REVIEW ARTICLES

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The Roles of Gut Microbiota in the Pathogenesis of Acute Pancreatitis

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Acute pancreatitis (AP), among the most common causes of acute abdomen, is characterized by persistent left upper abdominal pain and vomiting, without pain relief after vomiting. Its pathological features include abnormal activation of pancreatic enzymes and induction of pancreatic autodigestion by various etiologies. Emerging evidence indicates a strong association between the gut microbiota and AP progression, primarily mediated by intestinal barrier disruption, bacterial translocation, and immune dysregulation. Alterations in the gut microbiota, including overgrowth of pathogenic bacteria (eg, Enterobacteriaceae) and a reduction in beneficial commensals (eg, Lactobacillaceae and Bifidobacteriaceae), are consistently observed among patients with AP. The gut microenvironment, including factors such as bile acids, oxygen levels, and pH, shapes the microbial community and its interactions with the host. These changes can promote local and systemic inflammation, thereby exacerbating pancreatic necrosis and contributing to multiple organ dysfunction. Consequently, the bidirectional interaction between the gut microbiome and AP has received increasing attention. This review provides a comprehensive summary of the current understanding of how gut microbiota dysbiosis contributes to AP pathogenesis. We focus on mechanisms linking microbial and microenvironmental alterations to disease severity, including the roles of the gut-pancreas axis, short-chain fatty acids, and pattern recognition receptors. Finally, we discuss the potential of novel therapeutic strategies targeting these pathways for the management of AP.

Keywords: Gastroenterology • Intestinal Microbiome • Microbiota • Pancreatitis • Pathophysiology

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Introduction

Among digestive disorders, acute pancreatitis (AP) is relatively common and represents a frequent cause of acute abdominal disease, with presentations ranging from mild pancreatic edema to severe pancreatic necrosis [1]. Although most patients present with mild, self-limiting disease, 15% to 20% progress to severe acute pancreatitis (SAP). Intestinal barrier dysfunction—a key contributor to pancreatic infection and SAP mortality—is implicated in over 80% of SAP-related deaths [2,3].

The digestive tract harbors a diverse community of microorganisms, collectively known as the gut microbiota, which interact to maintain a balanced ecosystem [4]. The physical and chemical conditions that support this community are referred to as the gut microenvironment [5]. Changes in the gut microbiome (the collective genomes of these microorganisms) play important roles in pancreatic diseases [6]. The pancreas influences intestinal ecology through its exocrine function; in turn, intestinal dysbiosis promotes the progression of pancreatic disease [7]. Thus, modulation of the gut microbiota has emerged as a potential component of therapeutic strategies for AP [2].

Gut microbial composition varies across diseases and contributes to disease progression [8]. However, it remains unclear whether gut dysbiosis is a cause or consequence of AP [9]. Studies investigating alterations in the gut microbiota during AP pathogenesis and their underlying mechanisms are ongoing [10-12]. In this review, we summarize current advances in understanding the bidirectional relationship between the gut microbiota and pancreatitis, with a focus on clinical implications. We examine changes in the gut microbiota during AP, mechanisms by which these changes influence disease progression, and the potential of microbiota-targeted interventions as novel therapeutic strategies for AP.

Gut Microbiota and Pancreatitis: A Bidirectional Relationship

In AP, intestinal dysbiosis, often associated with intestinal infection, can further aggravate disease severity. Numerous experimental and clinical studies have investigated the relationship between alterations in intestinal microecology and pancreatitis. A Mendelian randomization study identified significant associations between AP and 9 gut microbiota taxa (genus *Eubacterium eligens* group, genus *Eubacterium fissicatena* group, genus *Coprococcus* 3, genus *Eggerthella*, genus *Erysipelatoclostridium*, genus *Flavonifractor*, genus *Haemophilus*, genus *Methanobrevibacter*, and genus *Prevotella* 9). Additionally, 4 taxa (family *Clostridiaceae* 1, genus *Lachnospiraceae* FCS020 group, genus *Prevotella* 9, and genus *Ruminococcaceae* UCG014) were associated with chronic pancreatitis, and 10 taxa (phylum *Lentisphaerae*, class *Erysipelotrichia*, class *Lentisphaeria*, order *Erysipelotrichales*, order *Victivallales*, family *Erysipelotrichaceae*, genus *Flavonifractor*, genus *Lachnospiraceae* UCG004, genus *Streptococcus*, and genus *Terrisporobacter*) were associated with pancreatic cancer [12].

During the course of AP, intestinal homeostasis and microbial composition are altered due to abnormal trypsin secretion and structural changes in the pancreas [13]. Patients with AP exhibit a 3.2% increase in *Enterobacteriaceae*, a 9.3% increase in potential pathogens (eg, *Enterococcus*), and a 9.2% decrease in beneficial *Bifidobacterium* compared with healthy controls [9]. The abundances of *Aspergillus* and Actinobacteria are increased in patients with SAP, whereas the abundances of Firmicutes and *Anaplasma* are decreased [11]. Moreover, analyses of bacterial communities indicate that the most pronounced microbiota alterations occur in the cecum and colon; the duodenum may serve as a reservoir for potential invasive pathogens [10]. Collectively, these findings suggest that intestinal microecology plays a critical role in AP progression. Characterization of microbial distribution and population changes in AP, based on controlled studies and community analyses, may provide insights concerning disease severity prediction and inform the development of novel therapeutic strategies.

