Clinical Nutrition 51 (2025) 362–372

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Narrative Review

The intricate interplay between acute pancreatitis and small intestinal bacterial overgrowth: Unraveling the unknown

Xiaorui Cui [a,1], Huaizhu Guo [a,1], Zhen Liu [a], Yuanyuan Lei [a], Yunxiong Wei [a], Guangyong Sun [a,b], Dong Zhang [a,b], Jianyu Hao [a], Donglei Zhang [a,*], Xinjuan Liu [a,**]

[a] Department of Gastroenterology, Beijing Chao-Yang Hospital, Capital Medical University, Beijing 100020, China
[b] Medical Research Center, Beijing Institute of Respiratory Medicine and Beijing Chao-Yang Hospital, Capital Medical University, Beijing 100020, China

ARTICLE INFO

Article history:
Received 19 March 2025
Accepted 11 June 2025

Keywords:
Acute pancreatitis
Small intestinal bacterial overgrowth
Gut dysbiosis
Bacterial translocation

SUMMARY

Small intestinal bacterial overgrowth (SIBO) refers to the overcolonization of bacteria in the small intestine. Multiple studies have shown a correlation between SIBO and the occurrence and development of various diseases. This review focuses on the relationship between SIBO and acute pancreatitis (AP), summarizing the current research on the interaction and development between SIBO, AP, and gut microbiota translocation. It is emphasized that AP may lead to the generation of SIBO by prolonging the migrating motor complex (MMC) time and weakening the intestinal barrier. SIBO also plays a critical role in the development and deterioration of AP, which is related to the poor prognosis of AP through the intermediate factor of bacterial translocation (BT). Dysregulated bacteria and their metabolites can promote the occurrence of inflammatory cytokine storms through a series of immune signaling pathways. Furthermore, we summarize the promising treatments to improve AP by clearing SIBO and form a new therapeutic intervention strategy based on regulating gut microbiota and improving intestinal motility. For AP patients, rifaximin, probiotics, butyrate, and others targeting SIBO may be more effective in reducing the complications of AP and achieving better clinical outcomes, but further research is needed to validate this hypothesis.

1. Introduction

Small intestinal bacterial overgrowth (SIBO) is defined as the presence of an excessive amount of bacteria in the upper gastrointestinal tract [1]. The traditional diagnostic threshold for SIBO is a bacterial concentration of $\geq 10^5$ colony-forming units (CFU)/mL in jejunal culture [2]. However, this criterion has long been a subject of debate. Recent studies have revealed that the microbial load in the small intestinal fluid of healthy individuals typically remains below 10^3 CFU/mL. Clinically significant bacterial overgrowth, reaching concentrations of 10^6–10^7 CFU/mL, is generally observed only in post-surgical conditions such as gastrectomy [3]. The conventional diagnostic threshold for SIBO has been reconsidered due to its excessive stringency. Current clinical guidelines, including both the North American consensus and the American College of Gastroenterology (ACG) recommendations, now define SIBO as a bacterial concentration of $\geq 10^3$ CFU/mL in jejunal aspirate cultures [4]. An alternative measurement of exhaled hydrogen and methane during the breath test is considered a non-invasive, safe, functional, and cost-efficient method for SIBO. The most used breath test standard for diagnosing SIBO at present is the North American consensus. It recommended that a rise in hydrogen of ≥20 parts per million (ppm) or methane levels ≥10 ppm by 90 min during a glucose or lactulose breath test was considered positive [4]. The concept of gut methane-producing microorganism overgrowth has emerged as an important development in gastrointestinal research. Critically, these methane-producing organisms are not true bacteria (which comprise the "B" in SIBO) but rather belong to the domain Archaea, representing a phylogenetically distinct group of prokaryotes. In recognition of this fundamental taxonomic difference, we propose adopting the term intestinal methanogenic overgrowth (IMO) to properly characterize this condition, where methanogenic archaea, particularly *Methanobrevibacter smithii*, predominate instead of

* Corresponding author.
** Corresponding author.
E-mail addresses: zdlzdl52973@sina.com (D. Zhang), Liuxinjuan@mail.ccmu.edu.cn (X. Liu).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.clnu.2025.06.008
0261-5614/

conventional SIBO-associated bacteria [5,6]. Epidemiological retrospective studies have found that SIBO is more common in the elderly and is a common cause of diarrhea and malnutrition. Abdominal pain, bloating, belching, and diarrhea are the four most common symptoms in SIBO patients. In more severe cases of SIBO, patients may also experience steatorrhea and malabsorption of fat-soluble vitamins. Thus, no single symptom can be attributed explicitly to SIBO [5]. Its diagnosis is prone to confusion with other diseases, such as inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), and functional dyspepsia [7]. Studies have found that the relationship between SIBO and IBD is complex, and many IBD patients may also have SIBO [8]. However, there is currently limited research on the mechanism of action of SIBO in pancreatic diseases, and specific intervention measures still need to be further explored. At present, there is still no clear and unified conclusion about the pathogenesis of SIBO. Myogenic or neurogenic intestinal motility disorders (such as intestinal obstruction, scleroderma, diabetes, hypothyroidism), operations that change the anatomical structure of the gastrointestinal tract (such as diverticulum, gastrectomy), Impaired gastrointestinal defense function, and immune deficiency diseases are all susceptible factors of SIBO [9].

Acute pancreatitis (AP) is a common acute abdominal disease, mainly caused by biliary tract disease and excessive alcohol consumption. Other causes may include post-endoscopic retrograde cholangiopancreatography (ERCP), medication, viral infection, metabolic disorders, and abdominal trauma, with some cases being idiopathic [10]. Although most cases have mild and self-limiting conditions, 15–20 % of them will progress to severe acute pancreatitis (SAP), with a mortality rate of up to 30 % [11]. Infectious pancreatic necrosis (IPN) is associated with a higher mortality rate, with over 80 % of SAP deaths associated with enterogenous infections [12]. The translocation of bacteria has been proven to be a significant factor in the secondary acute inflammation and septic shock of AP [13]. Previous studies have found that the acute physiology and chronic health evaluation II (APACHE-II) score of AP patients is positively correlated with the presence or absence of bacteremia, indicating that an increase in the number of bacteria in the patient's circulation can lead to an increase in the severity of AP [14].

The overall balance of the gut microbiota maintains normal physiological functions in the host. Recent studies have confirmed the importance of the human gut microbiota in maintaining health and participating in disease processes. The composition of the gut microbiota plays a crucial role in regulating the immune response to invading pathogens in humans, and it also helps prevent pathogens from crossing the intestinal barrier [15]. The disruption of the intestinal barrier can exacerbate bacterial translocation (BT) and enterogenous infections, leading to the progression of AP [16]. However, only a small portion of research focuses on exploring the correlation between SIBO and AP, as well as how the two interact and influence each other. This review can fill the gap in this field by summarizing the current research on the interaction and development between SIBO, AP, and gut microbiota translocation. We also hope our research can provide prospects for novel treatments for AP patients in the future: improving AP through targeted BT in the intestine.

2. Small intestinal bacterial overgrowth attributed to acute pancreatitis

Retrospective studies have shown a higher prevalence of SIBO in patients with AP. Moreover, there are statistically significant differences in the occurrence of SIBO among patients with different severities of AP. Specifically, the incidence of SIBO in mild acute pancreatitis (MAP), moderate-severe acute pancreatitis (MSAP), and SAP is reported to be 8.42 %, 25.58 %, and 25.92 %, respectively [17]. Additionally, studies have found that AP patients exhibit relatively higher concentrations of exhaled H_2 and CH_4, indicating a correlation between elevated levels of intestinal bacteria and AP [18].

2.1. Acute pancreatitis triggers the occurrence of SIBO through abnormal small intestinal motility

As previously mentioned, myogenic or neurogenic motility disorders are susceptibility factors for SIBO [19]. It has been reported that the average small intestine transit time of SIBO patients is twice that of healthy individuals, indicating that small intestine motility stasis may play an essential role in the occurrence of SIBO. The migrating motor complex (MMC), acting as the “housekeeper” of the gastrointestinal tract and a necessary indicator of gastrointestinal motility, is closely related to the occurrence of SIBO [20,21]. The inappropriate extension of the MMC cycle can impair the ability to clear food residues from the digestive system, which has been reported to be associated with conditions including SIBO, gastroparesis, and intestinal pseudo-obstruction [22]. The pathogenic mechanism may be that prolonged MMC cannot inhibit bacterial attachment to the intestinal wall, and food residues stay in the gut for an extended period, causing the proliferation of aerobic and anaerobic microorganisms [23].

At present, studies from patients with multiple diseases have proved that prolonged MMC can lead to SIBO. For example, the prevalence of SIBO in the population with diabetes is higher than that in the normal control population significantly. Complications such as autonomic neuropathy triggered by poor control of diabetes are just one of the factors that damage gastrointestinal motility, cause gastroparesis, delay gastric emptying, and lengthen MMC [24,25]. It was found that the frequency of phase III MMC decreased in IBS patients with SIBO, indicating that the abnormal hydrogen breath test results in IBS patients may be secondary to gastrointestinal motility defects in the small intestine [26]. Systemic sclerosis, as a multisystem connective tissue lesion, has an impact on the gastrointestinal tract, manifested as gastric paresis or delayed gastric emptying, disrupting the normal cycle of MMC. Retrospective studies have found that the incidence of SIBO in patients with systemic sclerosis is as high as 40 % [27]. Delayed gastric emptying and prolonged gastrointestinal transit time were seen in Parkinson's disease, along with a higher prevalence of SIBO, as high as 25 % [28]. The study from the cohort of advanced radiation-induced enteropathy showed that abnormal colonization of Gram-negative bacteria in the duodenum was associated with the strength of MMC [29]. A meta-analysis revealed that patients with cirrhosis exhibit a significantly higher prevalence of SIBO than healthy controls. The pooled incidence of SIBO was 40.8 % in cirrhotic patients versus 10.7 % in the control group. Notably, decompensated cirrhosis was associated with an even greater likelihood of SIBO than compensated cirrhosis, suggesting a correlation with disease severity. This increased susceptibility may be attributed to delayed small intestinal motility, which is frequently observed in cirrhotic patients with SIBO [30]. And the MMC cycle was significantly prolonged compared to healthy people using an intraluminal pressure measurement to observe the small intestine contraction movement.

