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REVIEW

Gut microbiome in acute pancreatitis: A review based on current literature

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Abstract

The gut microbiome is a complex microbial community, recognized for its potential role in physiology, health, and disease. The available evidence supports the role of gut dysbiosis in pancreatic disorders, including acute pancreatitis (AP). In AP, the presence of gut barrier damage resulting in increased mucosal permeability may lead to translocation of intestinal bacteria, necrosis of pancreatic and peripancreatic tissue, and infection, often accompanied by multiple organ dysfunction syndrome. Preserving gut microbial homeostasis may reduce the systemic effects of AP. A growing body of evidence suggests the possible involvement of the gut microbiome in various pancreatic diseases, including AP. This review discusses the possible role of the gut microbiome in AP. It highlights AP treatment and supplementation with prebiotics, synbiotics, and probiotics to maintain gastrointestinal microbial balance and effectively reduce hospitalization, morbidity and mortality in an early phase. It also addresses novel therapeutic areas in the gut microbiome, personalized treatment, and provides a roadmap of

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human microbial contributions to AP that have potential clinical benefit.

Key Words: Acute pancreatitis; Gut microbiota; Biomarkers; Diagnostics; Dysbiosis

Core Tip: We live in a world of microbes. There is a distinct microbiome sighted in every niche of our body. This review is based on current knowledge to define an overview of how the gut microbiota has accelerated the frontiers of understanding recently and empowered its importance in influencing human physiology through its potential role in various diseases. It further explores the possible application of microbiota-targeted therapeutics in routine clinical practice, meaning manipulating gut microbiota into the current therapeutics to minimize the potential risk of various diseases, including acute pancreatitis.

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INTRODUCTION

Recent research has confirmed the importance of the human gut microbiota in maintaining health and its involvement in disease. The human gastrointestinal (GI) tract harbors a diverse microbial population of more than 10^{14} microorganisms, comprising more bacterial cells than human body cells[1] and more than 3.3 million unique genes[2]. The predominant commensal bacteria in the human GI tract are members of the phyla *Firmicutes* and *Bacteroidetes*, constituting 80%–90% of the total gut microbiota[3]. Other phyla include *Proteobacteria, Actinomyces, Actinobacteria, Fusobacteria,* and *Verrucomicrobia*[4]. The composition of the gut microbiome plays a key role in modulating human immune responses to invasive pathogens, and it also prevents the pathogens from crossing the intestinal barrier[5].

Recent improvement of advanced sequencing methods, such as next-generation sequencing and metagenomics, have added to our understanding of the involvement of gut microbiome in human health and disease[6] and the potential therapeutic value of interventions that target the composition of the gut microbiome. Such interventions would manipulate the host-microbiome community by eliminating harmful taxa or reconstituting missing beneficial taxa[6,7]. Recent evidence shows that, under ideal conditions, symbiotic relationships among the microbial species in the host GI tract can function to prevent opportunistic and nosocomial infections that have become more frequent because of the widespread use of antibiotics to treat various diseases[8-11].

Research performed over the past two decades has revealed the significance of gut dysbiosis in the pathogenesis of many diseases[12], including inflammatory bowel disease[13], irritable bowel syndrome[14], colon cancer[15], Alzheimer's disease[16], coronary heart disease[17], obesity[18], and diabetes mellitus[19]. Changes in the diversity, proportions, and dominant species of the gut microbiome are probably associated with intestinal barrier dysfunction that influences onset and clinical course of multiple diseases, including pancreatic disorders[20]. In a healthy individual, no gut microbes are present in the pancreas, but changes of the gut microbiota may be involved in the pathogenesis of pancreatic disease, including acute pancreatitis (AP)[21]. AP is a common disorder of the digestive system with high morbidity and mortality worldwide. Managing AP is challenging and has a heavy financial burden on the patient and society[22,23]. Therefore, it is important to understand the primary causes and mechanism of the pathogenesis and progression of AP to facilitate early diagnosis and treatment, avoid a course leading to severe disease, and reduce AP-associated fatality[23]. Ongoing studies of AP in humans have found that premature activation of trypsinogen, dysfunctional calcium signaling, impaired endoplasmic reticulum stress-related autophagy, unfolded protein response, and mitochondrial

dysfunction all promote AP. However, the cause of multiorgan dysfunction in AP is poorly understood[24]. The potential role of the intestine in promoting systemic inflammation and organ dysfunction is of interest.

In AP, hypovolemia, reflex splanchnic vasoconstriction, intestinal ischemia, and reperfusion injury due to fluid resuscitation may result in bacterial translocation [25, 26]. Systemic inflammatory response syndrome accompanied by intestinal bacterial translocation is associated with high AP mortality[26]. A change in gut permeability/motility that causes bacterial translocation and leads to the activation of gut-associated lymphoid tissues may result in systemic complications in AP[27]. This review summarizes relevant human and animal studies that provide insights into the potential role of the gut microbiome in AP pathogenesis. It also summarizes treatment perspectives that target the gut microbiome.

PATHOPHYSIOLOGY OF AP

Previous studies of microbiome involvement in AP described a complex cascade of events with significant involvement of pancreatic acinar cells, but the mechanisms involved in the initiation of AP are still poorly understood[28]. Development of a well-defined clinical management protocol is challenging. Most investigations of AP pathophysiology have documented injury or disruption of the pancreatic acini that triggered the activation of pancreatic enzymes (trypsin, chymotrypsin, and elastase) in pancreatic tissue. Activated proteases (trypsin and elastase) and lipase breakdown tissue and cell membranes, leading to edema, vascular damage, hemorrhage, and necrosis[28].

