International Journal of General Medicine

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

# Gut Microbiota Metabolites Targeting the Immune Response in Sepsis: Mechanisms and Therapies

Peng Xu

Emergency Department, The Second Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou, People's Republic of China

Correspondence: Peng Xu, Emergency Department, The Second Affiliated Hospital of Zunyi Medical University, Interchange of Xinlong Avenue and Xinpu Avenue, Xinpu New District, Zunyi, Guizhou, 563006, People's Republic of China, Email xupeng140704@163.com

**Abstract:** Sepsis is a global health challenge, affecting millions annually and remaining a leading cause of mortality in intensive care units. Gut microbiota plays a complex role in the onset and progression of sepsis, with its alterations reflecting disease severity. Recently, modulating gut microbiota and its metabolites has emerged as a promising therapeutic strategy for sepsis. This review highlights the role of gut microbiota in sepsis and systematically identifies key immune response targets directly influenced by gut microbiota metabolites, such as short-chain fatty acids (SCFAs), bile acids, and indoleacetic acid, among other important metabolites. Additionally, it offers a full overview of current research on gut microbiota-regulated therapeutic approaches, including fecal microbiota transplantation (FMT) and artificial intelligence (AI) applications. These insights offer a novel perspective for advancing the understanding of sepsis pathogenesis and its treatment.

**Keywords:** sepsis, gut microbiota, metabolites, immune response, direct targets, therapeutic strategies

## Introduction

Sepsis, a life-threatening syndrome of organ dysfunction, poses a significant challenge in the field of critical care medicine worldwide. According to statistics, there were 189 hospitalized sepsis cases per 100,000 people annually, with 58 requiring intensive care unit admission due to severe conditions.[1] The mortality rate of sepsis is 10% to 20%, and for septic shock, a subtype of sepsis, the mortality rate is 40% to 50%.[2] Despite advancements in early diagnosis and treatment of sepsis, such as antimicrobial therapy, fluid resuscitation, vasopressor support, and organ function support, the prognosis remains poor. Coagulase-negative staphylococci account for a significant proportion of early-onset sepsis cases, exhibiting 86% to penicillin resistance in recent retrospective analyses.[3]

The gut microbiota, often referred to as the "second genome" of the human body, plays a crucial role in maintaining immune homeostasis and health.[4,5] Through the metabolism of dietary components and host-derived substances, gut microbiota produce various metabolites that not only affect the local intestinal environment but also influence systemic organs through the bloodstream.[6] Studies indicate that metabolites from the gut microbiota, such as short-chain fatty acids, bile acids, and tryptophan metabolites, may have potential protective effects in sepsis.[7]

Imbalances in the gut microbiota, characterized by reduced diversity, decreased commensal bacteria, and overgrowth of pathogenic bacteria, not only serve as triggering factors for sepsis but also exacerbate disease progression.[8] Conversely, the occurrence of sepsis can disrupt the balance of the gut microbiota, thereby worsening the severity of the condition.[9] While the association between gut microbiota and the development of sepsis is compelling, our understanding in this field remains largely indirect and speculative, with the exact mechanisms yet to be fully elucidated.[10] Furthermore, effective and mature treatments for sepsis are still lacking. Therapeutic strategies based on modulating the gut microbiota, such as FMT, selective digestive decontamination (SDD), and probiotics, face challenges in clinical application.[8] Although FMT has potential therapeutic effects, it may cause adverse events such as abdominal pain and infection. The complexity of its operation (such as donor screening and maintaining an anaerobic environment) also limits its clinical application. Studies have found that FMT can lead to varying degrees of adverse events (including

Received: 8 May 2025
Accepted: 5 August 2025
Published: 25 August 2025

International Journal of General Medicine 2025:18 4709–4734

severe infections), and strict control of donor microbiota safety and operational conditions is necessary to avoid unpredictable risks.[11,12] SDD has an unclear effect on reducing mortality in sepsis patients, and it may induce the colonization of antibiotic-resistant bacteria.[13] A randomized clinical trial by the Australian and New Zealand Intensive Care Society showed that SDD did not significantly reduce the in-hospital mortality rate in critically ill patients with mechanical ventilation, and there was a potential risk of promoting the emergence of drug-resistant strains.[14] The efficacy of probiotics, prebiotics, and synbiotics is controversial. Some studies have shown that they can improve immunity and microbiota balance,[15,16] but multicenter trials have not confirmed their preventive effect on infections, and the use of probiotics by immunocompromised individuals may increase the risk of infection.[17]

Therefore, a deeper exploration of the role of gut microbiota in the onset and progression of sepsis, along with the identification of microbial metabolite targets that could effectively intervene in sepsis, holds promise for opening new avenues in sepsis treatment. This review summarizes the direct targets of gut microbiota metabolites on sepsis immune responses and explores related strategies in microbiota modulation for sepsis therapy, offering new insights and hope for improving patient outcomes.

## The Role of Gut Microbiota in the Development and Progression of Sepsis

The gut microbiota is an essential component in maintaining immune system balance and preventing systemic inflammation.[18] Under healthy conditions, the gut hosts a diverse community of beneficial, neutral, and potentially harmful bacteria, all of which contribute to overall homeostasis.[19,20] A Mendelian randomization study utilizing genetic variation as an instrumental variable has provided valuable insights into the causal relationship between the gut microbiota and sepsis. The results underscore the significant role that different microbial species play in the onset and progression of sepsis.[21] Certain microbes, such as *Lentisphaeria* species, demonstrate protective effects, while others, including *Clostridiaceae* (a family of *Clostridia*) and *Gordonibacter* species, have been shown to exert detrimental effects. As shown in Figure 1, disruptions in the composition, abundance, and relative proportions of these microbial communities are strongly associated with the development and worsening of sepsis.[9,22]

### Dysbiosis of the Gut Microbiota: An Important Risk Factor for the Development of Sepsis

As early as 1999, MacFie et al[23] began investigating the relationship between the gut and postoperative sepsis. Disruption or translocation of the relatively balanced microbial community in the proximal gut has become a significant source of infection in postoperative sepsis. The primary causes of gut microbiota imbalance include antibiotic use, improper dietary patterns, underlying diseases, aging, environmental factors, and more.[24]

Antibiotics, considered one of the greatest medical advancements of the 20th century, hold an irreplaceable position in controlling infectious systemic diseases, significantly reducing mortality rates and shortening hospital stays.[25] Unfortunately, antibiotics have been increasingly overused in the 21st century,[26–28] with the risk of resistance becoming increasingly prominent.[29] The empirical use of broad-spectrum antibiotics is a common clinical strategy for treating sepsis, but this approach exacerbates gut dysbiosis.[30] A study by Kuppala et al[31] found that among preterm infants without sepsis during the first week of life, prolonged (≥5 days) empiric antibiotic treatment was associated with an increased risk of late-onset sepsis and adverse outcomes, including mortality. Moreover, a retrospective analysis of hospitalized patients using hospital pharmacy databases assessed the relationship between specific antibiotics and the risk of developing sepsis after hospital discharge. By applying multivariable logistic regression models to control for potential confounders, the study examined the association between the use of specific antibiotics and the risk of sepsis after hospital discharge.[32] The analysis of single hospitalization records from randomly selected eligible patients across 516 hospitals revealed that 0.17% of patients developed sepsis within 90 days of discharge. Notably, patients who received antibiotics associated with microbial disruption during hospitalization had a 65% higher risk of developing sepsis compared to those who were not exposed to antimicrobial agents. This further supports the notion that gut dysbiosis is likely a contributing factor to the development of sepsis.