Etiology-Specific Interactions With the Gut Microbiota

The etiology of AP is predominantly cholelithiasis, followed by ethanol use [14]; in recent years, hypertriglyceridemia-induced pancreatitis (HTGP) has become increasingly prevalent [15]. Interactions between different etiologic factors and the intestinal microbiota influence AP progression (**Figure 1**). Bacteria in the gallbladder and pancreas may migrate via the lymphatic system, exacerbating reciprocal inflammatory responses [16]. The predominant microorganisms in bile belong to Firmicutes, *Bacteroides uniformis*, Actinobacteria, and *Aspergillus*; *B. uniformis* is the most abundant species in affected individuals. Additionally, bile salts secreted into the intestine exert antimicrobial effects through mechanisms including DNA damage, cell membrane disruption, extensive protein unfolding (disulfide bond stress in vivo), and cytoplasmic protein aggregation; these mechanisms impair bacterial enzyme activity and inhibit microbial growth. Such processes alter gut microbiota composition; interactions among the microbiota, pathogens, and host immune system may contribute to intestinal dysbiosis [17]. The gut microbiota also regulates bile acid metabolism. For example, *Desulfovibrio* enrichment may suppress the expression of bile acid synthesis genes, particularly those that encode rate-limiting enzymes. Microbial products such as lipopolysaccharide (LPS) can upregulate mucin production via the tumor necrosis factor alpha (TNF-α)-converting enzyme/

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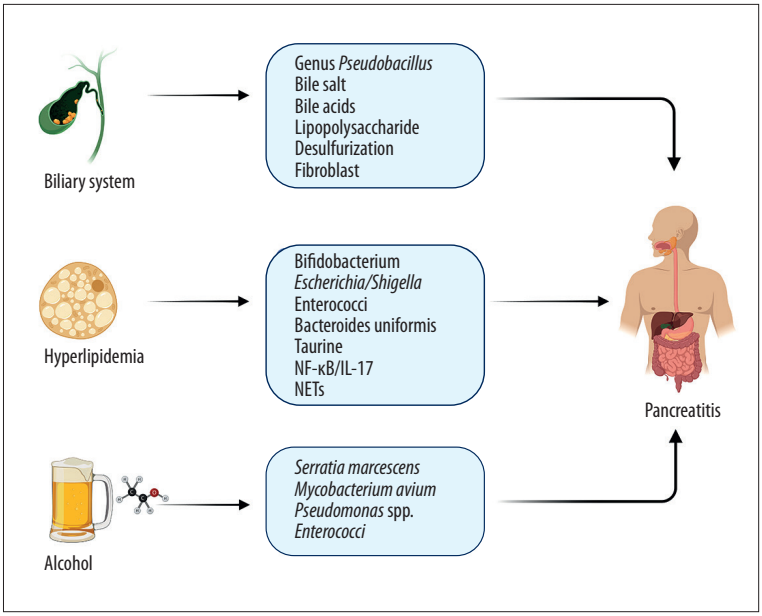

Figure 1. Etiology-specific interactions between the gut microbiota and pancreatitis. This figure illustrates distinct interactions between the gut microbiota and the host across different etiologies of acute pancreatitis. (**Left**) In biliary pancreatitis, bacteria can migrate between the gallbladder and pancreas via the lymphatic system, promoting reciprocal inflammatory responses. Bile salts secreted into the intestine can disrupt gut microbiota composition by damaging bacterial DNA and cell membranes. Conversely, the gut microbiota regulates bile acid metabolism, thus influencing the risk and severity of biliary disease. (**Center**) In hypertriglyceridemia-induced acute pancreatitis, there is a reduced abundance of beneficial bacteria (eg, *Bifidobacterium*) and an overgrowth of *Escherichia/Shigella* and *Enterococcus*. Decreased microbial production of taurine, potentially by taxa such as *Anaeroplasma*, leads to increased colonic interleukin (IL)-17 levels and formation of neutrophil extracellular traps (NETs), which exacerbate pancreatic injury. (**Right**) In alcoholic pancreatitis, ethanol is metabolized by gut bacteria to acetaldehyde, which disrupts tight junctions and increases intestinal permeability. Together with increased small intestinal bacterial overgrowth, this facilitates bacterial translocation and aggravates pancreatic inflammation.

transforming growth factor-α/epidermal growth factor receptor pathway and the EP4/p38 mitogen-activated protein kinase (MAPK) pathway. Furthermore, microbial enzymes (eg, β-glucosinolate enzymes and phospholipases) can accelerate calcium bilirubin precipitation, promoting biliary tract disease and increasing the risk or severity of pancreatitis [18]. Gut microbiota dysbiosis can also promote hepatobiliary injury through toxin translocation and activation of NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasomes, leading to bile duct and liver damage. Inhibition of the farnesoid X receptor (FXR) signaling pathway may further increase bile acid synthesis and exacerbate inflammation [19]. The activation of NLRP3 inflammasomes can be inhibited by intestinal probiotics, alleviating AP progression [20,21]. However, the mechanisms underlying interactions between the gut microbiota and bile acids in AP require further investigation [22].

A comparative study analyzing the composition of the gut microbiota in patients with chronic alcoholic pancreatitis detected reduced overall microbial abundance, with significantly increased levels of *Serratia* spp., *Fusobacterium* spp., *Pseudomonas* spp., and *Enterococcus* spp. [23]. The gut microbiota profile in acute alcoholic pancreatitis substantially differs from the profile in chronic alcoholic pancreatitis and may reflect the predominance of specific bacterial species during the acute phase [24]. A controlled trial evaluating small intestinal bacterial populations in chronic alcoholic pancreatitis using the glucose hydrogen breath test showed a higher prevalence of small intestinal bacterial overgrowth [25]. A rat study examining intestinal permeability after ethanol administration demonstrated increased permeability to small molecules, facilitating bacterial translocation [26]. In humans, intestinal bacteria metabolize ethanol to acetaldehyde via bacterial alcohol dehydrogenase. Acetaldehyde induces tyrosine phosphorylation of key components of tight junctions and adherens junctions, thereby disrupting the intestinal barrier and promoting bacterial translocation [27]. However, evidence regarding alcohol-induced alterations in the gut microbiota and their role in exacerbating AP remains limited.

The composition and abundance of the gut microbiota in HTGP also differ from those observed in other etiologies. Patients with HTGP exhibit reduced microbial diversity, decreased levels of beneficial bacteria (eg, *Bifidobacterium*), and increased abundances of *Escherichia/Shigella* and *Enterococcus* [28]. In experimental models, pancreatic injury is attenuated by inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and interleukin (IL)-17 signaling pathways in neutrophils by *Anabaena hominis* or taurine. Conversely, reduced abundance of *A. hominis* decreases taurine production and increases colonic IL-17 release, promoting neutrophil

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extracellular trap formation and exacerbating pancreatic injury [29]. Gut-microbiota-derived metabolites influence HTGP progression by regulating lipid metabolism and inflammatory responses. However, the pathogenic roles of the gut microbiota and their metabolites in HTGP remain incompletely understood; further mechanistic studies are needed [30].