A number of evidence from animal experiments support a strong association between SIBO and MMC. A study on the effect of gastrointestinal electromyographic complexes on the gut microbiota of rats found that the use of morphine to destroy MMC promoted excessive growth and translocation of bacteria in the

duodenum [31], especially Gram-negative bacterial colonization in the small intestine, suggesting that MMC is an important regulatory mechanism of the upper gut microbiota [32]. Another study on rats blocked the proximal common bile duct (CBD) showed that the length of the MMC cycle was prolonged compared to before obstruction, and the bacterial levels in the jejunum were higher than those in the control and significantly correlated with the length of the MMC cycle [33].

Similarly, AP can also affect MMC. The interruption of MMC cycle length resulted in a decrease in the dominant frequency and dominant power of slow waves in L-ornithine-induced acute necrotizing pancreatitis (ANP) rats [34]. Some studies have also induced AP in rats through bile duct ligation and found that the MMC interval was significantly prolonged, intestinal motility was damaged, and the intestinal migratory electromyography complex was inhibited after 48 h of bile duct ligation compared to before ligation [17,35]. Therefore, AP may generate SIBO by prolonging MMC time. AP leads to the destruction of MMC; thus, secondary gastrointestinal motility damage and activity reduction may be the main pathogenic factors of SIBO [36].

2.2. Acute pancreatitis triggers the occurrence of small intestinal bacterial overgrowth by disrupting the intestinal barrier

The intestinal barrier refers to a significant barrier that can separate the intestinal cavity from the internal environment of the organism, preventing harmful substances and pathogens from entering the internal environment of the organism and maintaining the stability of the internal environment. When the intestinal barrier mechanism fails, the disrupted “geographical distributions” bring about differences in the types and quantities of bacteria colonizing the small intestine [37]. AP can affect the permeability of the intestinal barrier, which is one of the main pathogenic pathways for SIBO.

The mechanical barrier is composed of intestinal mucosal epithelial cells (absorbing goblet cells and Pan cells) and intercellular junctions: tight junctions (TJs), gap junctions, adhesive junctions, and desmosome junctions. Among them, TJs are the most critical link, including occludin, claudin protein, perimembrane protein family (ZO protein), and connecting adhesion molecules [38]. AP can cause mechanical barrier dysfunction in the duodenum. The intestinal mucosal permeability of SAP patients increased due to the detection of ruptured intestinal mucus layer, actin rearrangement, and decreased cell connectivity [39]. Meanwhile, animal experiments verified the down-regulated expression of TJs in the duodenum of MAP and SAP mice in accordance with the severe duodenal pathological damage [40]. The mechanisms by which AP disrupts the intestinal mechanical barrier may be as follows. First, a large amount of fluid replacement leads to intestinal reperfusion, increases the permeability between intestinal epithelial cells, and reduces the function of the intestinal barrier [41]. Second, fasting and, if necessary, performing gastrointestinal decompression leads to a lack of nutrition in the intestinal mucosal epithelium, resulting in epithelial cell atrophy and apoptosis, thinning of villi, and damage to the mechanical barrier of the intestine. Suppose the integrity of the intestinal barrier is compromised. In that case, intestinal barrier leakage can occur, allowing luminal contents to enter the bloodstream, activating immune responses, triggering inflammation, and forming the basis of many diseases, including but not limited to SIBO [42].

The chemical barrier refers to chemical substances secreted by the gastrointestinal tract, such as bile, gastric acid, digestive enzymes, and lysozyme. In AP patients undergoing parenteral nutrition, chemicals are reduced, leading to the breakdown of the intestinal barrier [43].

The biological barrier is a microorganism competitively inhibiting the colonization and growth of pathogenic bacteria in the intestinal epithelium. The disruption of the intestinal barrier promotes the translocation of intestinal bacteria. Studies have observed that in the early stages of SAP, the abundance of beneficial bacteria such as *Bifidobacteria* decreases, weakening their inhibitory effect on pathogenic bacteria, which in turn increases the colonization of pathogenic bacteria such as *Escherichia coli* and *Streptococcus* in the ileum [13,44]. Bacteria are also more likely to infect the abdominal cavity through the bile duct or pancreatic duct, or the outside of the intestine retrogradely [45], indicating that maintaining the stability of the intestinal barrier is an integral part of AP treatment.

Secretory Immunoglobulin A (IgA) and complement are crucial immune defense factors of the intestinal mucosa to exert antibacterial effects. Previous studies have found that the levels of endotoxin core antibody Immunoglobulin M (IgM), the plasma levels of tumor necrosis factor-α (TNF-α), and interleukin (IL)-6/8/10 are higher than those in healthy individuals [46]. The disruption of the intestinal barrier and bacterial translocation (BT) can also have a negative impact on mucosal immune response [38]. The process of pathogenic bacteria crossing the epithelial barrier can activate mucosal immune responses and promote the release of a series of pro-inflammatory cytokines such as interferon-γ, TNF-α, IL-1 β, and IL-6, further disrupting the function of TJs protein and causing further damage to the mechanical barrier, exacerbating BT and disrupting the normal gut microbiota through a vicious cycle.

3. Small intestinal bacterial overgrowth exacerbates the progression of acute pancreatitis

Multiple objective indicators suggest that patients with AP complicated by SIBO show more terrible conditions. Organ failure in patients with AP who develop SIBO is significantly more severe than in those without SIBO [17]. Another study found that higher levels of H_2 and CH_4 in the breath of AP patients are associated with oral glucose intolerance and a higher risk of hyperglycemia, which is one of the indicators of worsening AP [18]. All of these findings indicate that SIBO can exacerbate the progression of AP. However, the occurrence rate of infection or local complications, such as pancreatic necrosis, pseudocysts, or pancreatic abscesses, is not related to the presence of SIBO [17]. Therefore, it is imperative to conduct a deeper exploration of SIBO and the outcome and prognosis of AP.

3.1. Small intestinal bacterial overgrowth and acute pancreatitis are both associated with the disruption of gut microbiota

3.1.1. Bacterial and concomitant immunity alterations in small intestinal bacterial overgrowth

The alterations of gut microbiota in SIBO can be summarized as a decrease in beneficial bacteria abundance and an increase in pathogenic bacteria abundance in the small intestine. At the phylum level, the study from duodenal aspirates showed a higher relative abundance of Proteobacteria and a lower relative abundance of Firmicutes in SIBO subjects compared to non-SIBO subjects [47]. Subjects with SIBO exhibited lower microbial diversity in accordance with Proteobacteria abundance, indicating that dysbiosis related to Proteobacteria may serve as a microbial marker for SIBO [48,49]. At the genus level, the small intestinal microbiota of SIBO patients using 16S rRNA sequencing revealed an increased relative abundance of *Escherichia* and *Klebsiella*, members of the Proteobacteria, which was associated with symptoms such as abdominal pain and bloating. Histamine produced by *Klebsiella* has been found to have a significant impact on

visceral hypersensitivity. It is related to the disruption of the regular microbial network in the duodenum [50], with detrimental effects on microbial metabolism pathways [51]. A study using the same 16srRNA method for sequencing fecal samples from subjects found that compared to the healthy control group, the abundance of *Coprococcus* in SIBO increased and showed a positive correlation with the severity of a series of discomfort symptoms in SIBO patients [52]. Studies analyzing bacteria in patients with hydrogen-predominant SIBO and methane-predominant SIBO separately found characteristic bacteria for each subtype. Anaerobic bacteria, such as *Bacteroides*, and facultative anaerobic bacteria, such as *Streptococcus* and *Escherichia coli,* were characteristic bacteria in patients with hydrogen-predominant SIBO [53]. At the same time, *Methanobrevibacter* was characteristic in patients with methane-predominant SIBO [54]. Examination of mucosal-associated microbiota in the upper (duodenum), middle (jejunum), and lower (ileum) gastrointestinal tracts through sequencing analysis revealed a lower Shannon diversity index in the mucosal samples of the jejunum in SIBO-positive subjects compared to SIBO-negative subjects [55]. The composition of mucosal bacteria in the duodenum was significantly different from that in the jejunum and ileum. However, some similar trends were observed across all segments, such as decreased levels of *Rothia*, *Prevotella*, *Lactobacillus*, and *Ruminococcus*, which are beneficial bacteria involved in food digestion, maintaining intestinal barrier integrity, and regulating intestinal immunity [55]. The characteristic alterations in gut microbiota induced by SIBO can also create a pro-inflammatory environment in the duodenum. PCR testing of duodenal fluid in SIBO patients revealed a higher prevalence of elevated levels of three pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) compared to non-SIBO subjects. Notably, the detection of *Klebsiella pneumoniae* and *Methanobrevibacter*, characteristic bacteria of SIBO, was positively correlated with IL-6 and TNF-α levels and IL-1β levels, respectively [56]. The rearrangement of intestinal microbiota in SIBO patients is summarized in Table 1.

3.1.2. Disturbance of gut microbiota and secondary impact on acute pancreatitis

Similarly, patients with AP exhibit reduced gut microbiota diversity, characterized by alterations in the relative abundance of specific bacteria, with a decrease in beneficial bacteria and an increase in pathogenic bacteria. The gut microbiota diversity was lower in AP patients compared to healthy controls from fecal samples using 16S rRNA sequencing [57]. At the phylum level, AP patients had an increased abundance of Proteobacteria and decreased abundances of Firmicutes and Bacteroidetes [58]. At the genus level, opportunistic pathogens such as *Enterococcus* and *Escherichia-Shigella* were more abundant in AP patients, whereas beneficial bacteria like *Blautia*, *Prevotella*, and *Bifidobacterium* were depleted [59,60]. Recent studies using duodenal mucosal samples also revealed significant enrichment of facultative pathogens such as *Escherichia-Shigella*, *Enterococcus*, and *Staphylococcus* in SAP patients [40]. Animal studies support these findings. Bile acid-induced ANP rats showed a reduced microbial diversity, an increase in the abundance of *Escherichia-Shigella,* and a decrease in beneficial bacteria such as *Prevotella* and *Lactobacillus*, with concomitant changes in clinical outcomes [61]. Microbial composition changes further exacerbate the disease and reflect the severity of AP. Rectal swab sequencing revealed that *Streptococcus*, *Escherichia*, and *Enterococcus* were the most representative gut microbiota in MAP, MSAP, and SAP, respectively [62,63]. Gut microbiota profiles in AP patients are associated with intensive care unit (ICU) stay duration, overall hospital stay, C-reactive protein (CRP) levels, and the duration of organ failure. This suggests that gut microbiota characteristics may serve as predictive markers for disease severity [64]. Above gut dysbiosis indicates that gut microbiota not only suffer during AP but may also play a crucial role in disease progression. The microbial profiles of AP are detailed in Table 2.