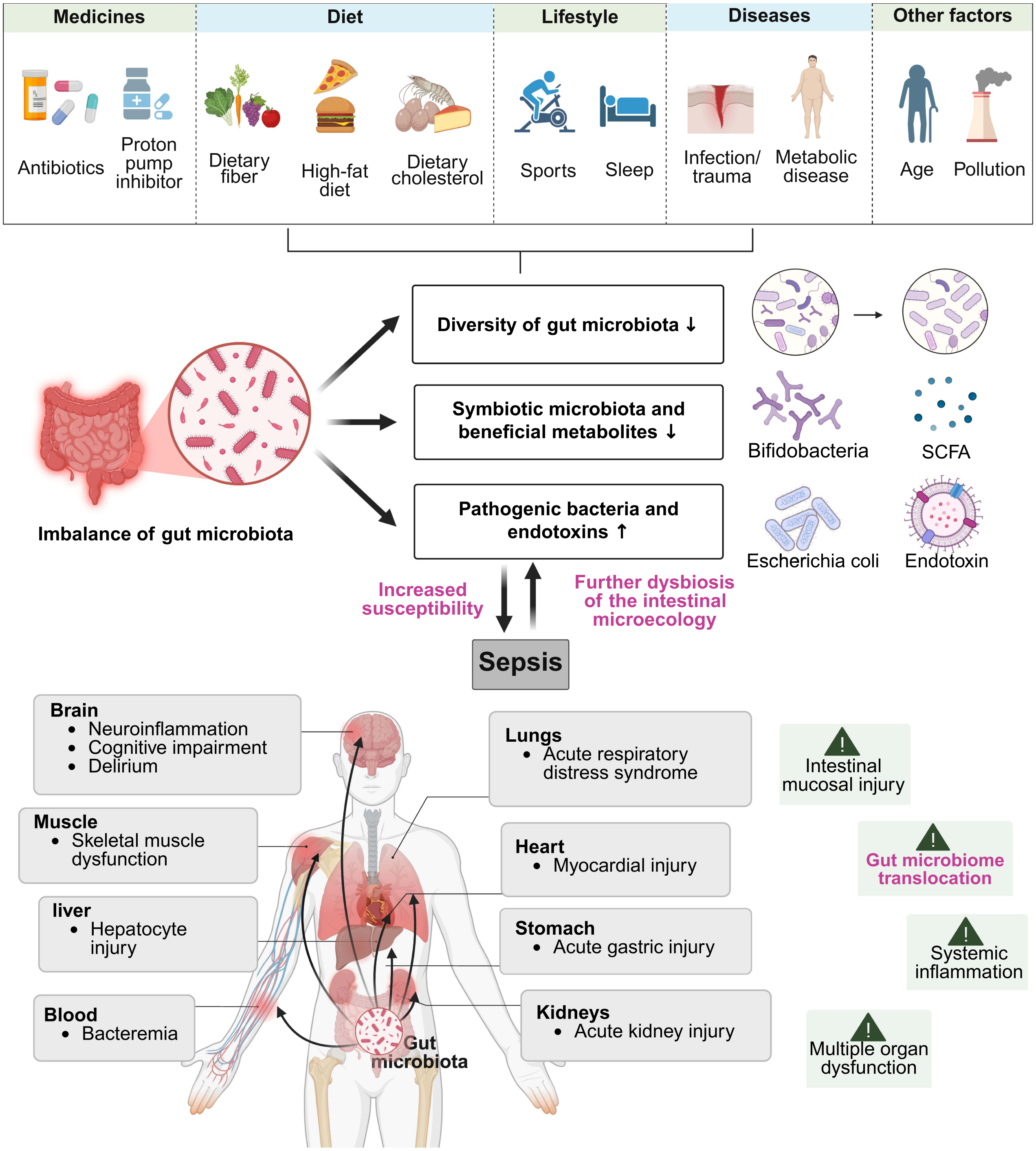

**Figure 1** Drugs, diet, lifestyle, disease, and environmental factors influence the composition of the gut microbiota. Reduced diversity of gut microbiota, decreased commensal bacteria, and overgrowth of pathogenic bacteria are important risk factors for the development of sepsis. Following the beginning of sepsis, worsened bacterial imbalance, intestinal mucosal injury, aberrant microbiota transfer, and the induction of inflammatory storms can all contribute to multiorgan dysfunction.

## Reduced Diversity of Gut Microbiota

A notable phenomenon observed in intensive care unit (ICU) patients is the dramatic decline in the diversity of their microbiomes, which often occurs even before pathogenic bacteria have entered the body.[33] When the diversity of the intestinal microbiota decreases, its ability to prevent the colonization of foreign microorganisms is compromised, thereby increasing the body's susceptibility to opportunistic pathogens that would otherwise remain harmless. Lankelma et al[34] conducted a study analyzing the fecal microbiomes of 34 ICU patients with sepsis and other critical conditions, as well as 15 healthy individuals. In these patients, 13 had gut microbiotas dominated by a single bacterial genus accounting for more than 50% of the microbiome, and 4 had more than 75% dominance, with half of the patients showing a significant decline in microbial diversity.

Some studies suggest that higher gut microbiota diversity is associated with a lower risk of sepsis. A prospective cohort study by Graspeuntner et al[35] involving more than 200 preterm infants found that when the gut microbiota of preterm infants was more diverse, the risk of developing sepsis was lower. Additionally, the colonization of anaerobic bacteria has been linked to the prevention of sepsis. Anaerobes can inhibit the growth and reproduction of harmful bacteria by competing for nutrients, producing antimicrobial substances, or modulating gut immunity, thus helping to maintain the stability of the gut microbiota and reducing the likelihood of sepsis in newborns. Similarly, Fay et al[36] demonstrated that the α-diversity of the gut microbiota was positively correlated with the resistance of mice to sepsis, meaning that higher α-diversity contributed to improved survival rates in sepsis. By altering the living environment of mice to allow them to share microbial communities, researchers were able to regulate the diversity of their gut microbiotas and, in turn, enhance their resistance to sepsis.