During the initial phase of pancreatic injury, acinar cells release proinflammatory cytokines, like tumor necrosis factor (commonly referred to as TNF)-α, interleukin (IL)-1 and IL-6, and anti-inflammatory mediators, such as IL-10 and IL-1 receptor antagonist[29]. These mediators recruit neutrophils and macrophages to enter the pancreatic parenchyma, to propagate both local and systemic responses. Reactive oxygen metabolites, prostaglandins, platelet-activating factor, and leukotriene may also be involved[29].

Recent epidemiological studies have shown that a local inflammatory response aggravates pancreatitis by increasing permeability, which damages the microcirculation and results in local hemorrhage and pancreatic necrosis in cases of severe AP. Some of the inflammatory mediators released by neutrophils aggravate pancreatic injury by activating pancreatic enzymes (see Figure 1)[26,30]. Figure 1 is a schematic description of AP pathogenesis. The acinar cells of the pancreas cause trypsin activation followed by impairment of cell membrane trafficking and activation of the zymogen cascade mediated by trypsin. Attraction and activation of leukocytes occur with the release of pro- and anti-inflammatory cytokines and chemokines. Overt, sustained activation of proinflammatory mediators leads to systemic inflammatory response syndrome (SIRS) and may progress to multiorgan failure, infection, pancreatic necrosis, and sepsis as late complications of AP.

CLASSIFICATION OF AP

Approximately 15%–25% of patients diagnosed with AP may progress to severe AP. The 2012 revised Atlanta classification and definitions by international consensus include three degrees of AP severity (*i.e.* mild, moderately severe, and severe)[31]. The three degrees primarily manifest as transient organ failure, persistent organ dysfunction, and local or systemic AP[31]. The determinant-based classification of AP is highly dependent on clinical data, and also on the available feedback from patients (to a lesser extent)[32]. Table 1 summarizes both the Atlanta and determinant-based classifications.

VARIOUS SCORING SYSTEMS USED IN THE DIAGNOSIS OF AP

The initial diagnosis of AP made on arrival at a clinic or hospital relies on known medical history, comprehensive physical examination, and increased serum amylase or lipase, with or without additional imaging evaluation. Currently, there are no specific laboratory tests with consistent accuracy and reliability for predicting AP

Table 1 Revised Atlanta classification and determinant-based classification of acute pancreatitis

Revised Atlanta classification of disease severity	
Mild AP	No organ failure
	No local or systemic complications
Moderately severe AP	Organ failure that resolved within 48 h (transient organ failure) and /or
	Local or systemic complications without persistent organ failure
Severe AP	Persistent organ failure > 48 h
	Single organ failure
	Multiple organ failure
A modified Marshal score defines a persistent organ failure	
Determinant-based classification of disease severity	
RACAP	**DBCAPS**
Mild AP	Mild AP
Absence of organ failure	Absence of organ failure
Absence of local complications	Absence of (peri-) pancreatic necrosis
Moderately severe AP	Moderate AP
Local complications and/or	Sterile (peri-) pancreatic necrosis and/or
Transient organ failure	Transient organ failure
Severe AP	Severe AP
Persistent organ failure	Persistent organ failure or
	Infected (peri-) pancreatic necrosis
	Critical AP persistent organ failure
	Infected (peri-) pancreatic necrosis

AP: Acute pancreatitis; DBCAPS: Determinant-based classification of acute pancreatitis severity; RACA: Revised Atlanta classification. Persistent organ failure is defined by a modified Marshal score or a sepsis-related organ failure assessment score.

severity. However, several scoring systems are available and are routinely used by hospital physicians to predict AP severity and prognosis (Table 2)[33-41].

BIOMARKERS AND PREDICTORS TO CONFIRM THE SEVERITY OF AP

In addition to the various clinical scoring systems, several biomarkers have also been applied as predictors of AP severity and are shown in Table 3[42-47].

microRNAs as biomarkers in AP diagnosis

Recently, circular microRNAs have been studied as potential diagnostic biomarkers in AP because of their specific properties, such as stability in biological fluids, simple identification, and sequence conservation among different species (Table 4)[48-60].

GUT MICROBIOME AND MICROBIOME IN AP

The human GI tract is home to a diverse and complex microbial community of bacteria, viruses, and fungi that help to maintain health and are involved in the pathogenesis of various diseases. The gut contains at least 1000 bacterial species and 100-fold more genes than have been identified in the human genome[4,61]. The microbiome is considered a hidden "metabolic organ", and it has a significant impact on well-being because of its influence on our metabolism, physiology, nutrition, and immune function[62]. It has been shown that the gut microbiome co-evolves with us;

Table 2 Prediction scoring systems used in acute pancreatitis diagnosis

No.	Multifactorial scoring system	Timeline	Threshold	Area under the curve	Ref.
1	Ranson score	48 h	≥ 3	0.81–0.88	[33-35]
2	Glasgow score	48 h	2	0.73–0.784	[36,37]
3	Acute Physiology and Chronic Health Evaluation-II score (APACHE-II)	24 h	7	0.80–0.895	[33,38,39]
4	Acute Physiology and Chronic Health Evaluation II score-Obesity (APACHE:-O)	24 h	7	0.893	[40]
5	Bedside Index of Severity score (BISAP)	24 h	≥ 3	0.79–0.875	[33-35,41]
6	Pancreatitis Activity Scoring System (PASS)	24 h	> 160	0.71	[36]
7	Systemic inflammatory response syndrome (SIRS)	24 h	≥ 2	0.73	[34,39]