The production of short-chain fatty acids (SCFAs) by the primary producers such as *Bifidobacterium*, *Bacteroides*, *Blautia*, and *Gemmiger* is reduced in AP [65–68]. *Eubacterium hallii*, a primary SCFAs-producing bacterium, shows a significant reduction in SAP and MSAP patients. This decrease in SCFAs production in AP patients contributes to the impairment of the gut barrier function and may exacerbate the condition by promoting dysbiosis and inflammation. The diminished SCFAs levels highlight the importance of maintaining a healthy gut microbiota composition to support gut barrier integrity and overall health, particularly in the context of AP [62].

Inflammatory cytokines, along with the changes in gut microbiota, are associated with the severity of AP patients, indicating that gut microbiota plays a crucial role in the progression of AP. Elevated levels of IL-6, IL-1, and TNF-α were observed in patients with SAP and those with systemic complications in later stage [59,69,70]. Serum IL-6 levels were positively correlated with the presence of *Escherichia coli* and *Enterococcus* and negatively correlated with *Bifidobacterium* [57]. Higher plasma endotoxin levels were also positively correlated with *Enterococcus* [71,72]. Animal models with depleted gut microbiota exhibited less pancreatic damage and reduced plasma levels of inflammatory cytokines [59,73]. This evidence indicates that dysbiosis of AP is

Table 1
Summary of gut microbiota alterations in SIBO patients.[a]

Study	Reference	Type of sample	Microbial evaluation	Phylum level	Family level	Genus level
Gabriela Leite	[47]	Duodenal Aspirates	16s rRNA sequencing	NA	Enterobacteriaceae↑	Escherichia↑ Klebsiella↑
Jia Li	[55]	Duodenum Biopsy	16s rRNA sequencing	Firmicutes↑ Proteobacteria↑ Bacteroidetes↑	NA	Bacteroides↑ Escherichia-Shigella↑ Streptococcus↑ Lactobacillus↓ Prevotella↓ Bifidobacterium↓
Gabriela Leite	[51]	Duodenal Aspirates	16s rRNA sequencing	Proteobacteria↑ Firmicutes↓	Enterobacteriaceae↑ Aeromonadaceae↑ Moraxellaceae↑	Klebsiella↑ Escherichia/Shigella↑ Acinetobacter↑
Andrea S. Shin	[48]	Small bowel aspirate and mucosal samples	16s rRNA sequencing	NA	NA	Clostridium↑ Granulicatella↑
Guo H	[52]	Feces	16s rRNA sequencing	NA	NA	Bacteroides ↓ Coprococcus↑

[a] ↑, elevated abundance; ↓, reduced abundance; NA, not available.

Table 2
Summary of gut microbiota alterations in AP patients.[a]

Study	Reference	Type of sample	Microbial evaluation	Phylum level	Family level	Genus level
Tan C	[57]	Feces	PCR-DGGE	NA	NA	Enterococcus↑ Enterobacteriaceae↑ Bifidobacterium↓
Zhang XM	[58]	Feces	16s rRNA sequencing	Bacteroidetes↑ Proteobacteria↑ Firmicutes↓ Actinobacteria↓	NA	NA
Zhu Y	[59]	Feces	16s rRNA sequencing	Proteobacteria↑	Enterobacteriaceae↑	Escherichia Shigella↑ Enterococcus↑ Blautia↓ Faecalibacterium↓ Bifidobacterium↓
Yu S	[62]	Rectal swab samples	16s rRNA sequencing	NA	NA	Bacteroides↑ Escherichia-Shigella↑ Enterococcus↑ Eubacterium hallii↓ Blautia↓
Yu S	[63]	Rectal swab samples	Shotgun metagenomic sequencing	NA	NA	Streptococcus↑ Escherichia-coli↑ Enterococcus↑
Zhao MQ	[40]	Duodenal mucosal biopsies	16s rRNA sequencing	Firmicutes↑ Proteobacteria↓ Bacteroidetes↓	Streptococcaceae↑	Streptococcus↑ Neisseria↑

[a] ↑, elevated abundance; ↓, reduced abundance; NA, not available.

linked to inflammatory cytokines and endotoxins, exacerbating systemic inflammatory response syndrome (SIRS) and increasing the risk of organ failure.

Changes in the gut microbiota of AP are associated with various immune pathways. The abundance of pathogenic bacteria such as *Escherichia coli*, *Proteobacteria*, and *Enterococcus* can mediate immune responses through pathogen-associated molecular patterns (PAMPs), which stimulate dendritic cells and macrophages to secrete pro-inflammatory cytokines, leading to the differentiation of immature T cells into Th1/Th17 cells while inhibiting Tregs and B cells. This results in a further decrease in anti-inflammatory cytokines and sIgA [74], pathologically activating the immune response and promoting an "inflammatory storm" through the activation of mitogen-activated protein kinase (MAPK) or nuclear factor kappa B (NF-κB) pathways. It ultimately leads to epithelial cell necrosis and damage to TJs [75]. Pathogenic bacteria enriched in AP rats, such as *Escherichia coli* and *Shigella,* are considered M1 alveolar macrophages (AMs), exacerbating inflammation and promoting the development of pancreatitis-associated lung injury (PALI) [76–80]. This elevates the abundance of Toll-like receptor 4 (TLR4)/MyD88/p38 MAPK and leads to endoplasmic reticulum stress (ERS) signaling, causing intestinal epithelial damage [73]. The lipopolysaccharides of abundant *Escherichia coli* bind to receptors like TLR on intestinal epithelial cells, activating NF-κB signaling and leading to the release of excessive cytokines and inflammatory mediators such as IL-6 [39]. Additionally, the dysbiosis of the gut microbiota during the acute phase of AP stimulates intestinal inflammation through the activation of the nucleotide-binding oligomerization domain-like receptor protein 3(NLRP3), damaging the epithelial barrier and promoting the translocation of intestinal bacteria to distant organs [81].

3.2. Bacterial translocation secondary to intestinal microbiota disorder in small intestinal bacterial overgrowth exacerbates the progression of acute pancreatitis

Many studies have indicated the presence of BT during the progression of AP. 39.4 % of surgery samples from ANP patients could culture gut microbiota [82]. It was found that opportunistic pathogens originating from the gut, including *Escherichia coli*, *Shigella*, *Enterobacter*, and *Enterococcus faecalis*, were likely the main components of translocated bacteria according to peripheral blood samples collected from AP patients [14]. Spearman correlation analysis showed that specific operational taxonomic units (OTUs) such as OTU44 (Muribaculaceae), OTU117 (Halomonas), and OTU27 (Anaeroplasma) had correlated abundances in the pancreas and ileum, which indicates that these bacteria might translocate from the gut to the pancreas by crossing the intestinal barrier [83]. To explore the potential sources of BT in AP, further animal studies verified that the source of pancreatic infection that occurred within 8–16 h post sodium taurocholate induction was likely the colon or terminal ileum [84]. In experiments where the gut bacterial load was reduced via cecostomy formation and colonic lavage in AP-induced rats, there was a significant reduction in serum endotoxin levels and mortality compared to controls [85]. Another study performed gut decontamination of either the small intestine or colon in rats before inducing ANP, and BT was assessed by culturing intestinal mucosa, mesenteric lymph nodes, and pancreas. The results indicated that BT from the colon was less frequent than from the small intestine, suggesting that the small intestine might be the primary source of gut bacteria leading to infective pancreatic necrosis in AP. Infective pancreatic necrosis is currently a significant determinant of prognosis in SAP, and BT from the gut microbiota is considered an important causative factor [13]. The movement of bacteria from the gut to other organs plays a crucial role in the development of systemic infections and complications in SAP, highlighting the importance of maintaining gut barrier integrity and targeting gut microbiota in therapeutic strategies for AP [86].

Researchers have outlined the pathophysiological mechanisms of gut BT in AP. First, the disruption of the normal ecological barrier and the secretion of various gastrointestinal peptides damage the interstitial cells of Cajal, reducing gut motility [87]. Impaired gut motility leads to stasis of intestinal contents, overgrowth of intestinal bacteria, and an increase in pathogenic bacteria such as *Enterobacter* and *Enterococcus*, promoting SIBO [35]. Secondly, the

mechanical barrier of the gut is compromised, increasing intestinal permeability, and the local and systemic bacterial clearance capacity is impaired [88]. Finally, the immune barrier is weakened, as evidenced by a decrease in sIgA [89], which further facilitates bacterial translocation. These findings indicate potential therapeutic strategies for AP that focus on restoring gut barrier function and improving gut microbiota to prevent BT. Such a strategy could better control the progression of AP at an early stage.

In summary, the development of AP is intricately linked to the dysbiosis caused by SIBO. AP facilitates the occurrence of SIBO, which further disrupts gut microbiota homeostasis, exacerbating the condition. Dysbiotic gut microbiota inhibits the secretion of antimicrobial peptides, damages intestinal epithelial cells and TJs, and impairs the gut barrier. This dysbiosis promotes the activation of macrophages and the recruitment of neutrophils through immune and metabolic pathways. While the metabolites of beneficial gut bacteria, such as SCFAs, can suppress inflammatory responses, this beneficial effect is diminished due to microbial homeostasis disruption. Bacteria, pro-inflammatory factors, and endotoxins can translocate through the compromised gut barrier, contributing to the progression of AP.

4. Treatment for small intestinal bacterial overgrowth may improve the prognosis of acute pancreatitis

As summarized earlier, SIBO is one of the risk factors for the progression of AP, and the intermediate factor connecting these two diseases is intestinal BT, which includes disruption of intestinal barrier integrity. Therefore, restoring the stability of the intestinal microbiota and intestinal barrier is of significant value for AP patients. Early treatment targeting SIBO may be more effective in reducing complications of AP, but further research is needed to validate this hypothesis.