Mechanisms Linking Gut Microbiota Dysbiosis to Acute Pancreatitis

Increasing research on gut microorganisms has shown that the gut microbiota participates in the progression of various diseases. It influences systemic disease through multiple axes, including the gut-lung, gut-pancreas, gut-pancreas-hepatic, and gut-brain axes [31-34]. Among these, the gut-pancreas axis plays a key role in AP, with evidence indicating that gut microorganisms affect disease severity through this pathway. Under normal physiological conditions, the gut-pancreas axis also bidirectionally regulates pancreatic secretion and maintains intestinal microbial homeostasis [32]. Gut microbiota dysbiosis is often associated with more severe AP [35]. Most existing studies have focused on the regulatory effects of the gut microbiota on pancreatic function; the molecular mechanisms by which pancreatitis then drives gut microbiota dysbiosis remain poorly understood. Elucidation of the key signaling pathways through multi-level experimental studies is essential.

Intestinal Barrier Disruption and Bacterial Translocation

Intestinal mucosa integrity is largely maintained by the normal gut microbiota. Approximately 59% of patients with AP exhibit intestinal barrier damage, which contributes to disease progression [2]. The intestinal barrier comprises physical, chemical, immune, and microbial components that collectively prevent the invasion of harmful substances [36]. Although the pancreas lacks its own microbiota, intestinal flora dysbiosis in AP can disrupt the gut barrier and indirectly influence disease progression [37]. The incidence of intestinal barrier dysfunction is higher in patients with severe pancreatitis than in those with mild disease [38]. The intestinal barrier includes luminal enzymes, bile acids, the mucus layer, and the epithelial barrier. Dysfunction affecting any of these components can compromise barrier integrity and contribute to disease progression [39].

When the gut microbiota becomes dysbiotic, levels of glutathione S-transferase pi (GSTpi) are substantially reduced in intestinal tissues, weakening inhibition of colonic NLRP3 inflammasome activation and thus exacerbating intestinal barrier damage and AP severity [40]. The inflammatory response in AP also alters the gut microbiota. For example, the abundance of *Desulfovibrio vulnificus* is increased in patients with AP; this organism is associated with sulfate reduction, and changes in its abundance may induce inflammatory responses that damage the intestinal epithelium and impair the mucosal barrier. Additionally, SAP reduces the abundance of beneficial mucosa-associated microbiota in the inner layer of the intestinal mucosa, leading to decreased levels of short-chain fatty acids, including propionate and butyrate. This reduction suppresses mucin 2 (*MUC2*) mRNA expression in the human goblet cell line LS174T, resulting in decreased mucin *MUC2* expression and impaired intestinal barrier function [41].

An increased abundance of *Escherichia coli-Shigella* is associated with elevated serum IL-6 levels, promoting inflammatory responses and increasing intestinal permeability [9]. Commensal *E. coli* MG1655 exacerbates TNF-α-induced inflammation and loss of tight junction proteins, while activating Toll-like receptor (TLR)4/myeloid differentiation primary response 88 (MyD88)/p38 MAPK and endoplasmic reticulum stress signaling pathways. These effects induce intestinal epithelial injury and worsen acute necrotizing pancreatitis, as demonstrated by 16S rRNA gene sequencing and quantitative polymerase chain reaction [42]. During AP, increased stimulator of interferon genes (STING) signaling activates interferon regulatory factor 3 and NF-κB, leading to pronounced upregulation of interferons and proinflammatory cytokines. This process disrupts intestinal barrier function and further exacerbates disease severity [43].

In a normal intestinal ecosystem, diverse bacterial communities maintain a dynamic balance and colonize the intestinal tract. When the intestinal barrier is disrupted by disease, bacteria may translocate to other organs and contribute to disease onset or progression, although the precise mechanisms remain unclear. Disruption of any component of the gut barrier—physical, chemical, immune, or microbial—can permit bacterial translocation into the bloodstream, leading to sustained inflammation and disease progression [44]. Bacterial translocation occurs via paracellular and transcellular pathways, either independently or in combination. The paracellular pathway is more common and involves disruption of tight junction proteins; the transcellular pathway is mediated by epithelial cell transport mechanisms, including specific channels and membrane pumps. These processes can damage the cytoskeleton, including actin filaments and microtubules, thus promoting bacterial translocation [45].

Belizário et al [46] identified *E. coli*, *Klebsiella*, *Proteus*, *Enterobacter*, *Shigella*, *Salmonella*, and *Serratia* as the bacterial groups most frequently associated with bacterial translocation. During AP, intestinal barrier impairment allows harmful substances to enter the mesenteric lymph nodes and subsequently disseminate via systemic circulation to otherwise sterile

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Table 1. Mechanisms by which gut microbial metabolites affect acute pancreatitis.

Metabolite	Mechanism of action	Impact on AP	References
Butyrate	Inhibits NLRP3 inflammasome activation; promotes regulatory T-cell function	Reduces intestinal barrier damage and inflammation, ameliorating AP	Pan et al [50] Xiao et al [51]
Vitamin D	Blocks NF-κB activation via VDR; inhibits apoptosis in intestinal epithelial cells	Protects intestinal barrier at moderate levels; excessive levels may exacerbate AP	Liu et al [52]
Bile acids, alcohol	Activates Orai1, leading to Ca^{2+} overload and impaired ductal cell secretion	Increases pancreatic ductal cell necrosis, aggravating AP	Pallagi et al [54]
Hydrogen sulfide (H2S)	Activates K_ATP channels; increases TNF-α and IL-6 via the PI3K/Akt/Sp1 pathway	Proinflammatory effects, exacerbating AP	Liu et al [55]
Nicotinamide mononucleotide	Increases pancreatic NAD+ levels; activates SIRT3-PRDX5 pathway	Anti-inflammatory and antioxidant effects, reducing AP severity	Liu et al [56]
Docosahexaenoic acid	Inhibits JAK2/STAT3 pathway at low concentrations; activates PKC at high concentrations	Protective at low concentrations; exacerbates AP at high concentrations	Jeong et al [57]
Lactic acid	Lowers macrophage and neutrophil activity via TLR4/MyD88 and NLRP3/caspase-1 pathways	Reduces inflammation, ameliorating AP	Li et al [58]