Table 3 Blood biomarkers predicting disease severity in acute pancreatitis

No.	Blood biomarkers	Timeline	Threshold	Area under the curve	Ref.
1	Interleukin 8	Preoperative	196 pg/mL	0.778	[42]
2	Interleukin 6	24 h	50 pg/mL	0.9	[39]
3	Hepcidin	24 h	234.4 ng/mL	0.82	[43]
4	Red blood cell distribution width	24 h	13.35%	0.787	[44]
5	Procalcitonin	24 h	1.77 ng/mL	0.797	[45]
6	Blood urea nitrogen	24 h	5.945 mg/dL	0.677	[44]
7	Oleic acid chlorohydrin	24 h	32.40 nM	1	[46]
8	C-reactive protein	24 h	150 mg/L	0.61	[47]
9	C-reactive protein	48 h	150 mg/L	0.73–0.91	[33,39,47]

hence, any changes to the microbial community can have significant consequences, both beneficial and harmful[63]. Disruption of the gut microbiota, or dysbiosis, has been associated with diverse systematic conditions, such as obesity[64,65], malnutrition[66], diabetes[67], and chronic inflammatory diseases, such as inflammatory bowel disease, ulcerative colitis, and Crohn's disease[68].

Researchers have continued to study the microbiome at an accelerated pace over the past two decades, revealing the myriad ways these microorganisms affect our day-to-day lives. The microbiome in our gut is now understood to be a significant contributor to the development of chronic disease. Gut microbiota is now known to play a critical role in human health and disease. With the advances in microbiome research over time, more and more data has become available showing the gut microbes' overall composition and functional potential. Additionally, the number of diseases associated with changes in our gut microbial community has increased simultaneously[4,6]. The human gastrointestinal tract is a habitat crowded with microorganisms contributing to the host's immunity and pathogenesis of several diseases, including acute pancreatitis [69]. Human gastrointestinal microflora is divided into three different types by the way they present themselves in the body and perform multiple functions: *e.g.*, There are three major categories of bacteria: Physiological bacteria, that hold over 90% and are nourishing and immune-modulating; opportunistic bacteria, which are pathogenic in situations of lower immune resistance or antibiotic abuse; and pathogenic bacteria, which have lower numbers and invade difficultly[70]. Progression in AP has been more complicated by gastrointestinal motility dysfunction, which is probably related to the neuroendocrine system, hypoxia-ischemia, ischemia-reperfusion injury (IRI), inflammatory mediators, and cajal cells[71].

Since many discoveries have postulated that commensal intestinal microbiomes play a crucial role in humans' health, immune system, and homeostasis recently, there has been a surge of interest in this area of study. The overall function of the intestine in the entire mechanism of AP pathogenesis (such as in acute and critical illnesses) is essential to understand, but often it is overlooked. This pathogenesis mechanism involves several factors contributing to the loss of gut barrier function, allowing bacteria and endotoxins to translocate into the bloodstream, which is critical for

Table 4 MicroRNAs used as biomarkers in the diagnosis of acute pancreatitis

No.	miRNAs	Patients	Sample	Expression change	Reference gene	Ref.
1	miR-216a	AP	Plasma	Up	None	[49]
2	miR-551b-5p	AP	Plasma	Up	miR-16	[50]
3	miR-216a-5p, miR-375, and miR-551b-5p	AP	Serum	Up	miR-103a-3p	[51]
4	miR-7, miR-9, miR-122, and miR-141	AP	Serum	Up	Exogenous reference genes	[52]
5	miR-216a	AP	Plasma	Up	U6	[53]
6	miR-551-5p	AP	PBMC-	Up	U6	[54]
7	miR-155	AP	Serum	Up	U6	[55]
8	miR-29a	AP	Plasma	Up	U6	[56]
9	miR-24-3p, miR-222-3p, miR-361-5p, and miR-1246	HTG-AP	Serum	Up	U6	[57]
10	miR-1260b, miR-762, miR-22-3p, miR-23b, and miR-23a	AP-associated ALI	Serum	Up	U6	[58]
11	miR-92b, miR-10a, and miR-7	AP	Plasma	Down	miR-16	[50]
12	miR-155	AP	Serum	Down	Not mentioned	[59]
13	miR-181a-5p	HTG-AP	Serum	Down	U6	[57]
14	miR-550a, miR-324-5p, miR-484, miR-331-3p, miR-140-3p, miR-342-3p, and miR-150	AP-associated ALI	Serum	Down	U6	[58]
15	miR-127	AP-associated ALI	Plasma	Down	miR-16	[60]

ALI: Acute lung injury; AP: Acute pancreatitis; HTG-AP: Hypertriglyceridemic-acute pancreatitis; mi: Micro.

generating the second inflammatory hit of AP[72]. The data of Johnson *et al*[73] suggests gut bacteria translocation (*via* hematogenous, lymphatic, and reflux) is involved in AP infection progression, which indicates the presence of a possible correlation between gut microbiota and AP infection progression. An abnormality of the gastrointestinal microbiota (dysbiosis) is associated with the systematic inflammatory response syndrome (SIRS) and a broad range of diseases[74].

When the mucosal barrier of the intestine is damaged, intestinal bacteria may migrate into the blood or to other tissues and organs, further accelerating AP[75]. In recent years, several studies have been conducted investigating changes in intestinal flora associated with AP severity. AP progression involves the abnormal release of trypsin and destruction of pancreatic tissue due to abnormal cells. Several recent studies examined the changes in intestinal flora during AP development concerning disease severity. It is observed that abnormal trypsin secretion has occurred due to AP progression and that pancreatic structure destruction leads to an abnormal pancreatic secretion, resulting in the intestinal flora and homeostasis changes[76,77].