Compared with younger populations, sepsis in the elderly is characterized by difficulty in early identification, rapid disease progression, high mortality, and slow recovery.[37] With increasing age, certain changes occur in the composition and function of the intestinal microbiota,[38] and these differences become more pronounced in the context of sepsis. Compared with healthy elderly individuals, the intestinal microbiota of elderly sepsis patients shows a further reduction in diversity and evenness. A study on sepsis patients with a mean age of 64 years revealed significant differences in fecal bacterial composition between these patients and healthy individuals, with over half of the patients having only one bacterial genus in their feces.[34] Animal experiments have also confirmed this conclusion: the intestinal microbial diversity of elderly septic mice is significantly lower than that of adult septic mice, with more severe disruption of the microbiota structure, including an increase in the abundance of inflammation-related microbiota and a decrease in the abundance of microbiota associated with short-chain fatty acid production (such as *Mucispirillum* and *Bacteroides*).[39] Due to the presence of inflammatory responses and the potential use of antibiotics during treatment, elderly sepsis patients may experience a reduction in beneficial microbiota such as *Bifidobacterium* and *Lactobacillus*, along with an increase in potential drug-resistant pathogens such as *Enterococcaceae* and *Klebsiella*. These changes in intestinal microbiota diversity are closely associated with the pathogenesis and severity of sepsis.[40]

## Reduction of the Symbiotic Microbiota

In cases of reduced gut microbiota diversity, the abundance of symbiotic probiotics, such as *Bifidobacterium*, tends to decrease. Symbiotic microbial communities are an essential component of the gut microbiota ecosystem. Under certain conditions, symbiotic bacteria like *Coprococcus* may activate specific signaling pathways, promoting the synthesis and release of interleukin-1β (IL-1β) by immune cells such as macrophages and monocytes. On the other hand, this activation initiates and enhances the acute inflammatory response, which helps to clear pathogens.[41] Moreover, symbiotic microorganisms significantly influence the types, quantities, and functions of immunoglobulin A in serum. The immunoregulatory network formed by symbiotic microbes, serum immunoglobulin A, and T cells plays a protective role against bacterial infections that may lead to bacterial sepsis.[42] Some researchers have found that *Lactobacillus murinus*, a beneficial probiotic, has a positive effect in resisting *Klebsiella pneumoniae* invasion and colonization, helping to protect animals from infections and sepsis caused by *Klebsiella pneumoniae*.[43] These findings highlight the importance of symbiotic microorganisms in defending against bacterial sepsis.

*Bifidobacterium, Bacteroides*, and other bacteria produce beneficial metabolites, such as short-chain fatty acids (SCFAs).[44] SCFAs play a crucial role in regulating intestinal immunity, promoting gut barrier function, and maintaining the acid-base balance in the intestines, all of which are essential for gut health and microbiome stability.[45] When the abundance of SCFA-producing bacteria is insufficient, the risk of developing sepsis increases.[9] A prospective study showed that compared to full-term infants, preterm infants had lower abundances of *Bacteroides, Bifidobacterium*, and *Lactobacillus* in their gut microbiotas, a change that increased the risk of late-onset sepsis in preterm infants.[46] Mai et al[47] selected 10 preterm infants with late-onset sepsis as the case group and 18 matched control infants. They collected fecal samples and used the 16S rRNA method to compare microbiome diversity. They found that, in the two weeks prior to onset, the microbial species in late-onset sepsis preterm infants decreased, with a particularly low abundance of *Bifidobacterium*, which may be associated with the occurrence of late-onset sepsis. These findings support the aforementioned viewpoint. In another study, an increase in the abundance of *Megasphaera* species, which produce butyrate, may confer protective effects against sepsis, while a lower abundance of butyrate-producing bacteria could be a risk factor for sepsis.[48]

In the elderly population, butyrate-producing gut microbiota are significantly reduced. Through 16S rRNA sequencing, Yatsunenko et al found that the number of *Bifidobacteria* also decreases with age.[49] Such changes in the composition of gut microbiota directly affect the production of intestinal metabolites. Studies have shown that compared with younger populations, the concentrations of short-chain fatty acids (SCFAs, particularly acetate, butyrate, and propionate) in the intestines of the elderly are significantly lower. Additionally, as the main butyrate-producing microbiota, the number of *Firmicutes* also decreases with age.[38] This imbalance in the intestinal microecology reduces the gut's resistance to pathogens, making the elderly more susceptible to developing sepsis when faced with infections. Meanwhile, it may exacerbate intestinal damage and systemic inflammatory responses during the course of sepsis, forming a vicious cycle.

## Overgrowth of Pathogenic Bacteria

A decrease in the number of beneficial gut bacteria may promote the overgrowth of pathogenic bacteria.[50] Pathogenic bacterial overgrowth is a key feature of gut microbiota dysbiosis. An increase in microbiota dominated by *Bacillus* species and the accumulation of fermentation products have been linked to the occurrence of late-onset sepsis. Moreover, the colonization of *Streptococcus pyogenes*, a highly virulent pathogen, in the gut may be a contributing factor to the increased risk of late-onset sepsis.[35] A large retrospective cohort study involving 10,996 participants examined the relationship between three different types of hospitalization (non-infection-related hospitalization, infection-related hospitalization, and *Clostridium difficile* infection-related hospitalization) and the risk of developing severe sepsis within 90 days of discharge.[51] The results indicated that the reason for hospitalization was closely associated with the probability of developing severe sepsis. Infection-related hospitalization, particularly *Clostridium difficile* infection, significantly increased the risk of severe sepsis. Furthermore, the incidence of severe sepsis was 70% higher in patients hospitalized for *C. difficile* infection compared to those with other infection-related hospitalizations. These findings further emphasize the significant role of *C. difficile* infection in increasing the risk of sepsis, suggesting that prevention and treatment of *C. difficile* infections may be crucial in reducing sepsis incidence.

In septic patients, changes in the gut microbiota composition trigger a chain reaction, akin to a domino effect. Dysbiosis promotes damage to the intestinal mucosal barrier.[52,53] When the intestinal mucosal barrier is compromised, its dysfunction triggers pro-inflammatory responses, allowing pathogenic bacteria to traverse the intestinal wall and enter the bloodstream, causing infections.[54,55] In newborn mice treated with broad-spectrum antibiotics, the immune system was affected, making the mice more susceptible to sepsis when challenged with *Klebsiella pneumoniae* infection.[56] Similarly, in an experiment involving newborn mice,[43] *K. pneumoniae* was introduced into the gut, where it proliferated and later translocated from the gut to the bloodstream, leading to systemic infection and ultimately late-onset sepsis in the mice.