Abbreviations: Akt, protein kinase B; AP, acute pancreatitis; JAK2, Janus kinase 2; IL-6, interleukin-6; MyD88, myeloid differentiation primary response 88; NAD, nicotinamide adenine dinucleotide; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NLR family pyrin domain containing 3; Orai1, calcium-release-activated calcium channel protein 1; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; PRDX5, peroxiredoxin 5; SIRT3, sirtuin 3; Sp1, specificity protein 1; STAT3, signal transducer and activator of transcription 3; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor alpha; VDR, vitamin D receptor.

tissues and organs, thereby initiating or exacerbating disease progression [47]. Intestinal barrier dysfunction is a key prerequisite for bacterial translocation, and the migration of intestinal bacteria to the pancreas can aggravate AP severity. Further investigation of the mechanisms underlying intestinal barrier disruption in AP is essential to prevent disease progression.

Roles of Microbial Metabolites

The impacts of the gut microbiota on AP are not limited to bacterial translocation; microbial metabolites also play critical roles (**Table 1**). In recent years, the relationship between metabolites and disease has received increasing attention, with evidence linking microbial metabolites to inflammatory responses across various conditions, including pancreatitis [48]. Intestinal microbial metabolites—such as short-chain fatty acids, bile acids, vitamins, hydrogen sulfide, and alcohol—affect AP progression through multiple mechanisms [49].

Butyrate, a short-chain fatty acid, significantly inhibits the interaction of histone deacetylase 1 with activator protein 1 (AP1) and signal transducer and activator of transcription (STAT)1, thereby suppressing activation of the NLRP3 inflammasome and reducing mortality in SAP. It also promotes the generation of $Foxp3^+$ regulatory T cells, which prevent inappropriate innate and adaptive immune responses and help maintain intestinal homeostasis, thus reducing gut barrier damage in AP [50,51].

Vitamin D exhibits a dual role. At moderate levels, it may protect the intestinal barrier in SAP. The epithelial vitamin D receptor can directly interact with inhibitor of nuclear factor kappa B kinase subunit beta (IKKβ) to inhibit NF-κB activation and downregulate p53 upregulated modulator of apoptosis (PUMA), thus reducing apoptosis in intestinal epithelial cells, preserving barrier integrity, and decreasing bacterial translocation; these effects ultimately alleviate AP severity [52]. However, excessive vitamin D can exacerbate AP [53]. Bile acids and alcohol can activate calcium-release-activated calcium channel protein 1 (Orai1), leading to sustained intracellular Ca^{2+} overload in acinar cells. Such overload disrupts ductal cell secretion and increases pancreatic ductal cell necrosis, thereby worsening AP [54].

In a mouse model, hydrogen sulfide (H_2S) signaling has been shown to modulate AP progression. Quantitative polymerase

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chain reaction, western blotting, and immunohistochemical analyses demonstrated that H_2S activates K_ATP channels, leading to membrane hyperpolarization and inactivation of voltage-dependent L-type Ca^{2+} channels, thus reducing intracellular Ca^{2+} levels and inducing smooth muscle relaxation. H_2S also inhibits intestinal motility, increases the secretion of TNF-α and IL-6, and elevates levels of cystathionine-γ-lyase and cystathionine-β-synthase. These effects promote inflammation in AP via the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/specificity protein 1 (Sp1) signaling pathway [55].

Nicotinamide adenine dinucleotide (NAD) is a key redox cofactor in microorganisms. Its metabolite, nicotinamide mononucleotide, increases pancreatic NAD levels, thereby attenuating AP-induced mitochondrial dysfunction, oxidative stress, and inflammation. During AP, nicotinamide mononucleotide metabolism activates the sirtuin 3 (SIRT3)-peroxiredoxin 5 (PRDX5) pathway. The NAD-dependent mitochondrial deacetylase SIRT3 deacetylates PRDX5, enhancing its expression and antioxidant capacity, which contributes to reduced inflammation and disease severity in AP [56].

Jeong et al [57] reported that docosahexaenoic acid (DHA), an omega-3 polyunsaturated fatty acid, may reduce AP severity by inhibiting the Janus kinase (JAK)2/STAT3 inflammatory signaling pathway in pancreatic tissues. However, high concentrations of DHA can activate protein kinase C (PKC-α, PKC-δ, PKC-ε, and PKC-ζ) and promote zymogen activation in pancreatic acinar cells, resulting in pancreatic injury and exacerbation of AP.

In patients with AP, the abundance of *Bifidobacterium* is reduced, accompanied by decreased levels of its metabolite, lactate. Reduced lactate availability affects TLR4/MyD88- and NLRP3/caspase-1-dependent pathways, diminishing its inhibitory effects on macrophages and neutrophils and thus contributing to disease progression [58]. Other microbial metabolites have also been shown to strongly influence AP.

Overall, intestinal microbial metabolites act as key mediators of the interaction between the gut microbiota and the pancreas; they represent important components of the gut-pancreas axis. Through advances in biological research, their mechanisms of action are expected to be further clarified, providing new insights into the role of intestinal microorganisms in AP.

Regulation of the Gut Microbial-Metabolic-Immune Axis

Gut microbes and their metabolites can either promote or mitigate AP by modulating immune responses (**Figure 2**). Gut microbiota dysbiosis disrupts intestinal immune homeostasis and contributes to inflammatory processes and disease progression [59].

Differences in microbial composition are recognized by pattern recognition receptors on innate immune cells, which distinguish between beneficial and harmful bacteria by detecting pathogen-associated molecular patterns (eg, bacterial endotoxins and LPS) [60]. The release of pathogen-associated molecular patterns activates both local innate and adaptive immune responses, amplifying inflammation in AP [61]. TLRs, key mediators of innate immune activation, play critical roles in regulating inflammation. A retrospective study showed that TLR2, TLR4, and TLR9 are significantly upregulated in AP. TLR2, typically associated with recognition of gram-positive bacteria, signals through MyD88-dependent pathways to induce proinflammatory responses. Endogenous ligands such as heat shock proteins, released during necrotic cell death, can interact with CD14/TLR2 and stimulate the production of inflammatory cytokines, particularly TNF-α. TLR4 recognizes bacterial LPS and pancreatic elastase, activates NF-κB signaling, and induces TNF-α secretion, which is strongly associated with systemic inflammatory response syndrome [62].