Numerous studies have now demonstrated the function of normal gut microbes to promote healthy gut mucosa. Gut mucosal ischemia and reperfusion during AP progression can compromise the integrity of the gut barrier, causing bacterial reabsorption from the gut to other parts of the body and causing local and systemic infections[78]. Some further research findings have also revealed that intestinal mucosal barrier injury is a significant complication in many AP patients. The intestinal mucosal barrier can be destroyed by affecting intestinal inflammation and the immune response[75]. Many studies are supporting now to demonstrate that normal gut microbes play a primary role in maintaining gut mucosal integrity. However, gut mucosal ischemia and reperfusion during AP progression can damage the overall integrity of the gut barrier and lead to gut bacterial translocation to other locations, causing local and systemic infections[78]. Thus, a significant complication of an AP patient's condition involves intestinal mucosal barrier damage. This is caused by intestinal inflammation and immune response defects. Other research has also found injuries of the intestinal mucosal barrier to patients with AP[75].

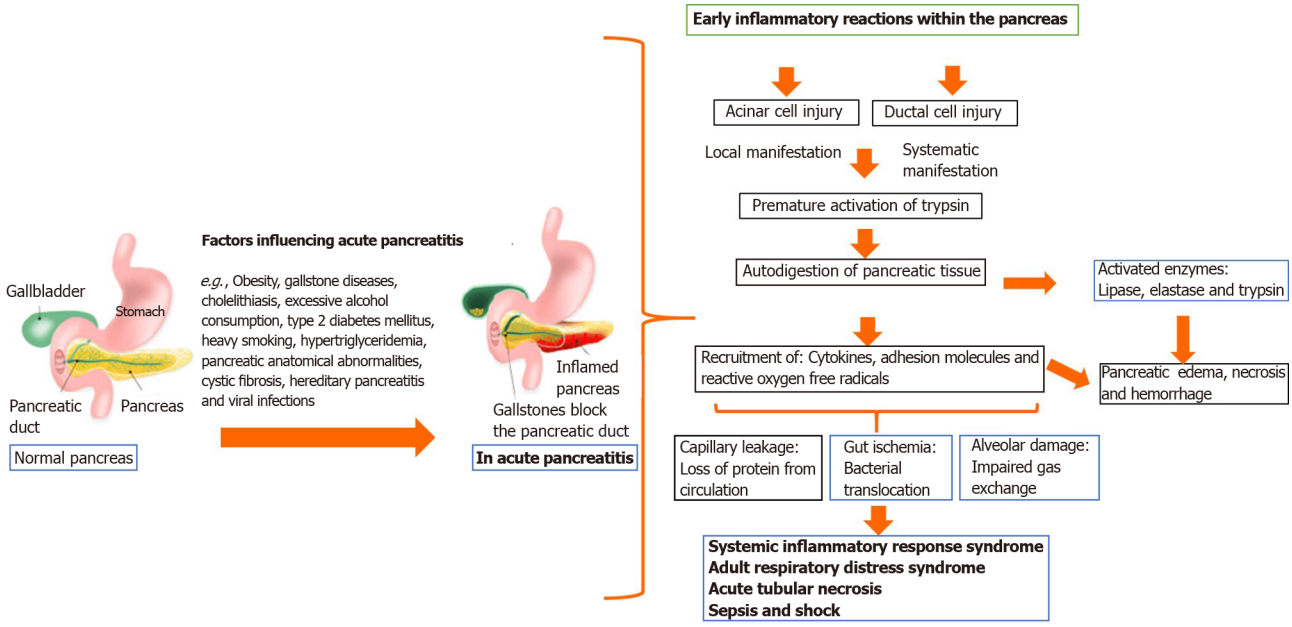

Figure 1 Pathophysiology of acute pancreatitis. Damage in the pancreas' acinar cell causes trypsin activation following cell membrane trafficking impairment, with subsequent activation of the zymogen cascade by trypsin. Attraction and activation of leukocytes occur with the release of many proinflammatory and anti-inflammatory cytokines, as well as chemokines. An overt and sustained activation of proinflammatory mediators leads to systemic inflammatory response syndrome (SIRS), which may further proceed to multiorgan failure, pancreatic necrosis and sepsis with late complications of acute pancreatitis.

In brief, the pancreas-gut communication has been described as being in AP, with bacterial translocation as a possible consequence and the homeostatic host response noted. Translocation of bacteria from the lower gastrointestinal tract occurs *via* the portal circulation - the oral course and/or the mesenteric lymph nodes. The acinar cells of the pancreas secrete pancreatic antimicrobial peptides (AMPs). AMPs have homeostatic bidirectional communication with the gastrointestinal tract[79]. The lower level of the microbiome in the gastrointestinal tract may increase pancreatic antimicrobial peptide production by short-chain fatty acid metabolites. Consequently, it induces a pancreatic immunoregulatory environment which decreases proinflammatory immune cells. Conversely, decreased antimicrobial peptide production facilitates the overgrowth of the gastrointestinal microbiota leading to the induction of proinflammatory immune cells. Thus, it subsequently alters the gut microbiome and the intestinal immune system[79].