4.1. Rifaximin

Currently, Rifaximin is thought effective and safe for the treatment of SIBO, considering its broad spectrum of action and non-absorbed nature in order to achieve low gastrointestinal absorption while retaining good antibacterial activity with low resistance and toxicity [90–92]. A meta-analysis evaluated the efficacy and safety of rifaximin in treating SIBO, concluding that it can safely eradicate SIBO by approximately 64 % and normalize breath test results by 49.5 % [92,93]. Rectal rifaximin administration exhibited a significant reduction in colonic BT to the mesenteric lymph nodes and a decrease in pro-inflammatory cytokines in colonic tissues from colitis mouse models, suggesting that rifaximin may exert immunomodulatory effects by reducing BT, thereby inhibiting the induction of pro-inflammatory cytokines and accelerating the recovery for AP [94].

Several cohort and experimental studies provided clinical evidence for the effect of rifaximin in AP. The results showed that the median length of hospital stay and the number of patients with infected pancreatic necrosis in the rifaximin treatment group were significantly lower than those in the control group, with no difference in mortality rates between the two groups [95]. The research results conducted in experimental AP rats showed that treatment with rifaximin can reduce pancreatic injury and the spread of intestinal bacteria in the abdominal cavity [96]. Rifaximin may also participate in SAP through the regulation of the gut microbiota structure. However, antibiotic use is also associated with risks, including increased incidence of resistant bacteria and fungal infections [97,98]. Rifaximin appears to be a promising new treatment option for AP.

4.2. Probiotics

Probiotics have been investigated as a treatment for AP. Some randomized controlled trials found that the addition of probiotics to early enteral nutrition brought reduced pancreatic necrosis and the need for surgical intervention, lowered plasma CRP levels, decreased infection complications, and significantly shorter hospital stays [99–102]. Recent animal studies also support the effectiveness of probiotics in AP rats with improved histological scores, reduced edema, parenchymal necrosis, mononuclear cell infiltration, and polymorphonuclear leukocyte infiltration, reducing the incidence of infectious complications and mortality [103–105]. Various probiotics application in experimentally induced AP rats reduced duodenal bacterial overgrowth, notably decreasing the abundance of *Enterococcus* and *Escherichia coli*, subsequently reducing BT in the mesenteric lymph nodes and pancreas of rats [106]. It provides a strategy that probiotics may use to treat SIBO by improving gut microbiota, thereby alleviating AP.

The mechanisms by which probiotics regulate the gut microbiota primarily involve (1) producing bioactive substances, such as organic acids, to inhibit the growth of pathogenic bacteria [107,108]; (2) stimulating mucus secretion in the intestinal mucosa to prevent pathogenic bacteria from adhering to the intestinal epithelium, thereby reducing BT [109]; (3) promoting the biosynthesis of glutathione, which eliminates superoxide and hydroxyl radicals, thus improving intestinal mucosal barrier function and inhibiting BT [110]; (4) upregulating the expression of molecules related to intestinal barrier function, such as tight junction proteins and mucin 2 (MUC2), enhancing intestinal barrier function and inhibiting BT [111–114].

Systematic reviews have demonstrated that probiotic supplementation significantly benefits patients with SIBO. Clinical evidence indicates probiotics effectively reduce hydrogen concentrations and alleviate abdominal pain symptoms [115]. Furthermore, probiotics serve as a valuable adjunct to established SIBO treatments, as shown in multiple clinical investigations. In a 90-day real-world observational study to evaluate the therapeutic approach combining rifaximin, low-FODMAP (fermentable, oligo-, di-, mono-saccharides and polyols) diet, Chinese herbal medicine, and probiotics for hydrogen-dominant and IMO subtypes. While the experimental group (additional herbal supplements, probiotics, prebiotics, and glutamine) showed similar breath test normalization rates compared to the control group (antibiotics + low-FODMAP diet), they demonstrated superior gastrointestinal symptom relief [116]. This benefit was especially pronounced in IMO patients [117]. Among various probiotic strains investigated for SIBO management, *Saccharomyces boulardii* currently represents the most extensively studied and clinically applied option, with substantial evidence supporting its therapeutic role [118,119]. However, some researchers are skeptical on account of the fact that double-blind trials and meta-analyses have not demonstrated improvements in intestinal permeability, mortality, or ICU stay duration for SAP patients treated with probiotics [120,121]. A multicenter, randomized, double-blind trial even found increased mortality in AP patients treated with probiotics [122]. This indicates potential variability in probiotic efficacy among different patients, underscoring the need for further multicenter, large-scale, randomized controlled trials. Such studies should consider the etiology of AP, specific probiotic strains, timing of intervention, dosage, and individual patient differences [123–128].

4.3. Fecal microbiota transplantation

As previously mentioned, dysbiosis of intestinal microbiota exacerbates pancreatic injury and inflammatory responses in AP. By improving gut microbiota and reducing BT, fecal microbiota transplantation (FMT) has shown potential in treating AP. Studies have demonstrated that FMT treatment in mice models with gut microbiota dysbiosis led to the alleviation of intestinal mucosal barrier damage and increased levels of sIgA, indicating the restoration of intestinal mucosal barrier integrity and reduction of BT, thus rebuilding the gut ecosystem [129]. Further research on the impact of FMT on gut microbiota in AP mice revealed an increased microbial diversity index, accompanied by reduced pancreatic tissue damage and decreased serum markers of AP. However, the exact role of FMT in AP still requires further investigation. Experimental studies on animal models of AP have not demonstrated a beneficial effect of FMT. Instead, significant pancreatic damage and increased mortality rates were observed after FMT treatment [59,130].

FMT can also be effective in SIBO with reduced gastrointestinal symptoms, increased rates of negative breath tests, and enhanced diversity of gut microbiota [131]. A case study investigated FMT as a therapeutic intervention for a patient with SIBO. Post-FMT evaluation revealed significant improvements in several key parameters: (1) enhanced intestinal barrier function, (2) increased bacterial species richness and microbiome evenness, (3) reduced fungal α-diversity, and (4) progressively elevated SCFAs levels. These findings suggest that FMT may exert its therapeutic effects through a dual mechanism: first by restoring eubiosis of the gut microbiota, and subsequently by preserving intestinal barrier integrity. This restoration process appears to prevent the translocation of pathogenic microorganisms and their metabolic byproducts from the intestinal lumen into the systemic circulation [132]. Although FMT is considered a promising therapeutic approach for gut microbiota restoration, the potential risks are not yet fully understood and require further research [133].

4.4. Enteral nutrition

The latest guidelines for managing SAP recommend the early use of enteral nutrition over parenteral nutrition for patients [134]. Enteral nutrition in AP had a reduced risk of postoperative sepsis, improving the acute-phase response and severity scores of AP [135–137]. Animal experiments have reported that short-peptide enteral nutrition (SPEN) can improve intestinal microcirculation in SAP mice, thereby preventing intestinal BT that may occur later in SAP [138]. Thus, the main reason enteral nutrition is recommended in the treatment of AP patients is its advantage in protecting mucosal barriers.

Studies have shown that enteral nutrition supplements rich in glutamine, dietary fiber, and oligosaccharides can improve intestinal damage caused by bacterial overgrowth models and prevent bacterial overgrowth caused by intestinal BT [139]. Therefore, enteral nutrition may alleviate the severity of AP by improving impaired intestinal barrier permeability owing to SIBO.

4.5. Octreotide

Octreotide can reduce mortality and the incidence rate of complications in AP [140]. Octreotide can stimulate intestinal motility and induce migrating motor complex-like movements in the small intestine. The clinical study supported an increased frequency of intestinal migrating complexes and a significant reduction in hydrogen excretion in the glucose hydrogen breath test after octreotide treatment [141]. The improvement in intestinal motility disorder is accompanied by a decrease in bacterial overgrowth, indicating that the improvement of SIBO by octreotide may be one of the mechanisms inhibiting the worsening of AP.

4.6. Butyrate

Butyrate, as one of the SCFAs, possesses beneficial effects such as stabilizing the intestinal barrier, enhancing mucosal immune function, and restoring intestinal microbial balance [60,142–145]. A diet rich in fiber has been proven effective for many patients with concurrent SIBO symptoms, as this type of diet can increase SCFAs production and inhibit the growth of harmful bacteria [146]. Butyrate may improve SIBO by protecting the intestinal barrier and regulating the stability of the intestinal microbiota, thereby further inhibiting BT and alleviating the severity of AP. Therefore, butyrate is a promising therapeutic approach as a protective measure against intestinal damage during AP progression [147].

Oral administration of butyrate salts resulted in a significant reduction in serum endotoxin levels and mortality in ANP mice [130]. Additionally, butyrate-treated SAP mice revealed improved pancreatic tissue pathology and lower levels of inflammatory factors [148]. A study analyzing the fecal microbiota of SAP rats found that butyrate restored the intestinal microbiota of SAP rats, manifested by increased microbial diversity, increased beneficial bacteria such as *Lactobacilli* and *Fecalococci*, and decreased pathogenic bacteria such as *Pseudomonads* and *Escherichia coli* [149]. Butyrate can also upregulate tight junction proteins in SAP rats and restore goblet cell secretion of mucin, thereby protecting the intestinal barrier, reducing intestinal BT, and lowering the mortality rate of AP [150–152]. Therefore, supplementing SCFAs substrates such as butyrate can be one of the treatment strategies for AP.

5. Conclusions

Current evidence has shown the etiology of SIBO, including small intestinal motility and dysfunction of the intestinal barrier. The increased incidence of SIBO in AP patients indicates that AP is one of the causes of SIBO. AP can promote the occurrence of SIBO by prolonging MMC duration and weakening the intestinal barrier function. On the other hand, SIBO can exacerbate AP mainly due to dysbiosis caused by BT, characterized by a decrease in beneficial bacteria and an increase in pathogenic bacteria. The relationship between AP, SIBO, and intestinal microbiota is illustrated in Fig. 1. Recent research has also considered interventions such as antibiotics, primarily with rifaximin, probiotics, FMT, enteral nutrition, octreotide, and SCFAs in clinical practice.