Pancreatic injury leads to the release of key TLR4 ligands, including high-mobility group box 1 (HMGB1) and heat shock proteins, which stimulate local inflammation in alveolar and endothelial tissues and promote the production of inflammatory mediators. These processes increase the infiltration and activation of innate immune cells, further exacerbating AP [63]. Experimental studies involving Paneth cells and TLR signaling in mice have shown that ablation of Paneth cells worsens AP. The abundance of *Lactobacillus* is positively correlated with Paneth cell numbers, and anti-inflammatory *Lactobacillus* species are significantly reduced after TLR4 knockdown [64-66]. Collectively, these findings suggest that intestinal TLR4 deficiency can impair Paneth cell function through alterations in *Lactobacillus*, thereby exacerbating AP.

The immunomodulatory function of T cells also plays a critical role in AP. Prophylactic T cell depletion has been shown to stabilize the intestinal immune barrier, reduce Th17 cell and $CD8^+/\gamma\delta$ T cell receptor intraepithelial lymphocyte activity, and decrease bacterial translocation to the pancreas, thus attenuating disease severity [67]. Intestinal bacteria and their metabolites can activate nucleotide-binding oligomerization domain 1 (NOD1) and promote the expression of NF-κB and type I interferons in pancreatic acinar cells. NF-κB activation stimulates the release of cytokines and chemokines and promotes the recruitment of monocytes and neutrophils to injured pancreatic tissue, leading to a "cytokine storm" that exacerbates AP [68-70]. Through Amuc_1100 intervention in mice and 16S rRNA sequencing of intestinal contents, Wang et al demonstrated that Amuc_1100—a membrane protein derived from the

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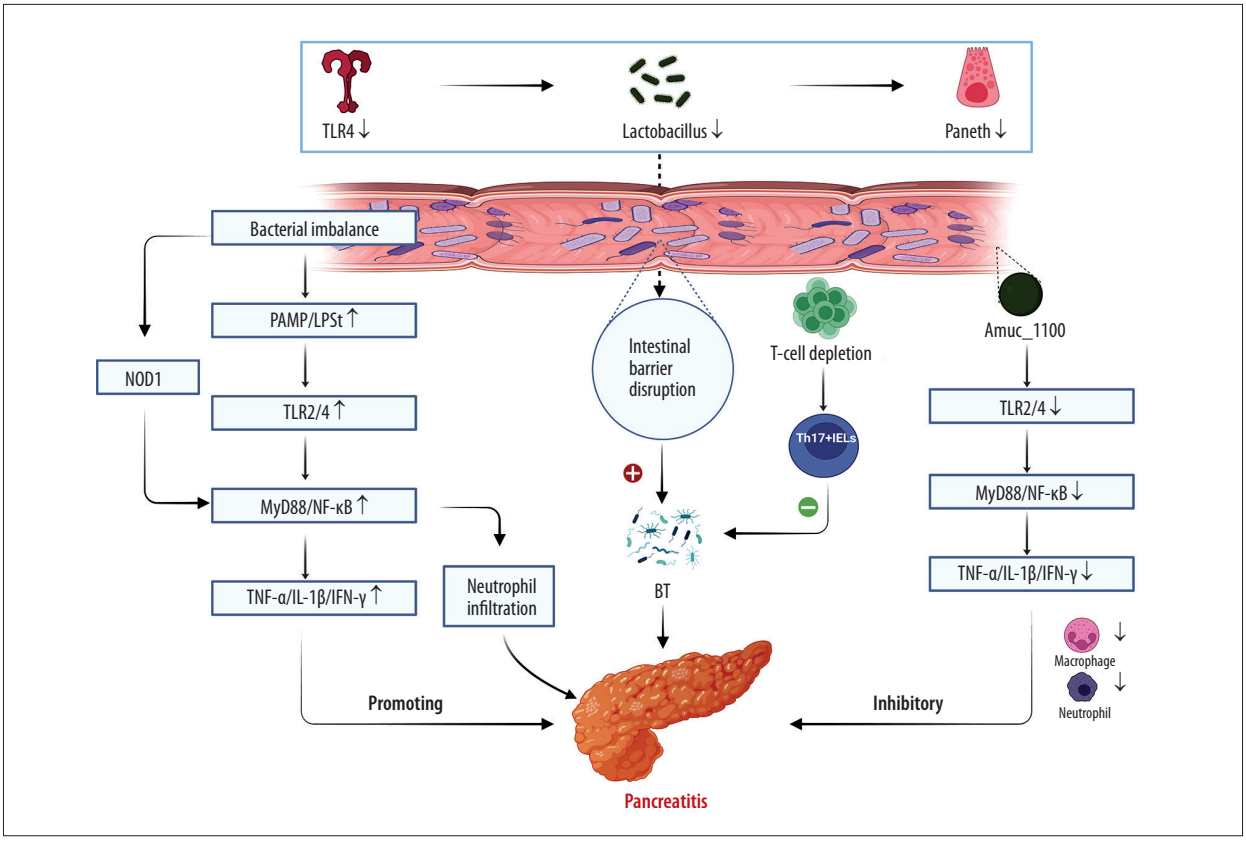

Figure 2. The gut microbial-metabolic-immune axis in acute pancreatitis. This schematic summarizes how gut microbiota dysbiosis influences the severity of acute pancreatitis through immune and metabolic pathways. Intestinal dysbiosis leads to the release of pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide (LPS). These PAMPs activate Toll-like receptors (TLR2 and TLR4) on immune and epithelial cells, triggering the myeloid differentiation primary response 88 (MyD88)/nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway and promoting a proinflammatory response. Disrupted microbial metabolites can also activate nucleotide-binding oligomerization domain 1 (NOD1), further enhancing NF-κB activation and neutrophil infiltration, thereby exacerbating acute pancreatitis. In contrast, under physiological conditions, beneficial metabolites such as butyrate and microbial-derived proteins (eg, Amuc_1100) inhibit NF-κB signaling and attenuate inflammation. A reduction in regulatory T cells can destabilize the intestinal immune barrier, promoting bacterial translocation (BT) and worsening disease severity. This complex interplay highlights the central role of the gut microbiota in modulating both local intestinal and systemic inflammatory responses during acute pancreatitis.

mucin-degrading bacterium *Akkermansia muciniphila*—plays an important role in maintaining host immune homeostasis in the gastrointestinal tract through TLR2 and TLR4 activation. During AP, Amuc_1100 strongly inhibits the expression of pancreatic proinflammatory cytokines (TNF-α, IL-1β, interferon-γ, and IL-6) by suppressing NF-κB signaling and reduces Ly6C$^+$ macrophage and neutrophil infiltration, thus exerting anti-inflammatory effects and mitigating disease severity [71].