POTENTIAL ROLE OF THE GUT MICROBIOME IN AP

Metagenomics and next-generation sequencing have facilitated the investigation of the involvement of the gut microbiome in human physiology and various diseases. The findings have allowed for consideration of the gut microbiome as a hidden organ[80]. The close interaction of the gut microbiome with host physiology can account for the harmful effects of disruptions in the former caused by various internal or external events that initiate inflammatory conditions and some types of cancer. Therefore, it is essential that specific microbial signals maintain the host immune response and other physiological functions that protect against pathogens[81].

Injury of the microcirculation and hypovolemia that occur during AP can lead to gut mucosal ischemia and reperfusion injury that result in loss of gut barrier function. Subsequent translocation of gut bacteria can result in local pancreatic and systemic infections[82]. Leading causes of AP mortality include pancreatic infection and peripancreatic necrosis[78]. The initial onset of cerulean-driven AP depends on NOD1 activation in acinar cells by commensal microbiota that have translocated from the gut. Following activation, NOD1 induces the expression of inflammatory mediators[83]. The role of the gut in neutrophil priming and release of proinflammatory cytokines is important for the initiation and propagation of inflammation and sepsis[84]. The loss of gut barrier function has been implicated in the pathogenesis of AP-related infections. Ahuja *et al*[76] reported that secretion of antimicrobials from pancreatic acinar cells regulated gut microbiota composition and innate immunity[76]. Blocking

acinar cell exocytosis in mice has been found to lead to gut dysbiosis, inflammation, systemic bacterial translocation, and ultimately, death. Additional evidence has revealed additional examples of crosstalk between pancreas acinar cells and the gut microbiome[76,77].

An ongoing investigation of the microbiota and AP has shown that microcirculatory disturbances associated with the loss of fluid into the "third space," lead to hypovolemia, ischemia, and reperfusion injury in AP patients. The gut is affected by AP, but it is not a passive victim because it plays an active role in the worsening of the illness[85]. In addition to bacterial translocation, the translocation of inflammatory compounds produced in the intestinal wall and the gut's toxic products might also be responsible for initiating SIRS and distant organ injury in AP patients[86]. The contribution of the gut microbiome for protection against pathogens in AP patients has not been clearly elucidated. An increase of such pathogenic bacteria as *Enterobacteriaceae* and *Firmicutes*, and a decrease in beneficial bacteria like *Bacteroidetes* and *Lactobacillus* has been observed in AP patients[87]. Furthermore, increased serum IL-6 has been found to be positively related to increased *Enterobacteriaceae* and *Enterococcus* and inversely related to *Bifidobacterium* and *Clostridium* cluster number. Tan *et al*[87] reported that the extent of gut microbiota modification predicted pancreatitis severity and the occurrence of systemic complications. Gerritsen *et al*[88] found that "AP-associated microbiota" replaced the normal intestinal flora in a study performed in a mouse model. In AP, changes in the populations of specific commensal bacteria have been associated with reduced levels of the inflammatory cytokines IL-1b, TNF-a, CXCL1, and IL-18, and inversely correlated with pancreatitis severity and the occurrence of systemic infectious complications. The evidence highlights the restoration of the physiological gut microbiota composition as a valuable strategy to treat AP[89].

The 16S rRNA gene is highly conserved in bacteria, and it is highly species-specific. Consequently, 16S rRNA gene sequencing is widely used to study the gut microbiota in various disease states[90]. Zhu *et al*[69] reported that the relative abundance of commensal microbiota in AP patients differed from that in a healthy individual. Members of the *Bacteroidetes* phylum decreased significantly, but *Proteobacteria* were over-represented in AP. AP patients also had a relative overabundance of *Escherichia/Shigella* compared to healthy control[69]. Increased abundance of two common opportunistic pathogens, including *Enterococcus* and an unknown genus in the *Enterobacteriaceae* family, were also observed in AP patients. Linear discrimination and effect size analysis revealed significant increases in *Acinetobacter, Stenotrophomonas,* and *Geobacillus* with decreased *Bacteroides, Alloprevotella, Blautia* and *Gemella* in patients with severe AP, as compared to those with mild and moderately severe AP[69]. Table 5[21,69,75,91] and Table 6[69,75,87,90,92] summarize the significant changes in the microbiome composition of healthy controls and in patients with mild, moderately severe, and severe AP.

Changes in the gut microbiota in AP include overexpression of opportunistic pathogens, such as *Escherichia/Shigella*, and reduced abundance of beneficial genera, such as *Bifidobacterium*[69]. It has been hypothesized that a reduction of beneficial bacteria might facilitate microbial translocation across a damaged gut barrier, thereby promoting the progression of AP. Studies performed by Li *et al*[75] and other investigators[93,94] found that dysbiosis that included the depletion of short-chain fatty acid-producing bacteria was associated with an impaired gut barrier and worsening of AP. Changes in the gut microbiome may thus serve as a diagnostic tool in AP. Restoring gut microbiota homeostasis and stabilizing the gut barrier might have therapeutic value in AP patients, as shown in Figure 2[21,30,69,75,87,93,94]. The overall literature suggests that there is an association between the gut microbiome and the severity of AP[95]. Additionally, in experimental acute pancreatitis, changes to the gut microbiome, *e.g.*, administration of *Clostridium butyricum* can suppress AP[27] pointing to the therapeutic potential of this approach is promising.