6. Perspectives

Currently, there are some limitations in the research between SIBO and AP. First of all, most studies on the microbiota of AP patients currently rely on fecal samples, which, despite their convenience, non-invasiveness, ample biomass, and low cost, may not fully reflect the actual members of the mucosal microbiota, thus failing to reveal changes in the gut microbiota accurately. Subsequently, although duodenal aspirate culture has long been considered the gold standard for diagnosing SIBO, its clinical application is limited due to its invasive nature and potential for contamination. Additionally, there is limited research describing the characteristics of the mucosal microbiota. Mucosal microbiota and luminal microbiota represent two functionally distinct ecosystems. The former may be more critical in terms of direct microbiota-mucosa interactions. At the same time, luminal bacteria are involved in digestion and interact with the host indirectly

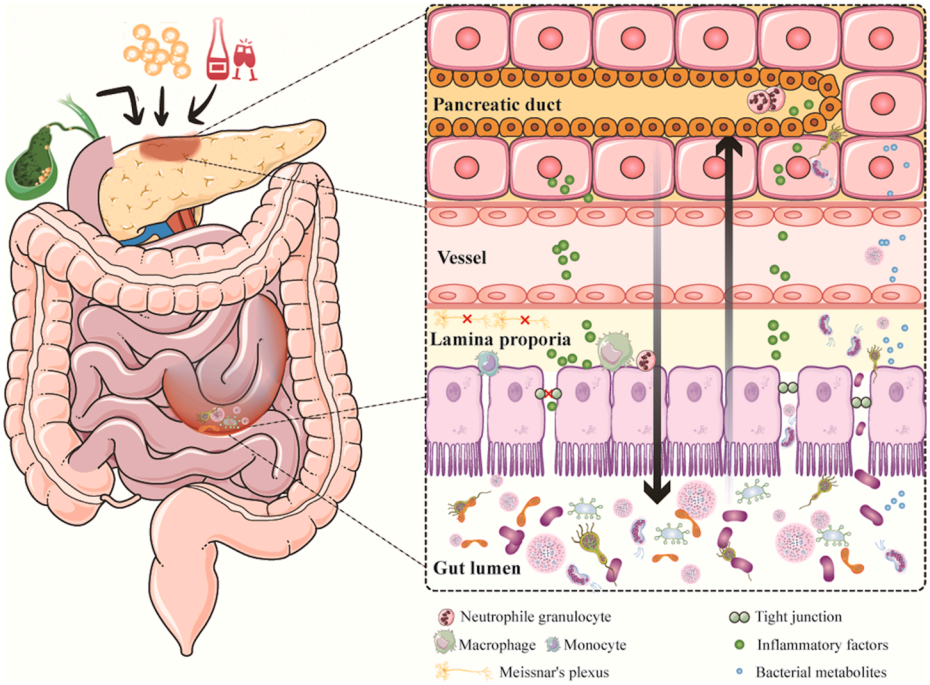

Fig. 1. A diagram of the relationship between AP, SIBO, and gut microbiota.

through the production of metabolites and toxins. Therefore, simultaneous analysis and comparison of the microbial characteristics of both could better enhance our overall understanding of the gut microbiota. After that, there is currently only research on the correlation between SIBO and the severity of AP, without further analysis of the specific impact of SIBO on the microbial characteristics of AP patients. Additional prospective studies are needed to examine the correlation between symptom spectrum and small intestinal aspirate and mucosal microbiota, combined with deep sequencing technology and consideration of functional and metabolic omics analyses, to characterize the microbial communities associated with the progression of AP and analyze the role of specific bacterial species in improving the diagnosis and management of AP. Finally, the development of techniques such as metagenomics, metabolomics, metatranscriptomics, and culturomics will bring breakthroughs in microbial research and microbiota-based therapies. In the future, we will further utilize animal studies and human trials better to validate the mechanisms of gut dysfunction in AP. While some results suggest that these therapies may represent promising new treatment options for AP and SIBO, conflicting evidence from studies also highlights the need for further large-scale research to understand the impact and risks better, enhancing the benefits of precise treatment for AP.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Xiaorui Cui: Investigation, Data curation, Methodology, Formal analysis, Writing—original draft. Huaizhu Guo: Conceptualization, Data curation, Formal analysis, Writing—original draft, Visualization. Zhen Liu, Yuanyuan Lei, and Yunxiong Wei: Data curation, Validation, Visualization, Writing—review & editing. Guangyong Sun and Dong Zhang: Conceptualization, Validation, Visualization, Writing—review & editing. Jianyu Hao: Resources; Supervision; Conceptualization, Writing—review & editing. Donglei Zhang: Conceptualization, Methodology, Visualization, Writing—review & editing, Supervision. Xinjuan Liu: Resources, Conceptualization, Methodology, Visualization, Writing—review & editing, Supervision.

Availability of data and materials

Not applicable.

Funding

This research was supported by the Beijing Key Clinical Specialty Project.

Conflict of interest

The authors declare that there is no conflict of interest.

Acknowledgments

The correspondence author discloses receipt of the following financial support for the research, authorship, and publication of this artical: Beijing Key Clinical Specialty Project.

References

[1] Quigley EMM, Murray JA, Pimentel M. AGA Clinical Practice Update on Small Intestinal Bacterial Overgrowth: Expert Review. Gastroenterology 2020;159(4):1526–32.
[2] Kerlin P, Wong L. Breath hydrogen testing in bacterial overgrowth of the small intestine. Gastroenterology 1988;95(4):982–8.