Therapeutic Strategies Targeting Gut Microecology

Based on the relationship between intestinal microecology and pancreatitis, current therapeutic strategies focus on restoring microbial balance and supplementing beneficial metabolites. These approaches include probiotics, antibiotics, fecal microbiota transplantation (FMT), traditional Chinese medicine, metagenomics- and metabolomics-guided interventions, and targeted modulation of specific microbial communities. Such strategies aim to restore a favorable microbial composition by increasing beneficial taxa and suppressing pathogenic bacteria. Additionally, supplementation of specific metabolites may help restore intestinal barrier function and reduce bacterial translocation, preventing progression of pancreatitis.

Probiotics are similar to naturally occurring beneficial bacteria in the human gut. Extensive research has focused on probiotics such as *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces cerevisiae*, which may delay the progression of AP by maintaining intestinal immune homeostasis through direct interactions with immune cells [72]. Notably, a meta-analysis indicated that

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combined probiotic therapy shortened hospital stay and did not significantly increase mortality in patients with SAP; nevertheless, it did not significantly reduce the risk of organ failure [73]. Further studies are needed to confirm the efficacy of probiotics in AP treatment. Numerous studies have demonstrated that antibiotics substantially affect the composition and function of the gut microbiota [74]. A controlled study showed that prophylactic antibiotic therapy significantly reduced mortality from sepsis, pancreatic infection, and SAP during pancreatitis [75]. Among patients with necrotizing pancreatitis, the antibiotic-naive group exhibited more infectious complications and higher mortality rates [76]. However, these benefits were primarily observed in patients with infected pancreatic necrosis. Routine use of antibiotics in AP management may disrupt intestinal microecology, reduce colonization resistance, and increase risks of pathogen overgrowth and bacterial translocation [77]. FMT, enteral nutrition, traditional Chinese medicine, and approaches based on metagenomics and metabolomics, as well as targeted modulation of specific microbial communities, have been explored to regulate intestinal microecology and reduce inflammatory markers and organ failure rates in patients with AP. Thus far, most of these strategies remain at the preclinical stage, and evidence is primarily derived from animal studies. Their safety and efficacy require further validation in well-designed clinical trials.

Probiotics and Prebiotics

Probiotics have been used as adjunctive therapy for various gastrointestinal disorders, but their efficacy in AP remains inconsistent. In a study using control, placebo, and probiotic-treated mouse groups, van Minnen et al [78] demonstrated that probiotics reduced the overgrowth of potential pathogens. Microbiological analyses and real-time quantitative polymerase chain reaction showed decreased bacterial translocation outside the gut, including to the pancreas. Probiotics are live microorganisms, most commonly *Lactobacillus* and *Bifidobacterium*, which help maintain intestinal microbial balance, neutralize toxins, and inhibit pathogenic bacteria [79]. However, concerns have been noted about randomized controlled trials in which prophylactic probiotic use increased the risks of intestinal ischemia and mortality in patients with SAP [80]. Probiotic supplementation has been shown to increase colonic occludin expression, reduce intestinal permeability, decrease mucosal ischemia and reactive oxygen species production, and ultimately inhibit bacterial translocation [81]. Additionally, probiotics may attenuate oxidative damage in the pancreas, reduce AP-induced NF-κB activation and lipid peroxidation, and enhance glutathione biosynthesis, thus protecting the intestinal barrier, reducing inflammation, and mitigating cellular injury [82]. Chitosan oligosaccharide, a natural polymer used for probiotic encapsulation, has been shown to inhibit the production of proinflammatory cytokines in the pancreas and ileum, reduce inflammatory infiltration and oxidative stress, and modulate multiple signaling pathways. Its effects include activation of the nuclear-factor-erythroid-2-related factor 2/heme oxygenase-1 (Nrf2/HO-1) pathway and inhibition of the TLR4/NF-κB and MAPK pathways. Chitosan oligosaccharide also promotes the growth of beneficial mucin-degrading *Akkermansia* while reducing harmful *E. coli* and *Enterococcus*, thereby restoring intestinal microbial homeostasis [83]. In mouse models, probiotic administration significantly reduced serum amylase levels; mixed-strain formulations showed greater effects. Combined use of probiotics and antibiotics was more effective than either treatment alone [84]. However, another study indicated that a multi-strain probiotic preparation containing *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus salivarius*, *Lactobacillus lactis*, *Bifidobacterium bifidum*, and *Bifidobacterium lactis* did not significantly affect amylase levels in mice [85]. These inconsistencies may be related to differences in probiotic composition. Overall, the role of probiotics in pancreatitis remains controversial; further studies are needed to clarify their mechanisms and therapeutic potential in AP.

Antibiotic Therapy

Patients with AP often improve with supportive care; however, the incidence of concurrent infections remains substantial. Bacterial infections cause the majority of deaths in patients with SAP; the role of antibiotics in reducing infection-related morbidity and mortality, as well as their prophylactic use, remains controversial.

In pancreatic and extrapancreatic infections associated with AP, *E. coli* and *Klebsiella pneumoniae* are the most common pathogens, and antimicrobial resistance frequently develops [86]. When pathogens are not identified, empiric antibiotic therapy should provide coverage against aerobic and anaerobic gram-negative and gram-positive organisms. The possibility of fungal infection should also be considered, particularly in patients with multiple risk factors for invasive candidiasis [87]. A meta-analysis showed that systemic antibiotics (eg, norfloxacin and metronidazole) and rifaximin (a non-systemic antibiotic) are effective and well tolerated for the treatment of small intestinal bacterial overgrowth, with the goal of restoring intestinal microbial balance by reducing bacterial overgrowth in the small intestine [88,89].