Certain pathogenic bacteria trigger the onset of sepsis by producing virulence factors. For example, Gram-negative bacteria produce lipopolysaccharides (LPS), some of which are potent endotoxins that damage host tissues and promote the spread of infection. A study analyzed over 100,000 extremely low birth weight infants over 14 years, identifying 1032 cases of early-onset sepsis and 12,204 cases of late-onset sepsis.[57] It was found that Gram-negative bacteria frequently caused early-onset sepsis, while Gram-positive bacteria were more commonly responsible for late-onset sepsis. Cernada et al[58] noted that, unlike Gram-negative bacterial infections, sepsis caused by Gram-positive bacteria generally results in a relatively milder inflammatory response and less tissue damage. To further explore the significant changes in the gut microbiota prior to late-onset sepsis, a study involving 753 premature infants analyzed fecal samples from 40 septic infants three days before the onset of clinical symptoms. The study found that these Gram-negative pathogens were already present in the intestines of the premature infants, whereas no such pathogens were detected in the control group of premature infants.[59] Over time, the population of Gram-negative bacteria continued to grow in the gut, potentially playing a critical role in the onset of sepsis. Among Gram-negative bacteria, *Pseudomonas aeruginosa* stands out as an opportunistic pathogen with a unique survival strategy in the host. It can adapt to the host's hostile environment by secreting various virulence factors, including LPS, outer membrane proteins, and flagella,[60] to enhance its survival.[61] Individuals with compromised immune function or underlying conditions, as well as those who use antibiotics or immunosuppressive drugs long-term, are more susceptible to *P. aeruginosa* infection and the development of sepsis.[8]

Studies on critically ill patients over 60 years of age have found that the abundance of pathogens such as *Escherichia-Shigella* (including various pathogenic bacteria) and *Hungatella* is significantly increased. This intestinal microecological imbalance, characterized by an increase in pathogenic bacteria, is accompanied by a higher incidence of sepsis and more severe conditions in elderly patients.[37] In addition, a research team suggests that the increased susceptibility to sepsis in the elderly is not solely due to host factors; it may also be related to the enhanced virulence of intestinal pathogens with advancing age. The team confirmed this view using two complementary models of experimental sepsis induced by intestinal microbiota.[62] A broader study involving patients aged 16–81 further verified that an imbalanced intestinal microbiota with an increase in pathogenic bacteria raises the risk of sepsis.[15] The clinical significance of these microbiota changes cannot be ignored. Rapid and accurate identification of harmful bacterial groups is crucial for sepsis patients, as it can facilitate the prompt initiation of appropriate treatment. For example, *Enterococcus faecium* detected in the urine culture during the initial diagnosis of a 69-year-old patient was not taken seriously, and sepsis developed subsequently.[63] *Enterococcus faecium* bacteremia may lead to sepsis in immunocompromised patients with a high mortality rate. Due to its non-specific manifestations, identification is quite challenging. Rapid and accurate identification of this bacterial infection, coupled with early administration of appropriate antibiotic therapy, is key to improving patient survival rates.

In summary, gut microbiota dysbiosis is a key factor in the development of sepsis. While the pathogenesis of sepsis is complex and multifactorial and remains not fully understood, numerous studies indicate that disruptions such as reduced gut microbiota diversity, decreased symbiotic bacteria, and excessive growth of pathogenic bacteria are significant contributors.[64] These disruptions increase the risk of sepsis by altering gut barriers and immune regulation.[30]

## Involvement of Gut Microbiota in the Development of Sepsis

The gut microbiota plays a crucial role in the progression of sepsis. From a negative perspective, when the gut microbiota becomes dysregulated, it can have a severely destructive effect on the course of sepsis.[50,65] Specifically, an imbalance between beneficial and harmful gut bacteria can impair the integrity of the intestinal barrier, thereby creating conditions for bacteria and their toxins to translocate into the bloodstream. This triggers a systemic inflammatory cascade, which not only exacerbates the severity of sepsis but also significantly increases the risk of multiple organ dysfunction.[66]

In contrast, beneficial metabolites derived from the gut microbiota demonstrate significant potential for improving sepsis outcomes. Take SCFAs, for example; they exert positive effects on multiple levels: locally within the gut, they strengthen the integrity of the intestinal barrier, forming the first line of defense against pathogen invasion; at the systemic level, they regulate immune responses, effectively suppressing excessive inflammation while promoting the release of anti-inflammatory cytokines, thus restoring immune homeostasis.[67] These mechanisms open new avenues for clinical treatment strategies in septic patients.

### Disruption of Sepsis by Disturbed Gut Microbiota

During sepsis, the gut's microecological environment, including pH and redox potential, undergoes changes, leading to a more pronounced imbalance in the gut microbiota and poorer sepsis prognosis. Sun et al[7] employed two approaches to investigate this issue. First, they analyzed fecal samples from septic patients and healthy controls to compare differences in gut microbiota between the two groups. Second, they used a cecal ligation and puncture mouse model for microbiome and transcriptome analysis, validating results previously obtained from human samples. The data revealed that during sepsis, the gut's previously stable and balanced microbial environment is disrupted, with an abnormal increase in *Enterococcus* species, which may play a role in the pathogenesis or progression of sepsis. The researchers also found a close correlation between high levels of *Bacteroides* species in the gut and the severity of sepsis. Other studies have reported significant disruption of the gut microbiota in septic patients. When feces from septic patients were transplanted into mice, the mice exhibited more severe liver inflammation and damage compared to the control group that received healthy feces. The primary pathological change in the septic mice was coagulopathy, which can lead to organ damage and is one of the main causes of death in septic patients.[68] In summary, gut microbiota composition is associated with complications and mortality.

Gut microbiota dysbiosis further deteriorates, not only with a continued decrease in beneficial bacteria but also with the overgrowth of antibiotic-resistant or opportunistic pathogens. These bacteria may produce more toxins and virulence factors, impacting the progression of sepsis. For instance, a reduction in strict anaerobes and an increase in pathogenic bacteria are associated with septic complications.[69] The decrease in strict anaerobes weakens the intestinal mucosal barrier, making it easier for pathogenic bacteria to translocate across the damaged gut barrier and enter the bloodstream, triggering systemic infection. The overgrowth of pathogenic bacteria leads to the production and release of large amounts of endotoxins, initiating an inflammatory cascade and increasing the risk of sepsis-related complications.[70] *Desulfovibrio* can degrade SCFAs and promote the production of more benzoic acid, acting as a pathogen that damages both the intestinal mucosa and the host. In a sepsis mouse model, the proliferation of *Desulfovibrio* may exacerbate acute gastrointestinal damage during sepsis.[71] Reports have also indicated that *Bacteroides* species can influence the development and severity of sepsis.[7] This is mainly due to *Bacteroides* species affecting the expression of numerous genes, thereby altering the physiological state and function of the gut. Moreover, Yu et al found that a diet high in methyl donors changes the gut microenvironment, reduces beneficial bacteria, and increases sepsis mortality. However, some studies suggest that although microbiome diversity is significant in many contexts, the reduction of gut microbiota diversity does not seem to be associated with mortality in sepsis patients.[34,72]