ANTIBIOTICS, PREBIOTICS, SYNBIOTICS, AND PROBIOTICS FOR THE TREATMENT OF AP

Antibiotic therapy in AP

In the past decade, substantial advancements have been made not only in understanding the pathophysiology of AP but also in treatment strategies and multidisciplinary management. Necrotizing pancreatitis occurs in about 30% of patients and has a poor prognosis and high mortality. About 80% of AP deaths are caused by infections

Table 5 Altered microbiome composition in acute pancreatitis *vs* healthy controls

No.	Techniques used for microbiome profiling	Healthy control	Acute pancreatitis	Ref.
1	qPCR (Fecal samples)	*Firmicutes*↑	*Firmicutes*↓	[84]
		Bacteroidetes↓	*Bacteroidetes*↑	
		Proteobacteria↓	*Proteobacteria*↑	
		Actinobacteria↑	*Actinobacteria*↓	
		Tenericutes↓	*Tenericutes*↑	
2	16S rRNA gene sequencing (Fecal samples)	*Proteobacteria*↓	*Bacteroidetes*↓	[83]
			Proteobacteria↑	
			Escherichia/Shigella↑	
			Enterococcus↑	
			Enterobacteriaceae↑	
			Prevotella↓	
			Faecalibacterium↓	
			Bifidobacterium↓	
3	16S rRNA gene sequencing (Fecal samples)	NA	*Bacteroidetes*↑	[85]
			Proteobacteria↑	
			Firmicutes↓	
			Actinobacteria↓	
4	16S rRNA gene sequencing (Fecal samples)	NA	*Enterobacteriaceae*↑	[21]
			Enterococcus↑	
			Bifidobacteria↓	

NA: Not available. ↑: Higher level; ↓: Lower level.

secondary to AP that might be attributable to gut translocation of intestinal bacteria [82,96]. Current guidelines recommend against routine antibiotic prophylaxis in AP [97]. Recent studies did not find benefits of antibiotic prophylaxis in reducing AP mortality, infections not involving the pancreas, or surgical interventions. The data on infections accompanying pancreatic necrosis in adults are conflicting[98,99].

The use of antibiotics, starting with carbapenems, quinolones, and metronidazole, has been advised in patients with AP and concomitant cholangitis symptoms, infected necrosis, or necrotizing pancreatitis accompanying a deteriorating clinical status[97]. Delaying surgical interventions decreases morbidity and mortality[100]. In some instances of AP, where infection is clinically suspected or confirmed, the use of antibiotics is recommended to avoid development of antimicrobial resistance. The predictive value of fine-needle aspiration for sampling and determination of bacterial sensitivities in diagnosing peri-pancreatic infection is comparable to that of clinical signs and imaging. The routine use of fine-needle aspiration is not recommended[101].

Early enteral nutrition is recommended in AP because it protects mucosal nutrition, the gut mucosal barrier, and gut-pancreas homeostasis[102]. In a previous randomized trial, decontamination of the gut with norfloxacin, colistin, amphotericin and standard AP therapy did not reduce mortality[103]. At present, selective gut decontamination cannot be recommended for AP patients.

Despite constant improvement in targeted therapeutics, a third of adult AP patients develop moderately severe AP and/or severe AP with SIRS, organ failure, and an increased risk of infection[104]. The gut mucosal barrier reduces the risk of infected pancreatic necrosis and thus helps to decrease mortality risk[85,105]. Microbiome-targeted therapies, such as genetic engineering of modified strains to outcompete pathogens, selective nutrient or prebiotic supplementation, or engineered bacteriophages, could steer the altered microbiome toward a healthy phenotype or change the course of critical illness[81]. Probiotics offer substantial health benefits and support the homeostasis of gut flora[81]. The most widely used probiotic bacteria in clinical trials are *Lactobacillus* and *Bifidobacterium*, which are easy to isolate from human feces or the

Table 6 Altered microbiome composition observed in acute pancreatitis of increasing severity

No.	Techniques used for microbiome profiling	MAP	MSAP	SAP	Ref.
1	qPCR (Fecal samples), performed only on MAP and SAP patients	*Enterococcus*↑ *Enterobacteriaceae*↑ *Bifidobacterium*↓	NA	*Enterococcus*↑ *Enterobacteriaceae*↑ *Bifidobacterium*↓	[79]
2	16S rRNA gene sequencing (Fecal samples)	*Finegoldia*↑	NA	*Acinetobacter*↑ *Stentrophomonas*↑ *Geobacillus*↑ *Bacteroides*↓ *Alloprevotella*↓ *Blautia*↓ *Gemella*↓	[83]
3	16S rRNA sequencing (Fecal sample)	*Enterobacteriaceae*↑ *Enterococcus*↑ *Bifidobacterium*↓	NA	*Enterobacteriaceae*↑ *Enterococcus*↑ *Bifidobacterium*↓ *Blautia*↓	[85]
4	16S rRNA gene sequencing (Rectal swab)	*Bacteroides*↑ *Escherichia/Shigella*↑ *Enterococcus*↑ *Finegoldia*↑ *Blautia*↓	*Bacteroides*↑ *Escherichia/Shigella*↑ *Enterococcus*↑ *Anaerococcus*↑ *Eubacterium hallii*↓	*Bacteroides*↑ *Escherichia/Shigella*↑ *Enterococcus*↑ *Eubacterium hallii*↓ *Acinetobacter*↓ *Stenotrophomonas*↓ *Bacteroides*↓ *Blautia*↓	[82]
5	Shotgun metagenomics (Fecal sample)	*Thermoprotei*↑ *Crenarchaeota*↑ *Streptococcus*↑ *Anaerostipes hadrus*↓	*Sulfolobus*↑ *Methanobrevibacter ruminantium*↑ *Methanosarcina - Thermophila*↑ *Anaerostipes hadrus*↓ *Escherichia coli*↑	*Sulfolobus*↑ *Methanomicrobiales - archaeon 53_19*↑ *Enterococcus*↑ *Blautia*↓	[86]

MAP: Mild acute pancreatitis; MSAP: Moderately severe acute pancreatitis; NA: Not available; SAP: Severe acute pancreatitis; ↑: Higher level; ↓: Lower level.

intestinal mucosa. Prebiotics are nondigestible foods required to propagate probiotics, and they stimulate the growth and activity of the healthy gut flora. Synbiotics are nutritional supplements that include both probiotics and prebiotics[106].