[3] Khoshini R, Dai SC, Lezcano S, Pimentel M. A systematic review of diagnostic tests for small intestinal bacterial overgrowth. Dig Dis Sci 2008;53(6):1443–54.
[4] Rezaie A, Buresi M, Lembo A, Lin H, McCallum R, Rao S, et al. Hydrogen and Methane-Based Breath Testing in Gastrointestinal Disorders: The North American Consensus. Am J Gastroenterol 2017;112(5):775–84.
[5] Pimentel M, Saad RJ, Long MD, Rao SSC. ACG Clinical Guideline: Small Intestinal Bacterial Overgrowth. Am J Gastroenterol 2020;115(2):165–78.
[6] Banaszak M, Gorna I, Wozniak D, Przyslawski J, Drzymala-Czyz S. Association between Gut Dysbiosis and the Occurrence of SIBO, LIBO, SIFO and IMO. Microorganisms 2023;11(3):573.
[7] Skrzydlo-Radomanska B, Cukrowska B. How to recognize and treat small intestinal bacterial overgrowth? J Clin Med 2022;11(20):6017.
[8] Shah A, Morrison M, Burger D, Martin N, Rich J, Jones M, et al. Systematic review with meta-analysis: the prevalence of small intestinal bacterial overgrowth in inflammatory bowel disease. Aliment Pharmacol Ther 2019;49(6):624–35.
[9] Bushyhead D, Quigley EMM. Small intestinal bacterial overgrowth-pathophysiology and its implications for definition and management. Gastroenterology 2022;163(3):593–607.
[10] Staubli SM, Oertli D, Nebiker CA. Laboratory markers predicting severity of acute pancreatitis. Crit Rev Clin Lab Sci 2015;52(6):273–83.
[11] Sternby H, Bolado F, Canaval-Zuleta HJ, Marra-Lopez C, Hernando-Alonso AI, Del-Val-Antonana A, et al. Determinants of Severity in Acute Pancreatitis: A Nation-wide Multicenter Prospective Cohort Study. Ann Surg 2019;270(2):348–55.
[12] Schepers NJ, Bakker OJ, Besselink MG, Ahmed Ali U, Bollen TL, Gooszen HG, et al. Impact of characteristics of organ failure and infected necrosis on mortality in necrotising pancreatitis. Gut 2019;68(6):1044–51.
[13] Fritz S, Hackert T, Hartwig W, Rossmanith F, Strobel O, Schneider L, et al. Bacterial translocation and infected pancreatic necrosis in acute necrotizing pancreatitis derives from small bowel rather than from colon. Am J Surg 2010;200(1):111–7.
[14] Li Q, Wang C, Tang C, He Q, Li N, Li J. Bacteremia in patients with acute pancreatitis as revealed by 16S ribosomal RNA gene-based techniques. Crit Care Med 2013;41(8):1938–50.
[15] Schmitt FCF, Brenner T, Uhle F, Loesch S, Hackert T, Ulrich A, et al. Gut microbiome patterns correlate with higher postoperative complication rates after pancreatic surgery. BMC Microbiol 2019;19(1):42.
[16] Zhou X, Wang W, Wang C, Zheng C, Xu X, Ni X, et al. DPP4 Inhibitor Attenuates Severe Acute Pancreatitis-Associated Intestinal Inflammation via Nrf2 Signaling. Oxid Med Cell Longev 2019;2019:6181754.
[17] Zhang M, Zhu HM, He F, Li BY, Li XC. Association between acute pancreatitis and small intestinal bacterial overgrowth assessed by hydrogen breath test. World J Gastroenterol 2017;23(48):8591–6.
[18] Kim DB, Paik CN, Lee JM, Kim YJ. Association between increased breath hydrogen methane concentration and prevalence of glucose intolerance in acute pancreatitis. J Breath Res 2020;14(2):026006.
[19] Massey BT, Wald A. Small Intestinal Bacterial Overgrowth Syndrome: A Guide for the Appropriate Use of Breath Testing. Dig Dis Sci 2021;66(2):338–47.
[20] Roland BC, Ciarleglio MM, Clarke JO, Semler JR, Tomakin E, Mullin GE, et al. Small Intestinal Transit Time Is Delayed in Small Intestinal Bacterial Overgrowth. J Clin Gastroenterol 2015;49(7):571–6.
[21] Chander Roland B, Mullin GE, Passi M, Zheng X, Salem A, Yolken R, et al. A Prospective Evaluation of Ileocecal Valve Dysfunction and Intestinal Motility Derangements in Small Intestinal Bacterial Overgrowth. Dig Dis Sci 2017;62(12):3525–35.
[22] Deloose E, Janssen P, Depoortere I, Tack J. The migrating motor complex: control mechanisms and its role in health and disease. Nat Rev Gastroenterol Hepatol 2012;9(5):271–85.
[23] Miele L, Valenza V, La Torre G, Montalto M, Cammarota G, Ricci R, et al. Increased intestinal permeability and tight junction alterations in nonalcoholic fatty liver disease. Hepatology 2009;49(6):1877–87.
[24] Feng X, Li XQ. The prevalence of small intestinal bacterial overgrowth in diabetes mellitus: a systematic review and meta-analysis. Aging (Albany NY) 2022;14(2):975–88.
[25] Malik A, Morya RK, Bhadada SK, Rana S. Type 1 diabetes mellitus: Complex interplay of oxidative stress, cytokines, gastrointestinal motility and small intestinal bacterial overgrowth. Eur J Clin Invest 2018;48(11):e13021.
[26] Pimentel M, Soffer EE, Chow EJ, Kong Y, Lin HC. Lower frequency of MMC is found in IBS subjects with abnormal lactulose breath test, suggesting bacterial overgrowth. Dig Dis Sci 2002;47(12):2639–43.
[27] Polkowska-Pruszynska B, Gerkowicz A, Szczepanik-Kulak P, Krasowska D. Small intestinal bacterial overgrowth in systemic sclerosis: a review of the literature. Arch Dermatol Res 2019;311(1):1–8.
[28] Tan AH, Mahadeva S, Thalha AM, Gibson PR, Kiew CK, Yeat CM, et al. Small intestinal bacterial overgrowth in Parkinson's disease. Parkinsonism Relat Disord 2014;20(5):535–40.
[29] Husebye E, Skar V, Hoverstad T, Iversen T, Melby K. Abnormal intestinal motor patterns explain enteric colonization with gram-negative bacilli in late radiation enteropathy. Gastroenterology 1995;109(4):1078–89.
[30] Maslennikov R, Pavlov C, Ivashkin V. Small intestinal bacterial overgrowth in cirrhosis: systematic review and meta-analysis. Hepatol Int 2018;12(6):567–76.
[31] Nieuwenhuijs VB, Verheem A, van Duijvenbode-Beumer H, Visser MR, Verhoef J, Gooszen HG, et al. The role of interdigestive small bowel motility in the regulation of gut microflora, bacterial overgrowth, and bacterial translocation in rats. Ann Surg 1998;228(2):188–93.
[32] Scott LD, Cahall DL. Influence of the interdigestive myoelectric complex on enteric flora in the rat. Gastroenterology 1982;82(4):737–45.
[33] Nieuwenhuijs VB, van Dijk JE, Gooszen HG, Akkermans LM. Obstructive jaundice, bacterial translocation and interdigestive small-bowel motility in rats. Digestion 2000;62(4):255–61.
[34] Zhou H, Liu L, Bai Y, Wu W, Li G, Li J, et al. Damage of the interstitial cells of Cajal and myenteric neurons causing ileus in acute necrotizing pancreatitis rats. Surgery 2011;149(2):262–75.
[35] Van Felius ID, Akkermans LM, Bosscha K, Verheem A, Harmsen W, Visser MR, et al. Interdigestive small bowel motility and duodenal bacterial overgrowth in experimental acute pancreatitis. Neurogastroenterol Motil 2003;15(3):267–76.
[36] Husebye E. Gastrointestinal motility disorders and bacterial overgrowth. J Intern Med 1995;237(4):419–27.
[37] Ponziani FR, Gerardi V, Gasbarrini A. Diagnosis and treatment of small intestinal bacterial overgrowth. Expert Rev Gastroenterol Hepatol 2016;10(2):215–27.
[38] Shu LZ, Ding YD, Xue QM, Cai W, Deng H. Direct and indirect effects of pathogenic bacteria on the integrity of intestinal barrier. Therap Adv Gastroenterol 2023;16:1–17.
[39] Zhang J, Yuan C, Hua G, Tong R, Luo X, Ying Z. Early gut barrier dysfunction in patients with severe acute pancreatitis: attenuated by continuous blood purification treatment. Int J Artif Organs 2010;33(10):706–15.
[40] Zhao MQ, Cui MY, Jiang QL, Wang JJ, Fan MY, Lu YY. Characterization of Duodenal Microbiota in Patients with Acute Pancreatitis and Healthy Controls. Dig Dis Sci 2023;68(8):3341–53.
[41] Marik PE, Zaloga GP. Meta-analysis of parenteral nutrition versus enteral nutrition in patients with acute pancreatitis. BMJ 2004;328(7453):1407.
[42] Lopetuso LR, Scaldaferri F, Bruno G, Petito V, Franceschi F, Gasbarrini A. The therapeutic management of gut barrier leaking: the emerging role for mucosal barrier protectors. Eur Rev Med Pharmacol Sci 2015;19(6):1068–76.
[43] Kecskés G, Belágyi T, Oláh A. [Early jejunal nutrition with combined pre- and probiotics in acute pancreatitis–prospective, randomized, double-blind investigations]. Magy Seb 2003;56(1):3–8.
[44] Fishman JE, Levy G, Alli V, Zheng X, Mole DJ, Deitch EA. The intestinal mucus layer is a critical component of the gut barrier that is damaged during acute pancreatitis. Shock 2014;42(3):264–70.
[45] Freedman SB, Ali S, Oleszczuk M, Gouin S, Hartling L. Treatment of acute gastroenteritis in children: an overview of systematic reviews of interventions commonly used in developed countries. Evid Based Child Health 2013;8(4):1123–37.
[46] Penalva JC, Martinez J, Laveda R, Esteban A, Munoz C, Saez J, et al. A study of intestinal permeability in relation to the inflammatory response and plasma endocab IgM levels in patients with acute pancreatitis. J Clin Gastroenterol 2004;38(6):512–7.
[47] Leite G, Morales W, Weitsman S, Celly S, Parodi G, Mathur R, et al. The duodenal microbiome is altered in small intestinal bacterial overgrowth. PLoS One 2020;15(7):e0234906.
[48] Shin NR, Whon TW, Bae JW. Proteobacteria: microbial signature of dysbiosis in gut microbiota. Trends Biotechnol 2015;33(9):496–503.
[49] Seekatz AM, Schnizlein MK, Koenigsknecht MJ, Baker JR, Hasler WL, Bleske BE, et al. Spatial and Temporal Analysis of the Stomach and Small-Intestinal Microbiota in Fasted Healthy Humans. mSphere 2019;4(2):10–1128.
[50] Quigley EMM. Exploring the Small Intestinal Microbiome: Relationships to Symptoms and Small Intestinal Bacterial Overgrowth. Clin Gastroenterol Hepatol 2024;22(2):241–2.
[51] Leite G, Rezaie A, Mathur R, Barlow GM, Rashid M, Hosseini A, et al. Defining Small Intestinal Bacterial Overgrowth by Culture and High Throughput Sequencing. Clin Gastroenterol Hepatol 2024;22(2):259–70.
[52] Guo H, Chen Y, Dong W, Lu S, Du Y, Duan L. Fecal Coprococcus, hidden behind abdominal symptoms in patients with small intestinal bacterial overgrowth. J Transl Med 2024;22(1):496.
[53] Bouhnik Y, Alain S, Attar A, Flourie B, Raskine L, Sanson-Le Pors MJ, et al. Bacterial populations contaminating the upper gut in patients with small intestinal bacterial overgrowth syndrome. Am J Gastroenterol 1999;94(5):1327–31.
[54] Triantafyllou K, Chang C, Pimentel M. Methanogens, methane and gastrointestinal motility. J Neurogastroenterol Motil 2014;20(1):31–40.
[55] Li J, Zhang R, Ma J, Tang S, Li Y, Li Y, et al. Mucosa-Associated Microbial Profile Is Altered in Small Intestinal Bacterial Overgrowth. Front Microbiol 2021;12:710940.
[56] Rizos E, Pyleris E, Pimentel M, Triantafyllou K, Giamarellos-Bourboulis EJ. Small Intestine Bacterial Overgrowth Can Form an Indigenous Proinflammatory Environment in the Duodenum: A Prospective Study. Microorganisms 2022;10(5):960.
[57] Tan C, Ling Z, Huang Y, Cao Y, Liu Q, Cai T, et al. Dysbiosis of Intestinal Microbiota Associated With Inflammation Involved in the Progression of Acute Pancreatitis. Pancreas 2015;44(6):868–75.