In 1966, Wolochow first introduced the term “bacterial translocation”,[73] defining it as the phenomenon in which resident bacteria in the gut pass through the mucosal epithelium into the lamina propria, and subsequently enter the mesenteric lymph nodes or even distant organs. In 1979, Berg et al[74] expanded this definition to include all phenomena in which microorganisms or their products cross the intestinal mucosal barrier. From the 1980s to the 1990s, numerous studies began to focus on the relationship between gut microbiota translocation and various diseases.[75,76] Research found that under pathological conditions such as trauma, burns, shock, and severe infections, the phenomenon of bacterial translocation becomes more pronounced and is closely associated with the development of multiple organ dysfunction syndrome (MODS).[77] For example, when gut-derived bacteria translocate to the brain in septic patients, they can cause cognitive dysfunction, leading to delirium.[78] Bacterial translocation via the bloodstream can damage the kidneys, affecting their normal function.[79] Severe renal ischemia-reperfusion increases intestinal permeability, allowing translocation of bacteria and endotoxins, which activate the renal TLR4 signaling pathway and trigger inflammation leading to severe ischemic acute kidney injury.[80] Further studies on microbiota translocation or dysbiosis leading to multiple organ dysfunction in septic patients are summarized in Table 1. Extensive microbiota displacement typically leads to multiple organ dysfunction and failure, and in severe cases, can result in death. A recent study revealed that in elderly septic mice, *Akkermansia muciniphila* (AKK) in the gut was significantly increased. This bacterium disrupts the intestinal barrier, facilitates microbial translocation, and may contribute to the inflammation and mortality observed in elderly septic patients.[39]

Studies have shown that bacteria such as *Enterococcus* spp. and *Parabacteroides distasonis* are closely associated with increased mortality risk in septic patients when their abundance in the human body rises.[33] In a prospective cohort study, rectal swabs and gene sequencing were performed on 301 patients to explore whether the characteristics of gut microbiota in critically ill patients upon admission could predict death or infection.[72] The results indicated that the abundance of *Enterococcus* was associated with increased mortality and infection in critically ill patients. This suggests that in the complex and specialized ICU environment, an increase in the abundance of these bacteria could significantly influence the progression and prognosis of sepsis. Specifically, by measuring the abundance of specific harmful gut microbiota upon ICU admission, it may be possible to predict the likelihood of sepsis and death, thereby providing valuable reference points for subsequent medical interventions and improving treatment outcomes.

## Amelioration of Sepsis by Beneficial Metabolites of Gut Microbiota

The improvement in sepsis associated with the gut microbiota is primarily attributed to the increase in beneficial bacteria and the secretion of beneficial metabolites by the gut microbiota. Agudelo et al[33] reported that when the abundance of

**Table 1** Study of Changes in Gut Microbiota and Shifts in the Destruction of Various Complications of Sepsis

| Organ System | Changes in Gut Microbiota After Sepsis | Mechanisms of Multi-Organ Dysfunction | Outcomes | Citations |
|---|---|---|---|---|
| Nervous system | A decrease in intestinal bacilli and an increase in *Aspergillus* spp | LPS translocation and systemic inflammation activate microglia-mediated synaptic phagocytosis | Sepsis-associated encephalopathy (SAE), cognitive dysfunction in mice | [81] |
| | *Proteobacteria* abundance significantly increased, *Firmicutes* abundance significantly decreased | Modulates microglial activity and pro-inflammation; affects mouse brain function via the vagus nerve | SAE | [82] |
| | Altered cerebral bacterial taxa | Sepsis Causes Bacteria to Transiently Spread to the Brain | Neuroinflammation due to sepsis | [78] |
| | Increased metabolism of *enterococci* and *Escherichia coli* | Increased 5-HT synthesis, imbalanced brain entry ratio of aromatic to branched-chain amino acids | Brain dysfunction during sepsis | [83] |
| | The abundance of anaerobic bacteria decreased significantly | Increasing glutamine levels in the brain microenvironment during sepsis | SAE | [84] |
| Respiratory system | Abnormal proliferation of *Enterococcus* and *Klebsiella pneumoniae* | Microbiota translocation further causes secondary lung and bloodstream infections in patients | Higher death risk in enterogenic acute respiratory distress syndrome (ARDS) | [85] |
| | *Proteobacteria* increased, *Firmicutes* decreased, *Klebsiella* abundance significantly elevated | Reduced SCFAs and elevated taurocholic acid increase intestinal permeability, *Klebsiella* may translocate to lungs, bloodstream, abdomen, causing secondary infections | Increased risk of death from sepsis and ARDS | [86] |
| | Gut microbiota imbalance | Promotes inflammation, damage to the intestinal mucosa and consequent bacterial translocation | Sepsis-related acute lung injury and ARDS | [87] |
| | *Bacteroides* was commonly present and abundant | Gut microbiota translocates to the lungs | Sepsis-induced ARDS | [88] |
| | *Escherichia coli* and *Staphylococcus aureus* increased in the lungs | Gut microbiota translocates to the lungs | Sepsis-induced ARDS | [89] |
| Digestive system | Gram-negative bacterial infections were observed | Impaired intestinal barrier function and endotoxin translocation | Sepsis-related liver injury | [90] |
| | Gut microbiota imbalance | Dysregulated microbial product translocation triggers inflammation, impairing hepatocyte function and detoxification | Sepsis-related liver injury | [91] |
| Urinary system | Bacterial imbalance | Impaired gut barrier function and bacterial translocation boost systemic inflammation | Slow renal recovery, increased acute kidney injury (AKI) mortality | [52] |
| | Altered intestinal microbiota | Mucosal barrier disruption and intestinal microbiota imbalance trigger systemic inflammation and promote acute kidney injury | Septic acute kidney injury | [92] |
| Muscular System | Gut microbiota imbalance | Sepsis-induced pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs), cytokines, and reactive oxygen species promote intestinal dysbiosis and exacerbate skeletal muscle dysfunction via circulating SCFAs, extracellular vesicles, and bacterial metabolites | Sepsis-induced skeletal muscle dysfunction | [93] |

microbial species such as *Ezakiella, Megasphaera*, and *Prevotella* increased, the severity of sepsis after onset was alleviated. Sun et al[7] identified certain beneficial bacteria, such as *Lachnospiraceae* species, that directly or indirectly promote tryptophan metabolism, potentially having a beneficial impact on the progression of sepsis. In animals treated with a GPR109A agonist, the dysbiosis of the gut microbiota and damage to the intestinal epithelial barrier were alleviated, reducing the intensity of the inflammatory response and improving survival in sepsis.[94]