A randomized controlled trial by Pan *et al*[107] evaluated the ability of synbiotics to restore intestinal barrier damage and reduce the infection rate in early AP. A group of 45 patients were given either live or heat-inactivated *Lactobacillus plantarum* 299 with an oat fiber supplement as early enteral nutrition. Supplementation plus the symbiotic significantly reduced both pancreatic necrosis and surgical interventions[107]. A subsequent clinical trial included 62 severe AP patients treated with early enteral nutrition with four different prebiotics (inulin, beta-glucan, resistant starch, and pectin) together with four *Lactobacillus* probiotic preparations. The treatment resulted in a reduced incidence of SIRS and organ failure, supporting the use of early enteral symbiotic nutrition in severe AP[108]. Olah *et al*[109] randomized 45 AP patients to receive either a freeze-dried preparation containing 10^9 live *L. plantarum* 299 in each dose together with oat fiber or a heat-inactivated *Lactobacillus* controlled by nasojejunal tube for one week. Infected pancreatic necrosis and abscesses were significantly lower

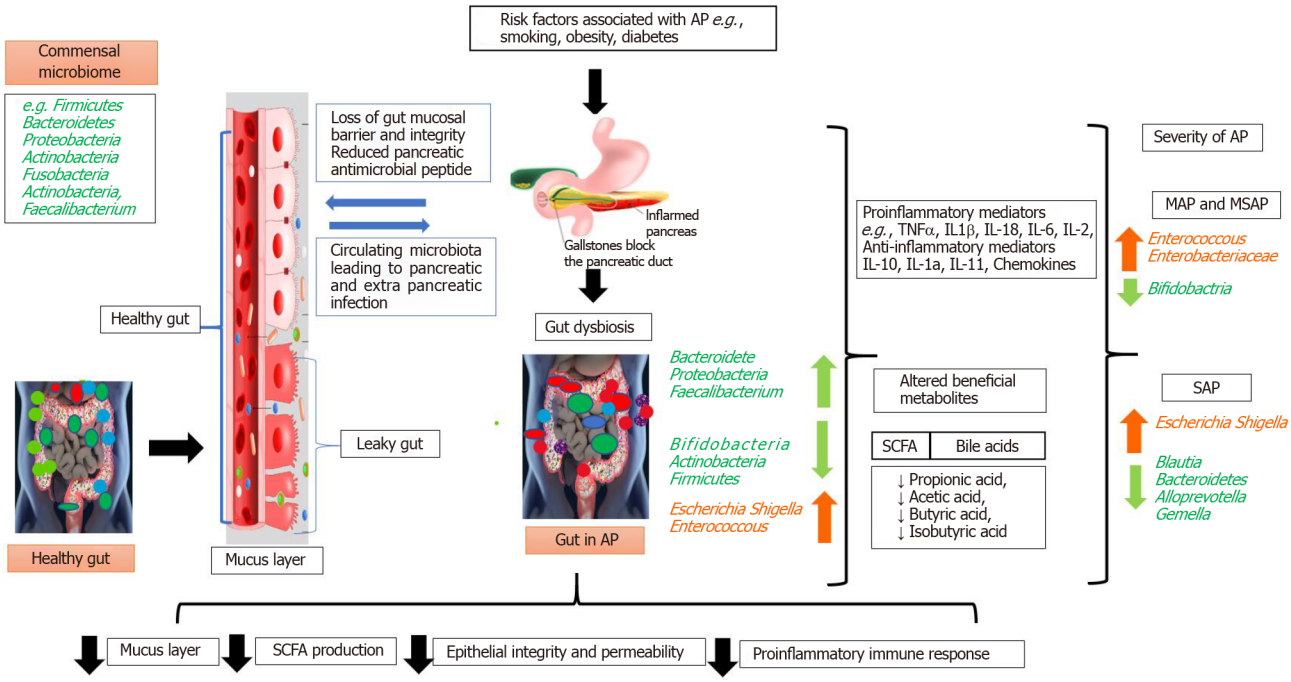

Figure 2 Role of the gut microbiota in inflammation of the pancreas and acute pancreatitis. Breakdown of the relationship between physiologic and pathogenic bacteria, the immune system, and the intestinal epithelial barrier leads to gut dysbiosis. Inflammation and gut dysbiosis causes the translocation of microbes to the pancreas. The translocation of bacteria results in pancreatic inflammation due to toxin diffusion and complications like fibrosis, digestive and absorption disorders, diabetes, and other metabolic disorders. AP: Acute pancreatitis; MAP: Mild acute pancreatitis; MSAP: Moderate severe acute pancreatitis; TNF: Tumor necrosis factor; IL: Interleukin; SAP: Severe acute pancreatitis; SCFA: Short-chain fatty acids.

in the treatment group than in the control group.