[58] Zhang XM, Zhang ZY, Zhang CH, Wu J, Wang YX, Zhang GX. Intestinal Microbial Community Differs between Acute Pancreatitis Patients and Healthy Volunteers. Biomed Environ Sci 2018;31(1):81–6.
[59] Zhu Y, He C, Li X, Cai Y, Hu J, Liao Y, et al. Gut microbiota dysbiosis worsens the severity of acute pancreatitis in patients and mice. J Gastroenterol 2019;54(4):347–58.
[60] Li XY, He C, Zhu Y, Lu NH. Role of gut microbiota on intestinal barrier function in acute pancreatitis. World J Gastroenterol 2020;26(18):2187–93.
[61] Chen J, Huang C, Wang J, Zhou H, Lu Y, Lou L, et al. Dysbiosis of intestinal microbiota and decrease in paneth cell antimicrobial peptide level during acute necrotizing pancreatitis in rats. PLoS One 2017;12(4):e0176583.
[62] Yu S, Xiong Y, Xu J, Liang X, Fu Y, Liu D, et al. Identification of Dysfunctional Gut Microbiota Through Rectal Swab in Patients with Different Severity of Acute Pancreatitis. Dig Dis Sci 2020;65(11):3223–37.
[63] Yu S, Xiong Y, Fu Y, Chen G, Zhu H, Mo X, et al. Shotgun metagenomics reveals significant gut microbiome features in different grades of acute pancreatitis. Microb Pathog 2021;154:104849.
[64] Zou M, Yang Z, Fan Y, Gong L, Han Z, Ji L, et al. Gut microbiota on admission as predictive biomarker for acute necrotizing pancreatitis. Front Immunol 2022;13:988326.
[65] Kellingray L, Gall GL, Defernez M, Beales ILP, Franslem-Elumogo N, Narbad A. Microbial taxonomic and metabolic alterations during faecal microbiota transplantation to treat Clostridium difficile infection. J Infect 2018;77(2):107–18.
[66] Liu J, Yue S, Yang Z, Feng W, Meng X, Wang A, et al. Oral hydroxysafflor yellow A reduces obesity in mice by modulating the gut microbiota and serum metabolism. Pharmacol Res 2018;134:40–50.
[67] Chen J, Kang B, Jiang Q, Han M, Zhao Y, Long L, et al. Alpha-Ketoglutarate in Low-Protein Diets for Growing Pigs: Effects on Cecal Microbial Communities and Parameters of Microbial Metabolism. Front Microbiol 2018;9:1057.
[68] Ma N, Wu Y, Xie F, Du K, Wang Y, Shi L, et al. Dimethyl fumarate reduces the risk of mycotoxins via improving intestinal barrier and microbiota. Oncotarget 2017;8(27):44625–38.
[69] Schmid RM, Adler G. Cytokines in acute pancreatitis–new pathophysiological concepts evolve. Eur J Gastroenterol Hepatol 1999;11(2):125–7.
[70] McKay CJ, Gallagher G, Brooks B, Imrie CW, Baxter JN. Increased monocyte cytokine production in association with systemic complications in acute pancreatitis. Br J Surg 1996;83(7):919–23.
[71] Wig JD, Kochhar R, Ray JD, Krishna Rao DV, Gupta NM, Ganguly NK. Endotoxemia predicts outcome in acute pancreatitis. J Clin Gastroenterol 1998;26(2):121–4.
[72] Buttenschoen K, Berger D, Hiki N, Buttenschoen DC, Vasilescu C, Chikh-Torab F, et al. Endotoxin and antiendotoxin antibodies in patients with acute pancreatitis. Eur J Surg 2000;166(6):459–66.
[73] Zheng J, Lou L, Fan J, Huang C, Mei Q, Wu J, et al. Commensal Escherichia coli Aggravates Acute Necrotizing Pancreatitis through Targeting of Intestinal Epithelial Cells. Appl Environ Microbiol 2019;85(12):e00059–19.
[74] Barbara G, Barbaro MR, Fuschi D, Palombo M, Falangone F, Cremon C, et al. Inflammatory and Microbiota-Related Regulation of the Intestinal Epithelial Barrier. Front Nutr 2021;8:718356.
[75] Wang Z, Li F, Liu J, Luo Y, Guo H, Yang Q, et al. Intestinal Microbiota - An Unmissable Bridge to Severe Acute Pancreatitis-Associated Acute Lung Injury. Front Immunol 2022;13:913178.
[76] Bernasconi E, Pattaroni C, Koutsokera A, Pison C, Kessler R, Benden C, et al. Airway Microbiota Determines Innate Cell Inflammatory or Tissue Remodeling Profiles in Lung Transplantation. Am J Respir Crit Care Med 2016;194(10):1252–63.
[77] Cheng P, Li S, Chen H. Macrophages in Lung Injury, Repair, and Fibrosis. Cells 2021;10(2):436.
[78] Chen X, Tang J, Shuai W, Meng J, Feng J, Han Z. Macrophage polarization and its role in the pathogenesis of acute lung injury/acute respiratory distress syndrome. Inflamm Res 2020;69(9):883–95.
[79] Dickson RP, Schultz MJ, van der Poll T, Schouten LR, Falkowski NR, Luth JE, et al. Lung Microbiota Predict Clinical Outcomes in Critically Ill Patients. Am J Respir Crit Care Med 2020;201(5):555–63.
[80] Christoffersen TE, Hult LT, Kuczkowska K, Moe KM, Skeie S, Lea T, et al. In vitro comparison of the effects of probiotic, commensal and pathogenic strains on macrophage polarization. Probiotics Antimicrob Proteins 2014;6(1):1–10.
[81] Li X, He C, Li N, Ding L, Chen H, Wan J, et al. The interplay between the gut microbiota and NLRP3 activation affects the severity of acute pancreatitis in mice. Gut Microbes 2020;11(6):1774–89.
[82] Beger HG, Bittner R, Block S, Buchler M. Bacterial contamination of pancreatic necrosis. A prospective clinical study. Gastroenterology 1986;91(2):433–8.
[83] Zhao M, Cui M, Jiang Q, Wang J, Lu Y. Profile of Pancreatic and Ileal Microbiota in Experimental Acute Pancreatitis. Microorganisms 2023;11(11):2707.
[84] Schwarz M, Thomsen J, Meyer H, Buchler MW, Beger HG. Frequency and time course of pancreatic and extrapancreatic bacterial infection in experimental acute pancreatitis in rats. Surgery 2000;127(4):427–32.
[85] Sulkowski U, Boin C, Brockmann J, Bunte H. The influence of caecostomy and colonic irrigation on pathophysiology and prognosis in acute experimental pancreatitis. Eur J Surg 1993;159(5):287–91.
[86] Zhou YM, Xue ZL, Li YM, Zhu YQ, Cao N. Antibiotic prophylaxia in patients with severe acute pancreatitis. Hepatobiliary Pancreat Dis Int 2005;4(1):23–7.
[87] Zhou H, Gao J, Zou D, Wu W, Li Z. Effect of octreotide on enteric motor neurons in experimental acute necrotizing pancreatitis. PLoS One 2012;7(12):e52163.
[88] Gianotti L, Solomkin JS, Munda R, Alexander JW. Failure of local and systemic bacterial clearance in rats with acute pancreatitis. Pancreas 1995;10(1):78–84.
[89] Sun JK, Mu XW, Li WQ, Tong ZH, Li J, Zheng SY. Effects of early enteral nutrition on immune function of severe acute pancreatitis patients. World J Gastroenterol 2013;19(6):917–22.
[90] Maccaferri S, Vitali B, Klinder A, Kolida S, Ndagijimana M, Laghi L, et al. 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(12):2556–65.
[91] Umezawa H, Mizuno S, Yamazaki H, Nitta K. Inhibition of DNA-dependent RNA synthesis by rifamycins. J Antibiot (Tokyo) 1968;21(3):234–6.
[92] 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(5):604–16.
[93] Shah SC, Day LW, Somsouk M, Sewell JL. Meta-analysis: antibiotic therapy for small intestinal bacterial overgrowth. Aliment Pharmacol Ther 2013;38(8):925–34.
[94] Fiorucci S, Distrutti E, Mencarelli A, Barbanti M, Palazzini E, Morelli A. Inhibition of intestinal bacterial translocation with rifaximin modulates lamina propria monocytic cells reactivity and protects against inflammation in a rodent model of colitis. Digestion 2002;66(4):246–56.
[95] Tatur J, Lipinski M, Sznurkowska M, Jozefik E, Rydzewska G. Rifaximin in gut microbiota modification in acute pancreatitis: 15 years of retrospective clinical study. Adv Clin Exp Med 2022;31(4):399–405.
[96] Marotta F, Geng TC, Wu CC, Barbi G. Bacterial translocation in the course of acute pancreatitis: beneficial role of nonabsorbable antibiotics and lactitol enemas. Digestion 1996;57(6):446–52.
[97] Singh RR, Mitchell W, David Y, Cheesman A, Dixon RE, Nagula S, et al. Pancreatic Fungal Infection in Patients With Necrotizing Pancreatitis: A Systematic Review and Meta-analysis. J Clin Gastroenterol 2021;55(3):218–26.
[98] Xue P, Deng LH, Zhang ZD, Yang XN, Wan MH, Song B, et al. Effect of antibiotic prophylaxis on acute necrotizing pancreatitis: results of a randomized controlled trial. J Gastroenterol Hepatol 2009;24(5):736–42.
[99] Wan YD, Zhu RX, Bian ZZ, Sun TW. Effect of probiotics on length of hospitalization in mild acute pancreatitis: A randomized, double-blind, placebo-controlled trial. World J Gastroenterol 2021;27(2):224–32.
[100] Pan LL, Li J, Shamoon M, Bhatia M, Sun J. Recent Advances on Nutrition in Treatment of Acute Pancreatitis. Front Immunol 2017;8:762.
[101] Qin HL, Zheng JJ, Tong DN, Chen WX, Fan XB, Hang XM, et al. Effect of Lactobacillus plantarum enteral feeding on the gut permeability and septic complications in the patients with acute pancreatitis. Eur J Clin Nutr 2008;62(7):923–30.
[102] Wang G, Wen J, Xu L, Zhou S, Gong M, Wen P, et al. Effect of enteral nutrition and ecoimmunonutrition on bacterial translocation and cytokine production in patients with severe acute pancreatitis. J Surg Res 2013;183(2):592–7.
[103] Muftuoglu MA, Isikgor S, Tosun S, Saglam A. Effects of probiotics on the severity of experimental acute pancreatitis. Eur J Clin Nutr 2006;60(4):464–8.
[104] Rychter JW, van Minnen LP, Verheem A, Timmerman HM, Rijkers GT, Schipper ME, et al. Pretreatment but not treatment with probiotics abolishes mouse intestinal barrier dysfunction in acute pancreatitis. Surgery 2009;145(2):157–67.
[105] Hooijmans CR, de Vries RB, Rovers MM, Gooszen HG, Ritskes-Hoitinga M. The effects of probiotic supplementation on experimental acute pancreatitis: a systematic review and meta-analysis. PLoS One 2012;7(11):e48811.
[106] van Minnen LP, Timmerman HM, Lutgendorff F, Verheem A, Harmsen W, Konstantinov SR, et al. Modification of intestinal flora with multispecies probiotics reduces bacterial translocation and improves clinical course in a rat model of acute pancreatitis. Surgery 2007;141(4):470–80.
[107] Park HJ, Lee GH, Jun J, Son M, Kang MJ. Multiple-unit tablet of probiotic bacteria for improved storage stability, acid tolerability, and in vivo intestinal protective effect. Drug Des Devel Ther 2016;10:1355–64.
[108] Sanchez E, Nieto JC, Boullosa A, Vidal S, Sancho FJ, Rossi G, et al. VSL#3 probiotic treatment decreases bacterial translocation in rats with carbon tetrachloride-induced cirrhosis. Liver Int 2015;35(3):735–45.
[109] Qin RY, Zou SQ, Wu ZD, Qiu FZ. Influence of splanchnic vascular infusion on the content of endotoxins in plasma and the translocation of intestinal bacteria in rats with acute hemorrhage necrosis pancreatitis. World J Gastroenterol 2000;6(4):577–80.
[110] Asemi Z, Zare Z, Shakeri H, Sabihi SS, Esmaillzadeh A. Effect of multispecies probiotic supplements on metabolic profiles, hs-CRP, and oxidative stress in patients with type 2 diabetes. Ann Nutr Metab 2013;63(1-2):1–9.
[111] Camilleri M. Human Intestinal Barrier: Effects of Stressors, Diet, Prebiotics, and Probiotics. Clin Transl Gastroenterol 2021;12(1):e00308.
[112] Lutgendorff F, Nijmeijer RM, Sandstrom PA, Trulsson LM, Magnusson KE, Timmerman HM, et al. Probiotics prevent intestinal barrier dysfunction in