Severe sepsis often causes damage to terminal organs, and the gut microbiota plays a key role in sepsis-induced liver and kidney injury. Reduced gut microbiota levels decrease renal macrophage and monocyte maturation, protecting against kidney damage. However, complete depletion of gut microbiota eliminates this protective effect.[95] In mouse experiments, microbiota from septic-resistant mice produced more glaricidins than those from septic-sensitive mice, which protected the mice from cecal ligation and puncture-induced mortality and liver injury.[96] Recent studies have shown that the gut microbiota metabolite D-serine can help improve kidney injury.[97,98] Another study found that beneficial metabolites, such as SCFAs, may offer some protective effects against renal damage induced by sepsis.[99,100] Conversely, a reduction in SCFAs leads to immune dysfunction in the gut, further exacerbating the systemic damage caused by sepsis.[101] AKK can produce SCFAs, and its abundance in the body is linked to the progression and ultimate outcome of sepsis.[102] The main producers of SCFAs are *Lachnospiraceae* and *Ruminococcaceae*.[103,104] In general, precisely adjusting the quantity and proportion of these bacteria can positively alleviate the effects of sepsis.

The gut microbiota composition has shown great promise in sepsis research and may serve as an effective biomarker. By analyzing the gut microbiota, it is possible to identify patients who are at relatively higher risk of sepsis. For instance, changes in the abundance of certain microbial species or the diversity of microbial communities may indicate an individual's risk of developing sepsis. In sepsis-related research, neonatal sepsis has been a key area of focus. However, there is currently limited research validating these findings in adults. While theoretically the gut microbiota could play many positive roles, there is insufficient empirical evidence supporting its reliability as a biomarker for accurately identifying high-risk individuals for sepsis in adults or guiding personalized prevention strategies.[64] Given the complexity of sepsis in adults and its severe impact on health, there is an urgent need for more studies to explore the mechanisms, risk factors, and other issues related to sepsis in this population. Further investigation into the application of the gut microbiota in adult sepsis could provide scientific evidence for the development of effective prevention and treatment strategies.[10]

## Targets of Gut Microbiota Metabolites Acting on Immune Responses in Sepsis

In the intricate pathophysiology of sepsis, disturbance of the immune system plays a large and damaging role.[105] As the body struggles against overwhelming infection, an uncontrolled inflammatory cascade is generated, often leading to multiple organ failure and a life-threatening conclusion. In recent years, the gut microbiota and its metabolites have emerged as crucial mediators connecting host health and disease vulnerability. These chemicals, produced by the symbiotic microbial community within the gut lumen, have the ability to control the immune response in basic ways.[106–108] Understanding the major targets via which gut microbiota metabolites influence the immune response during sepsis is not only crucial for dissecting the underlying mechanisms but also holds promise for the development of innovative treatment strategies. As shown in Figure 2, the following is a categorical review of the present targets of microbial metabolites in regulating immune responses during sepsis.

## Targets for Pattern Recognition Receptors

### Toll-Like Receptors (TLRs)

In the early stages of sepsis, pathogen infiltration or tissue injury leads to the release of considerable amounts of PAMPs and DAMPs.[109] TLRs act as key sensors for immune cells, enabling the identification of PAMPs.[110] For example, LPS, a component of the outer membrane of Gram-negative bacteria, activates TLR4, while peptidoglycan from Gram-positive bacteria activates TLR2.[111,112] These connections initiate either the MyD88-dependent or MyD88-independent signaling pathways, leading to the activation of downstream cascades such as nuclear factor-κB (NF-κB) and mitogen-activated protein kinases.[113,114] Subsequently, the production and secretion of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), are stimulated, culminating in a systemic inflammatory response.[115] Activated TLRs not only initiate the main inflammatory response but also perpetuate and enhance inflammation through positive feedback mechanisms. For instance, NF-κB activation leads to an increase in TLR expression and the recruitment of related adaptor molecules that sensitize immune cells. This hypersensitive condition results in prolonged inflammatory activation, further contributing to the pathogenesis of sepsis and implicating various organ systems.[116] Studies have indicated that SCFAs, notably butyric and propionic acids, can reduce LPS-induced TLR4-NF-κB activation. In a mouse model of sepsis, exogenous injection of butyric acid markedly lowered serum inflammatory markers and improved survival rates, emphasizing its anti-inflammatory effects via precise targeting of TLR4.[117] Bile acids activate nuclear receptors such as the farnesoid X receptor (FXR) and pregnane X receptor (PXR). In hepatic Kupffer cells, active FXR suppresses TLR4 gene transcription, ultimately lowering TLR4 surface expression.[118]