One study demonstrated that early treatment with carbapenems in patients with biliary SAP, or early treatment with quinolones combined with metronidazole in biliary mild acute pancreatitis (MAP), reduced hospital stay and in-hospital mortality. However, these benefits were not statistically significant in patients with non-biliary AP [90]. In experimental studies,

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the combination of vancomycin, neomycin, and polymyxin B inhibited activation of the colonic TLR4/NLRP3 inflammasome pathway and downregulated NLRP3 expression. These effects were associated with decreased levels of proinflammatory cytokines (IL-1β, IL-6, monocyte chemoattractant protein [MCP]-1), increased expression of tight junction proteins (occludin, claudin-1, and ZO-1), and enhanced intestinal barrier integrity, leading to reduced bacterial translocation and preventing progression to severe disease [9]. Given the risk of antimicrobial resistance, the timing and selection of antibiotic therapy require careful consideration. Routine early use of broad-spectrum antibiotics is not recommended in AP. Instead, narrow-spectrum agents targeting specific pancreatic or intestinal pathogens should be used when appropriate; differences in efficacy across pancreatitis etiologies should be considered. Inappropriate antibiotic use should also be minimized, and procalcitonin, rather than white blood cell count or C-reactive protein, should be used to guide clinical decision-making [91].

Fecal Microbiota Transplantation

FMT is a therapeutic strategy that remodels the intestinal microbiota by transferring fecal material from a healthy donor into the patient's gastrointestinal tract [92]. Current indications for FMT primarily include intestinal disorders (eg, inflammatory bowel disease, *Clostridioides difficile* infection, and irritable bowel syndrome) [93-96], as well as hepatic encephalopathy [97]; its utility in pancreatitis has not been fully explored. A randomized controlled trial demonstrated that FMT enhances bile acid metabolism by the intestinal microbiota. Specifically, *Bacteroides ovatus* and *Phocaeicola dorei* were associated with unconjugated bile acids, whereas *Bifidobacterium adolescentis*, *Collinsella aerofaciens*, and *Faecalibacterium prausnitzii* were associated with secondary bile acids. Because bile acids are important components of intestinal barrier function, enhanced bile acid metabolism after FMT may help protect the intestinal barrier and reduce bacterial translocation [98]. Short-chain fatty acids, particularly butyrate, have been shown to play a critical role in inhibiting AP progression. Chen et al reported that fecal microbiota enriched in short-chain fatty acids, including butyrate, can be transplanted to treat certain diseases via suppression of inflammatory pathways. Thus, transplantation of short-chain fatty acid-enriched microbiota or supplementation with butyrate may represent a therapeutic approach for pancreatitis [99].

Mao et al [100] used 16S rRNA sequencing to analyze fecal samples from healthy controls and patients receiving FMT; they found that FMT significantly increased the abundance of *Bifidobacterium longum* in patients with SAP. This increased abundance was associated with significant improvements in clinical parameters, including leukocyte count, C-reactive protein, neutrophil count, lactate dehydrogenase, and procalcitonin levels, as well as a reduced rate of organ failure in the FMT group. In a mouse model, FMT attenuated AP progression by increasing plasma nicotinamide mononucleotide levels, activating SIRT3, improving mitochondrial function, and modulating reactive oxygen species levels [56]. Overall, the efficacy and safety of FMT in pancreatitis have been supported by multiple studies; however, most evidence is derived from preclinical research, including animal models. Variability in therapeutic outcomes appears to be related to differences in FMT protocols, highlighting the importance of "targeted transplantation"—the selection of beneficial microbial strains. Although the application of FMT in pancreatitis remains at an early stage, its potential to restore microbial balance, suppress infection and inflammation, and improve metabolic dysfunction is promising. Further well-designed clinical studies are required to determine its efficacy, safety, and appropriate patient populations, and to establish FMT as a potential therapeutic strategy for pancreatitis.

Enteral Nutrition

Enteral nutrition—a widely used and effective therapy in clinical practice for inflammatory bowel disease—has been shown to benefit patients with AP. Early enteral nutrition helps maintain intestinal function, reduce pancreatic stimulation, promote nutrient absorption, and support immune function, thereby lowering the risk of bacterial translocation and infection-related complications [101]. This protective effect is partly mediated by active components such as glutamine, arginine, and n-3 fatty acids, which help regulate the intestinal microbiota and maintain mucosal barrier homeostasis [102]. Enteral nutrition provides a continuous supply of nutrients, including glutamine and short-chain fatty acids, to the intestinal mucosa. These nutrients directly support epithelial and goblet cells, preserve villus height, and regulate the expression of tight junction proteins (occludin, claudin, and ZO-1), enhancing barrier integrity and reducing bacterial translocation [103]. Additionally, enteral nutrition supplies dietary fiber and prebiotics that are fermented by commensal bacteria into short-chain fatty acids (eg, butyrate and propionate), which lower intestinal pH and inhibit the colonization of pathogenic bacteria such as *E. coli*, *Klebsiella*, and *C. difficile* [104]. Furthermore, enteral feeding via a nasojejunal tube can improve outcomes in patients with severe pancreatitis, even when initiated later in the disease course [105]. A fiber-rich diet can reduce systemic inflammatory responses in severe AP by reshaping the gut microbiota, increasing short-chain fatty acid levels (eg, butyrate), inhibiting histone deacetylase 3, and restoring intestinal barrier function [106]. Moreover, pectin-rich nutritional supplements can improve intestinal barrier function, increase beneficial bacteria, reduce harmful bacteria, and thus modulate microbial

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composition [107,108]. In summary, enteral nutrition—particularly when initiated early and combined with probiotic formulations—can regulate the intestinal microbiota, protect the intestinal barrier, and reduce bacterial translocation, thereby improving clinical outcomes in patients with AP.