Other experimental pancreatitis studies in rat models confirmed the efficacy of *L. plantarum* spp. in reducing microbial translocation and as a possible alternative to antimicrobials[110]. Several studies have shown that probiotics containing *Faecalibacterium* and *Bifidobacterium* species had beneficial effects, including stabilizing the gut barrier, increasing anti-inflammatory responses, and attenuating bacterial translocation[111,112]. Some studies have not found any significant benefit or adverse effect of probiotics in severe AP. Still, it is essential to note the considerable patient and probiotic regimen heterogeneity in the published clinical trials of probiotics. The PROPATRIA Probiotics[113] in Pancreatitis Trial randomized 298 patients with predicted severe AP to either a multispecies probiotic mixture containing two different *Bifidobacterium*, three *Lactobacillus*, and one *Lactococcus* species or a placebo. The infectious complications in the two groups were similar, but the probiotic group had higher mortality (16% *vs* 6%) and incidence of bowel ischemia (6% *vs* 0%) compared with the placebo group. The high load of the probiotic mixture used in the study was thought to have been responsible for the increased mortality[114]. The findings highlight the challenges of supplementing the gut microbiome with beneficial microbial species in the setting of AP. Nevertheless, eight years later, the PROPATRIA trial was reevaluated by Bongaerts *et al*[115]. The team of researchers analyzed and addressed all shortcomings identified in the trial. PROPATRIA researchers contend that a lethal combination of predominantly proteolytic pancreatic enzymes and probiotic therapy was responsible for the high mortality rate, and that elevated levels of lactic acid produced by bacterial fermentation of carbohydrates significantly contributed to the high death rate. Additionally, one of them was the latency time in the first administration of probiotics; indeed, some patients were treated 24 h after onset of symptoms. Furthermore, there were errors in randomization; in fact, the onset of multi-organ failure was already present during admission in more patients in the first group than in the placebo group (41 patients *vs* 23 patients). Finally, last but not least, the team of researchers suggested that in future studies, when considering substituting probiotics in AP, it is necessary to assess the appropriate, effective doses of probiotics. However, caution should be mandatory to prevent bacterial overgrowth while conducting clinical trials in AP patients.

Previous studies have shown that *L. plantarum* decreased the occurrence of infective necrosis in AP patients[110] and that *Saccharomyces boulardi* spp. administered concomitantly with antibiotics such as ciprofloxacin decreased histopathologic scores in acute

necrotizing pancreatitis[111]. Animal studies have provided strong evidence in support of probiotic benefits in animal models of AP. A mixture of *Lactobacillus acidophilus, Streptococcus thermophilus,* and *Bifidobacterium lactis* given by oral gavage reduced pancreatitis, bacterial translocation to extra-intestinal sites, and mortality in male albino rats because of reduced duodenal bacterial overgrowth[112].

Injury of the GI barrier is a key event in the development of AP. Few studies have reported prevention of disruption of the intestinal barrier with modulation of gut microbiome balance. In one such study conducted in a mouse model of AP, *Clostridium butyricum*, a producer of small-chain fatty acids, which have immunomodulatory properties, reduced infiltration of neutrophils and dendritic cells in the pancreas and inhibited inflammatory responses mediated by NLRP3 and TLR4 signaling pathways in the pancreas and colon[27]. In summary, probiotics help to maintain gut homeostasis. Research should improve the designs of future studies, for example, by detecting a peculiar strain of microorganisms (*i.e.*, their type), standardizing the dose and duration of treatment, or standardizing the state of disease progression when considering to use in current therapy scenarios.

CONCLUSION

The gut microbiome plays a significant role in health and diseases. The resident microbiota in the human GI tract influences host metabolism, physiology, and immune system development. Disruption of this bacterial community results in GI disease. Ongoing medical and clinical research has produced a substantial body of evidence of a clear correlation between changes in the commensal microbiota and the occurrence of pancreatic disease. Application of biochemical, microbiological, and molecular biological methods have provided a description of the constituents of the gut microbiome in health and disease, their niches, and their physiological roles. Additional study is needed to explain whether microbial dysbiosis is a cause or an effect of diverse pathologies. The microbiome profile and changes in dysbiosis may influence an increase in AP severity during its clinical course.

Damage of the intestinal mucosal barrier allows migration of intestinal microbes to the blood or other tissues and organs, which enhances or aggravates AP. Changes in the resident species and abundance of the intestinal flora during AP are closely related to damage of the intestinal mucosal barrier system. Regulating the intestinal flora to repair the intestinal mucosal barrier and restore its function may be useful in AP treatment. Changes in the gut microbiota composition in AP include over-representation of opportunistic pathogens such as *Escherichia/Shigella* species and a significant decrease in the beneficial *Bifidobacterium* genus. Early dysbiosis of the gut microbiota, especially the depletion of small-chain fatty acid-producing bacteria, is probably associated with impairment of the gut barrier and increased AP severity.

The mechanisms of gut dysbiosis and the etiology of AP are not yet fully understood. The relationship of GI microbial symbiosis and AP are avenues for further research. The concomitant use of probiotics and antibiotics together with conventional treatment, such as surgery, radiotherapy, chemotherapy and targeted therapies, are further areas for research. In summary, the clinical significance of GI homeostasis during AP is emerging step by step. Thus, restoring the homeostasis of gut microbiota and stabilizing the gut barrier could be a promising therapeutic target in preventing AP progression. Challenges and specific problems that stand in the way to developing a research platform for understanding AP and its interaction with the microbiome need to be overcome. This review has explored the role of the gut microbiome in AP and the targeted use of probiotics, prebiotics, and synbiotics to maintain or restore GI microbial balance.

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