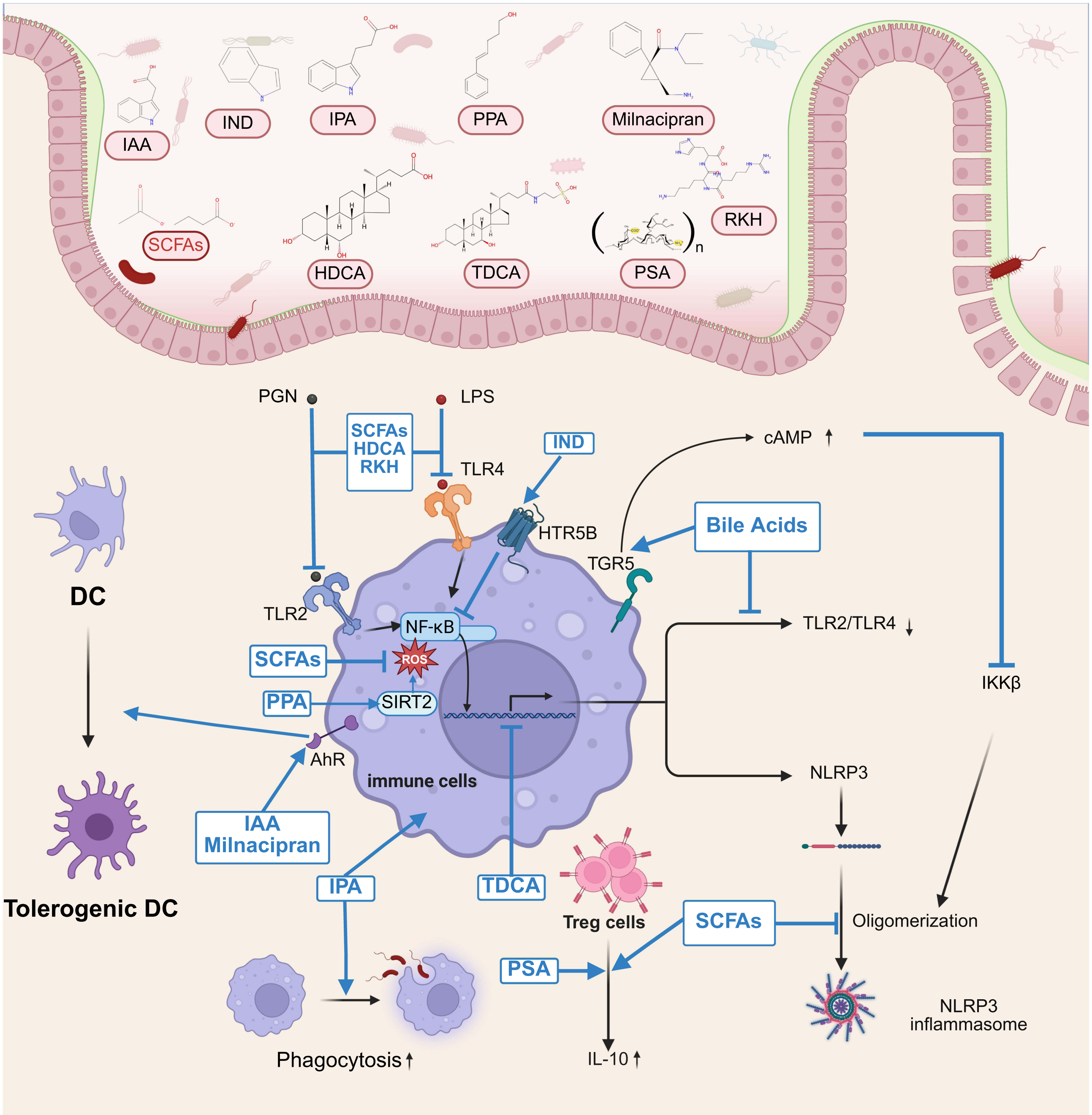

**Figure 2** A complete overview of the mechanisms by which metabolites of the gut microbiota directly attack the targets of the immune response. This figure systematically demonstrates the target mechanism of gut microbiota metabolites directly acting on immune response. Different kinds of gut microbiota metabolites are clearly presented in the figure, and their interaction pathways with various key targets of immune response, including the effects on immune cell activation and signaling pathways, are visualized by connecting arrows and lines.

This lowers susceptibility to LPS, decreases TNF-α production, and alleviates liver inflammatory damage during sepsis. Concurrently, bile acids control TLR2/TLR4 expression in intestinal epithelial cells via PXR, supporting intestinal immunological homeostasis and limiting the worsening of systemic illness induced by bacterial translocation from the gut.[119] Recent investigations have demonstrated that plasma levels of hyodeoxycholic acid (HDCA) in septic patients are considerably lower than those in age- and gender-matched healthy controls. Furthermore, HDCA plasma levels exhibit a negative connection with various indications of sepsis development. Supplementation with HDCA has been observed to decrease inflammatory damage associated with sepsis. Investigations into the underlying mechanisms of HDCA's anti-inflammatory activities have indicated that HDCA prevents the excessive activation of inflammatory macrophages by competitively preventing the binding of LPS to the TLR4/MD2 complex.[120] Tryptophan metabolites, especially indole-3-propionic acid, activate the aryl hydrocarbon receptor (AhR). Upon activation, AhR translocates to the nucleus and regulates the expression of different genes.[121] In immune cells, AhR activation inhibits the TLR2/TLR4 signaling pathway, lowering the release of pro-inflammatory cytokines such as IL-6 and IL-12. Additionally, AhR stimulates the development of dendritic cells into tolerogenic dendritic cells, thereby fine-tuning the immune response during sepsis. Metabolites of the kynurenine pathway exhibit diverse immunological actions. On one side, they can activate immune cells and boost anti-infective properties. On the other side, during sepsis-induced immunological imbalance, high kynurenine can upregulate TLR4 expression via an unknown mechanism, hence worsening inflammation.[122] This shows that tryptophan metabolites may bidirectionally influence TLRs and the immunological response in sepsis through the kynurenine pathway, a concept warranting further exploration. During the microbial metabolic process, numerous bacteria create different peptide metabolites. These peptide metabolites can serve as signaling molecules, antimicrobial compounds, or hold other physiological activities. A study, through fecal metagenomic sequencing, demonstrated that the quantity of AKK in the intestines of septic patients is much lower than that in non-septic individuals. Further metabolomics investigation indicated that AKK bacteria can create a new tripeptide, Arg-Lys-His (RKH). RKH directly binds to TLR4, suppresses the inflammatory signaling pathways in immune cells, and ameliorates sepsis.[123]

### Nod-Like Receptors (NLRs)

Members of the NLR family are ubiquitously dispersed across the surfaces of immune cells and epithelial cells. They exhibit the amazing capacity to PAMPs, DAMPs, as well as endogenous danger signals, hence playing a vital role in both beginning and increasing the immune responses during sepsis.

Extensive research has established that SCFAs, with butyric acid being particularly prominent, can directly target the NLRP3 inflammasome.[124] By perturbing the recruitment pathway of the ASC protein, it effectively thwarts the assembly of the inflammasome complex. In vitro cell-based experiments have shown that upon the addition of butyric acid to macrophages, a conspicuous reduction in the development of ASC speckles is observable, concomitantly leading to the suppression of NLRP3 inflammasome complex formation. As a result, the development and release of IL-1β and interleukin-18 are limited, considerably attenuating the inflammatory reaction.[125]

Within the liver domain, the FXR, once activated by bile acids, can exert transcriptional regulatory control to decrease the expression of the NLRP3 gene, therefore reducing the formation of NLRP3 inflammasomes.[126] Concurrently, certain bile acids are capable of interacting with the membrane receptor TGR5.[127] Upon activation, this connection produces an elevation in intracellular cyclic adenosine monophosphate levels, which in turn suppresses the activity of kinases fundamental to the NLRP3 inflammasome activation pathway, such as the inhibitor of NF-κB kinase subunit beta. By inhibiting the action of these kinases, the construction and activation of the NLRP3 inflammasome are successfully avoided, minimizing the inflammatory damage associated with sepsis. Notably, in the setting of intestinal inflammation models, TGR5 agonists have demonstrated efficiency in relieving intestinal inflammation and curbing the intestinal damage mediated by the NLRP3 inflammasome.[128]

## Targeting Cytokines and Immune Cells

Recent breakthroughs in gut microbiome research have identified complicated linkages between microbial metabolites, cytokines, and immune cells, demonstrating their critical function in modulating immune responses during sepsis. These metabolites operate as regulatory “keys”, influencing immune cell differentiation, polarization, and cytokine release to restore equilibrium in the dysregulated immunological milieu.