acute pancreatitis in rats via induction of ileal mucosal glutathione biosynthesis. PLoS One 2009;4(2):e4512.
[113] Liu Y, Wang J, Wu C. Modulation of Gut Microbiota and Immune System by Probiotics, Pre-biotics, and Post-biotics. Front Nutr 2021;8:634897.
[114] Werawatganon D, Vivatvakin S, Somanawat K, Tumwasorn S, Klaikeaw N, Siriviriyakul P, et al. Effects of probiotics on pancreatic inflammation and intestinal integrity in mice with acute pancreatitis. BMC Complement Med Ther 2023;23(1):166.
[115] 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(4):300–11.
[116] Liebana-Castillo AR, Redondo-Cuevas L, Nicolas A, Martin-Carbonell V, Sanchis L, Olivares A, et al. Should We Treat SIBO Patients? Impact on Quality of Life and Response to Comprehensive Treatment: A Real-World Clinical Practice Study. Nutrients 2025;17(7):1251.
[117] Redondo-Cuevas L, Belloch L, Martin-Carbonell V, Nicolas A, Alexandra I, Sanchis L, et al. Do herbal supplements and probiotics complement antibiotics and diet in the management of SIBO? A randomized clinical trial. Nutrients 2024;16(7):1083.
[118] Kazmierczak-Siedlecka K, Ruszkowski J, Fic M, Folwarski M, Makarewicz W. Saccharomyces boulardii CNCM I-745: A Non-bacterial Microorganism Used as Probiotic Agent in Supporting Treatment of Selected Diseases. Curr Microbiol 2020;77(9):1987–96.
[119] Martyniak A, Wojcicka M, Rogatko I, Piskorz T, Tomasik PJ. A comprehensive review of the usefulness of prebiotics, probiotics, and postbiotics in the diagnosis and treatment of small intestine bacterial overgrowth. Microorganisms 2025;13(1):57.
[120] Gao Z, Yin S, Jin K, Nie W, Wang L, Cheng L. Effectiveness and safety of probiotics on patients with severe acute pancreatitis: A systematic review and meta-analysis. Medicine (Baltimore) 2023;102(50):e36454.
[121] Sharma B, Srivastava S, Singh N, Sachdev V, Kapur S, Saraya A. Role of probiotics on gut permeability and endotoxemia in patients with acute pancreatitis: a double-blind randomized controlled trial. J Clin Gastroenterol 2011;45(5):442–8.
[122] Besselink MG, van Santvoort HC, Buskens E, Boermeester MA, van Goor H, Timmerman HM, et al. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. Lancet 2008;371(9613):651–9.
[123] Patel BK, Patel KH, Bhatia M, Iyer SG, Madhavan K, Moochhala SM. Gut microbiome in acute pancreatitis: A review based on current literature. World J Gastroenterol 2021;27(30):5019–36.
[124] Quigley EM, Quera R. Small intestinal bacterial overgrowth: roles of antibiotics, prebiotics, and probiotics. Gastroenterology 2006;130(2 Suppl 1):S78–90.
[125] Lu WW, Chen X, Ni JL, Zhu SL, Fei AH, Wang XS. The role of gut microbiota in the pathogenesis and treatment of acute pancreatitis: a narrative review. Ann Palliat Med 2021;10(3):3445–51.
[126] Zhu Y, Mei Q, Fu Y, Zeng Y. Alteration of gut microbiota in acute pancreatitis and associated therapeutic strategies. Biomed Pharmacother 2021;141:111850.
[127] Sornsenee P, Singkhamanan K, Sangkhathat S, Saengsuwan P, Romyasamit C. Probiotic Properties of Lactobacillus Species Isolated from Fermented Palm Sap in Thailand. Probiotics Antimicrob Proteins 2021;13(4):957–69.
[128] Kaku N, Matsumoto N, Sasaki D, Tsuda K, Kosai K, Uno N, et al. Effect of probiotics on gut microbiome in patients with administration of surgical antibiotic prophylaxis: A randomized controlled study. J Infect Chemother 2020;26(8):795–801.
[129] Li M, Liang P, Li Z, Wang Y, Zhang G, Gao H, et al. Fecal microbiota transplantation and bacterial consortium transplantation have comparable effects on the re-establishment of mucosal barrier function in mice with intestinal dysbiosis. Front Microbiol 2015;6:692.
[130] van den Berg FF, van Dalen D, Hyoju SK, van Santvoort HC, Besselink MG, Wiersinga WJ, et al. Western-type diet influences mortality from necrotising pancreatitis and demonstrates a central role for butyrate. Gut 2021;70(5):915–27.
[131] Xu F, Li N, Wang C, Xing H, Chen D, Wei Y. Clinical efficacy of fecal microbiota transplantation for patients with small intestinal bacterial overgrowth: a randomized, placebo-controlled clinic study. BMC Gastroenterol 2021;21(1):54.
[132] Prochazkova P, Roubalova R, Dvorak J, Tlaskalova-Hogenova H, Cermakova M, Tomasova P, et al. Microbiota, microbial metabolites, and barrier function in a patient with anorexia nervosa after fecal microbiota transplantation. Microorganisms 2019;7(9):338.
[133] Ding L, He C, Li X, Huang X, Lei Y, Ke H, et al. Efficacy and Safety of Faecal Microbiota Transplantation for Acute Pancreatitis: A Randomised, Controlled Study. Front Med (Lausanne) 2021;8:772454.
[134] Leppaniemi A, Tolonen M, Tarasconi A, Segovia-Lohse H, Gamberini E, Kirkpatrick AW, et al. WSES guidelines for the management of severe acute pancreatitis. World J Emerg Surg 2019;14:27.
[135] Moore FA, Feliciano DV, Andrassy RJ, McArdle AH, Booth FV, Morgenstein-Wagner TB, et al. Early enteral feeding, compared with parenteral, reduces postoperative septic complications. The results of a meta-analysis. Ann Surg 1992;216(2):172–83.
[136] Everitt NJ. Enteral nutrition is superior to parenteral nutrition in severe acute pancreatitis: results of a randomized prospective trial. Br J Surg 1998;85(5):716.
[137] Windsor AC, Kanwar S, Li AG, Barnes E, Guthrie JA, Spark JI, et al. Compared with parenteral nutrition, enteral feeding attenuates the acute phase response and improves disease severity in acute pancreatitis. Gut 1998;42(3):431–5.
[138] Zhang J, Yu WQ, Wei T, Zhang C, Wen L, Chen Q, et al. Effects of Short-Peptide-Based Enteral Nutrition on the Intestinal Microcirculation and Mucosal Barrier in Mice with Severe Acute Pancreatitis. Mol Nutr Food Res 2020;64(5):e1901191.
[139] Azuma H, Mishima S, Oda J, Homma H, Sasaki H, Hisamura M, et al. Enteral supplementation enriched with glutamine, fiber, and oligosaccharide prevents gut translocation in a bacterial overgrowth model. J Trauma 2009;66(1):110–4.
[140] Fiedler F, Jauernig G, Keim V, Richter A, Bender HJ. Octreotide treatment in patients with necrotizing pancreatitis and pulmonary failure. Intensive Care Medicine 1996;22(9):909–15.
[141] Soudah HC, Hasler WL, Owyang C. Effect of octreotide on intestinal motility and bacterial overgrowth in scleroderma. N Engl J Med 1991;325(21):1461–7.
[142] Kelly CJ, Zheng L, Campbell EL, Saeedi B, Scholz CC, Bayless AJ, et al. Crosstalk between Microbiota-Derived Short-Chain Fatty Acids and Intestinal Epithelial HIF Augments Tissue Barrier Function. Cell Host Microbe 2015;17(5):662–71.
[143] Wong JM, de Souza R, Kendall CW, Emam A, Jenkins DJ. Colonic health: fermentation and short chain fatty acids. J Clin Gastroenterol 2006;40(3):235–43.
[144] Tedelind S, Westberg F, Kjerrulf M, Vidal A. Anti-inflammatory properties of the short-chain fatty acids acetate and propionate: a study with relevance to inflammatory bowel disease. World J Gastroenterol 2007;13(20):2826–32.
[145] Liu Q, Yu Z, Tian F, Zhao J, Zhang H, Zhai Q, et al. Surface components and metabolites of probiotics for regulation of intestinal epithelial barrier. Microb Cell Fact 2020;19(1):23.
[146] Brown K, DeCoffe D, Molcan E, Gibson DL. Diet-induced dysbiosis of the intestinal microbiota and the effects on immunity and disease. Nutrients 2012;4(8):1095–119.
[147] Yan X, Li J, Wu D. The Role of Short-Chain Fatty Acids in Acute Pancreatitis. Molecules 2023;28(13):4985.
[148] Zhang T, Xia M, Zhan Q, Zhou Q, Lu G, An F. Sodium Butyrate Reduces Organ Injuries in Mice with Severe Acute Pancreatitis Through Inhibiting HMGB1 Expression. Dig Dis Sci 2015;60(7):1991–9.
[149] Zhao HB, Jia L, Yan QQ, Deng Q, Wei B. Effect of Clostridium butyricum and Butyrate on Intestinal Barrier Functions: Study of a Rat Model of Severe Acute Pancreatitis With Intra-Abdominal Hypertension. Front Physiol 2020;11:561061.
[150] Xiong Y, Ji L, Zhao Y, Liu A, Wu D, Qian J. Sodium Butyrate Attenuates Taurocholate-Induced Acute Pancreatitis by Maintaining Colonic Barrier and Regulating Gut Microorganisms in Mice. Front Physiol 2022;13:813735.
[151] Gao Y, Davis B, Zhu W, Zheng N, Meng D, Walker WA. Short-chain fatty acid butyrate, a breast milk metabolite, enhances immature intestinal barrier function genes in response to inflammation in vitro and in vivo. Am J Physiol Gastrointest Liver Physiol 2021;320(4):G521–30.
[152] Xia H, Guo J, Shen J, Jiang S, Han S, Li L. Butyrate ameliorated the intestinal barrier dysfunction and attenuated acute pancreatitis in mice fed with ketogenic diet. Life Sci 2023;334:122188.