-D patients: results of a randomized pilot study". *Dig Dis* 2023 [PMID: 36630947 DOI: 10.1159/000528954]
- 186 Lee SH, Joo NS, Kim KM, Kim KN. The Therapeutic Effect of a Multistrain Probiotic on Diarrhea-Predominant Irritable Bowel Syndrome: A Pilot Study. *Gastroenterol Res Pract* 2018; **2018**: 8791916 [PMID: 30622561 DOI: 10.1155/2018/8791916]
- 187 Liang S, Xu L, Zhang D, Wu Z. Effect of probiotics on small intestinal bacterial overgrowth in patients with gastric and colorectal cancer. *Turk J Gastroenterol* 2016; **27**: 227-232 [PMID: 27210778 DOI: 10.5152/tjg.2016.15375]
- 188 García-Collinot G, Madrigal-Santillán EO, Martínez-Bencomo MA, Carranza-Muleiro RA, Jara LJ, Vera-Lastra O, Montes-Cortes DH, Medina G, Cruz-Domínguez MP. Effectiveness of *Saccharomyces boulardii* and Metronidazole for Small Intestinal Bacterial Overgrowth in Systemic Sclerosis. *Dig Dis Sci* 2020; **65**: 1134-1143 [PMID: 31549334 DOI: 10.1007/s10620-019-05830-0]
- 189 Woodard GA, Encarnacion B, Downey JR, Peraza J, Chong K, Hernandez-Boussard T, Morton JM. Probiotics improve outcomes after Roux-en-Y gastric bypass surgery: a prospective randomized trial. *J Gastrointest Surg* 2009; **13**: 1198-1204 [PMID: 19381735 DOI: 10.1007/s11605-009-0891-x]
- 190 Prokopidis K, Giannos P, Kirwan R, Ispoglou T, Galli F, Witard OC, Triantafyllidis KK, Kechagias KS, Morwani-Mangnani J, Ticinesi A, Isanejad M. Impact of probiotics on muscle mass, muscle strength and lean mass: a systematic review and meta-analysis of randomized controlled trials. *J Cachexia Sarcopenia Muscle* 2023; **14**: 30-44 [PMID: 36414567 DOI: 10.1002/jcsm.13132]
- 191 Byeon HR, Jang SY, Lee Y, Kim D, Hong MG, Lee D, Shin JH, Seo JG. New Strains of *Akkermansia muciniphila* and *Faecalibacterium prausnitzii* are Effective for Improving the Muscle Strength of Mice with Immobilization-Induced Muscular Atrophy. *J Med Food* 2022; **25**: 565-575 [PMID: 35708632 DOI: 10.1089/jmf.2021.K.0148]
- 192 Hong AS, Tun KM, Hong JM, Batra K, Ohning G. Fecal Microbiota Transplantation in Decompensated Cirrhosis: A Systematic Review on Safety and Efficacy. *Antibiotics (Basel)* 2022; **11** [PMID: 35884093 DOI: 10.3390/antibiotics11070838]
- 193 Bajaj JS, Salzman NH, Acharya C, Sterling RK, White MB, Gavis EA, Fagan A, Hayward M, Holtz ML, Matherly S, Lee H, Osman M, Siddiqui MS, Fuchs M, Puri P, Sikaroodi M, Gillevet PM. Fecal Microbial Transplant Capsules Are Safe in Hepatic Encephalopathy: A Phase 1, Randomized, Placebo-Controlled Trial. *Hepatology* 2019; **70**: 1690-1703 [PMID: 31038755 DOI: 10.1002/hep.30690]
- 194 Tun KM, Hong AS, Batra K, Naga Y, Ohning G. A Systematic Review of the Efficacy and Safety of Fecal Microbiota Transplantation in the Treatment of Hepatic Encephalopathy and *Clostridioides difficile* Infection in Patients With Cirrhosis. *Cureus* 2022; **14**: e25537 [PMID: 35800791 DOI: 10.7759/cureus.25537]
- 195 Chen H, Xu C, Zhang F, Liu Y, Guo Y, Yao Q. The gut microbiota attenuates muscle wasting by regulating energy metabolism in chemotherapy-induced malnutrition rats. *Cancer Chemother Pharmacol* 2020; **85**: 1049-1062 [PMID: 32415349 DOI: 10.1007/s00280-020-04060-w]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