Traditional Chinese Medicine

At present, the use of traditional Chinese medicine in the clinical management of AP has gained increasing attention. Therapeutic approaches, including oral administration and enema, have demonstrated some efficacy; however, the underlying mechanisms remain unclear. A mouse study showed that Qingyi Decoction can modulate intestinal microbiota composition by increasing the abundances of short-chain fatty acid-producing genera and reducing pathogenic bacteria. It also activates the adenosine monophosphate–activated protein kinase (AMPK)/NF-κB/NLRP3 signaling pathway to attenuate inflammation in acute lung injury associated with SAP. Additionally, Qingyi Decoction regulates short-chain fatty acid levels, such as propionate and butyrate, via the gut-lung axis, restores intestinal barrier function, and reduces bacterial translocation [109].

Another study using a mouse model demonstrated that treatment with Chaihuang Qingyi Granules significantly reduced serum amylase, lipase, and endotoxin levels in SAP. It also alleviated pathological damage in the pancreas and colon and restored the expression of tight junction proteins, including ZO-1. Furthermore, this intervention improved intestinal dysbiosis, restoring microbial diversity and community structure. At the phylum level, the relative abundance of Firmicutes increased, whereas that of Proteobacteria decreased. At the genus level, the abundances of *Ruminococcus*, *Paracoccus*, *Prevotellaceae* UCG-001, NK4A136 group, and *Lactobacillus* increased, whereas those of *Escherichia*, *Enterococcus*, and *Enterobacter* decreased. These changes were associated with increased short-chain fatty acid levels in the intestinal contents and improvement in disease severity [110].

Polysaccharides derived from *Ganoderma lucidum* strain S3 (GLP-S3) alleviated pancreatitis in mice by reducing levels of lipase, amylase, interferon-γ, and TNF-α, while increasing superoxide dismutase activity and total antioxidant capacity. High-throughput sequencing analysis showed that GLP-S3 altered the composition and diversity of the gut microbiota, decreasing the relative abundances of certain bacterial phyla and increasing beneficial taxa. At the genus level, GLP-S3 increased the abundances of beneficial bacteria, including *Lactobacillus*. These findings suggest that GLP-S3 improves pancreatitis outcomes via modulation of intestinal microbiota [111].

A randomized controlled trial comparing a conventional treatment group with a Dachengqi Tang treatment group showed that time to first defecation and recovery of bowel sounds were significantly shorter in patients receiving Dachengqi Tang. Microbiome diversity analysis demonstrated higher microbial diversity and abundance in the Dachengqi Tang group. Linear discriminant analysis effect size (LEfSe) assessment revealed decreased relative abundances of *E. coli-Shigella* and *Clostridium erythrophilum*, along with increased abundances of beneficial bacteria, including *Lactobacillus*. In particular, *Lactobacillus mucosus* and *Lactobacillus conjunctivus* were significantly enriched in patients with MAP. These findings suggest that Dachengqi Tang reduces inflammation in MAP by modulating gut microbiota composition and promoting restoration of intestinal microecological balance and gastrointestinal function [112].

Overall, traditional Chinese medicine can regulate the gut microbiota and may contribute to the treatment of pancreatitis; however, its mechanisms of action remain unclear. Further studies regarding traditional Chinese medicine and its bioactive components are needed to provide new insights into AP management.

Metagenomics and Metabolomics

Metagenomic technologies have revealed potential clinical applications in AP by integrating analyses of the gut microbiota and associated metabolites. A study combining metagenomics and untargeted metabolomics identified systemic alterations in microbial and metabolic profiles during AP; the results indicated that expression of the *cysK* gene was associated with bufalin metabolites, suggesting that targeting microbiota-metabolite interactions can offer novel therapeutic approaches [113]. Additionally, high-throughput sequencing has been used to characterize changes in intestinal microecology. The dominant microorganisms in patients with MAP, moderately SAP, and SAP were *Streptococcus*, *E. coli*, and *Enterococcus*, respectively; these patterns significantly differed from findings in healthy individuals. Functional pathway analysis indicated that such microbial changes were associated with amino acid metabolism, glutathione metabolism, lipopolysaccharide biosynthesis, and the degradation of branched-chain amino acids (valine, leucine, and isoleucine), providing potential targets for microbiota-based therapeutic strategies [114].

The combined use of 16S rRNA gene sequencing and liquid-chromatography-mass-spectrometry-based metabolomics enables comprehensive analysis of intestinal microbial communities and their metabolites. These approaches may facilitate targeted interventions to modulate microbial composition and metabolite levels, thereby improving the intestinal environment

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in patients with AP [115]. However, metagenomic next-generation sequencing remains primarily a research tool, and its clinical application faces multiple challenges. Further methodological refinement and validation are required to support large-scale, multicenter studies.

Future Directions

As understanding of the role of the gut microbiota in pancreatitis advances, the range of potential therapeutic strategies continues to expand. However, no microbiota-targeted therapy is currently established for routine clinical use. Increasing evidence suggests that modulation of the intestinal microbiota can improve disease progression, and targeted microbiome interventions represent a promising direction for future treatment. Furthermore, specific microbial signatures may serve as predictive biomarkers for AP severity and prognosis. Nevertheless, most current evidence is derived from retrospective analyses and animal studies. Large-scale prospective studies and well-designed clinical trials are needed to validate the safety and efficacy of microbiome-based therapies. Although high-throughput sequencing technologies can identify differences in microbial composition between disease states and healthy conditions, establishment of causal relationships remains challenging. Future research should integrate multi-omics approaches, including metagenomics, transcriptomics, and metabolomics, to elucidate the molecular mechanisms that underlie host-microbiota interactions. The development of predictive models and application of microbial biomarkers in personalized therapy will be critical next steps.

Conclusions

This review enhances understanding of the bidirectional relationship between the gut microbiota and pancreatitis. Distinct microbial profiles are associated with different etiologies of pancreatitis. The gut microbiota influences AP progression through mechanisms including intestinal barrier disruption, bacterial-translocation-mediated secondary infection, reduced production of beneficial microbial metabolites, and dysregulated immune responses. Accordingly, microbiota-targeted therapies—such as probiotics, prebiotics, antibiotics, FMT, enteral nutrition, and traditional Chinese medicine—are under investigation. Advances in metagenomics and metabolomics have further expanded therapeutic possibilities. However, the field remains at an early stage, highlighting the need for large-scale, well-designed prospective clinical studies to enable clinical translation.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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