Several essential microbial metabolites with immunomodulatory activities have been identified: SCFAs, such as butyrate, are fermentation products of dietary fiber. Acting as histone deacetylase inhibitors, SCFAs promote regulatory T cell differentiation, suppress pro-inflammatory cytokines, and enhance IL-10 secretion, achieving immune balance,[129,130] acetate has shown promise in sepsis-associated AKI by inhibiting histone deacetylase activity, suppressing the NOX2/ROS pathway, and mitigating oxidative stress to protect against AKI.[99] Taurodeoxycholate (TDCA), modulates chromatin silencing, alternative splicing, and translation of the myeloid-derived suppressor cells immunoproteome, boosting anti-inflammatory molecule production while reducing pro-inflammatory mediators.[131] Indole (IND), generated from tryptophan metabolism, stimulates the 5-hydroxytryptamine receptor HTR2B, blocking the NF-κB signaling pathway. This alters macrophage polarization from the pro-inflammatory M1 type, lowering cytokines including IL-1β and TNF-α, and relieving gut inflammation.[132] 3-Indoleacetic acid (IAA), produced from gut microbiota, activates AHR in microglia, enhancing neuronal function and lowering cognitive impairment associated with sepsis.[133] Indole-propionic acid (IPA), improves macrophage phagocytosis, assisting in infection management and giving a unique therapeutic pathway for sepsis.[134] Phenylpyruvate (PPA), a metabolite of *Candida albicans*, interacts with SIRT2, promoting SIRT2-dependent reactive oxygen species generation. This improves macrophage phagocytosis and bactericidal activity, mitigates organ damage, and reshapes cytokine secretion patterns.[135] Minacipran activates the AHR in group 3 innate lymphoid cells, promoting IL-22 release and mitigating intestinal ischemia/reperfusion injury.[136] Polysaccharide A (PSA), which from *Bacteroides fragilis* induces regulatory T cells and IL-10 secretion, maintaining immune balance and reducing inflammation.[137]

Despite these discoveries, many mechanisms remain unexplained. For instance, how metabolites interact with immune cells and cytokines during the tissue repair phase of sepsis, or their roles within specific tissue microenvironments, are still to be explained. Furthermore, the complicated relationship between metabolites and host signaling pathways merits further research. Looking forward, the merging of multi-omics technology and clinical research shows potential for revealing these pathways. This insight could lead to the development of targeted medicines for sepsis, which would enhance patient survival and long-term results.

## Exploration of Sepsis Treatment Strategies Based on Gut Microbiota Regulation

Around the 1980s, it was standard practice in surgical care to provide at least five days of antibiotics to reduce infection rates. In a review of a 1986 report that included 81 hepatectomies, it was found that only 57 of the 81 patients received prophylactic antibiotics and 24 did not. Unexpectedly, no cases of sepsis were reported in patients who did not receive prophylactic antibiotics, and all manifestations of sepsis occurred in patients who received antibiotics.[138] This phenomenon triggered deeper thinking about the importance of the microbiota, and as its understanding deepened, attention was drawn to the possibility of repairing the gut and improving its function through probiotics, fecal transplants, and other therapeutic approaches.[9,64] Currently, regulating the gut microbiota has become an important direction in the treatment of sepsis.

### Probiotics, Prebiotics, Synbiotics

Beneficial bacteria or their derivatives, as alternative strategies, can help address the challenges posed by antibiotic resistance while maintaining the composition and function of the gut microbiome. Currently, the most common approaches include the use of probiotics, prebiotics, or synbiotics.[8]

Probiotics are live beneficial microorganisms that can help regulate the balance of the gut microbiome. The consumption of probiotics has shown positive effects in very low birth weight infants, reducing the risk of sepsis-related complications, mortality, and length of hospitalization, while also promoting weight gain. Optimal effects are seen when administered at specific doses and with multi-strain formulations.[139] A meta-analysis revealed that the incidence of late-onset sepsis in preterm infants treated with probiotics decreased from 16.3% in the placebo group to 13.9%. This difference remained significant across infants treated with *lactobacilli, bifidobacteria*, or a combination of single and multiple probiotic strains. Additionally, in developing countries, preterm infants treated with probiotics showed a significant reduction in the incidence and mortality of late-onset sepsis.[140] The intestinal microbiota of neonates is in a stage of dynamic colonization, and probiotic intervention at this time can promote the establishment of a healthy microbial community, enhance intestinal barrier function, and facilitate the development of the immune system.[141] In the field of adjuvant therapy for adult sepsis, probiotics combined with early enteral nutrition may have a positive impact.[142] However, they also exhibit a more complex efficacy profile and non-negligible safety risks, particularly in immunocompromised patients or those with severe underlying diseases.[143] This risk may stem from the relatively stable intestinal microbial community in adults, where exogenous probiotics have weak colonization ability and may instead translocate into the bloodstream.[144] Molecular biology studies have shown that after adults take probiotics, most strains only exist temporarily in the intestine (for approximately 2–4 weeks) and disappear rapidly after discontinuation, failing to achieve persistent colonization as in neonates.[145] Based on current evidence, the application of probiotics in the prevention and treatment of sepsis must strictly follow the principles of age stratification and risk assessment.

Prebiotics, such as fructooligosaccharides and fibers, promote the growth and proliferation of beneficial bacteria. Studies have shown that prebiotics also provide significant benefits to preterm infants by reducing the incidence of sepsis and mortality, shortening the duration of total enteral feeding and hospitalization, and increasing bowel movement frequency. Notably, prebiotics are most effective in infants born at 28 weeks gestation or later, and their effects are especially enhanced when combined with breast milk, infant formula, or galactooligosaccharides.[146] Moreover, fiber, as a source of microbial food that produces SCFAs, may have a beneficial role in the prevention and treatment of sepsis.[147]

Synbiotics refer to the combination of probiotics and prebiotics in a form that exerts synergistic effects. They have been shown to regulate the gut microbiome, reduce inflammatory responses, decrease the incidence of infections, and lower the rate of sepsis-related complications in sepsis patients.[148,149] However, a comprehensive analysis of 18 randomized controlled trials indicated that there was no significant difference in the incidence of postoperative sepsis between patients receiving synbiotics or probiotics. No clear advantages or positive effects were observed. Subgroup analyses also failed to detect any significant benefits in reducing urinary tract infections, pneumonia, or postoperative wound infections.[146] Table 2 lists additional studies on the impact of probiotics, prebiotics, and synbiotics in sepsis.

Probiotics have demonstrated certain efficacy in the clinical management of preterm infants, showing improvements in specific aspects of sepsis prognosis. However, in some cases, interventions have been ineffective or even led to adverse outcomes. The choice of bacterial strains and the dosage of probiotics are crucial, as certain LAB strains can influence immune functions, and even the same strain may exhibit different effects. Research and reports on the use of probiotics and prebiotics in adult sepsis treatment are relatively limited, and further exploration is urgently needed to fill this knowledge gap. While some successful cases have been reported where synbiotics promote the growth of symbiotic bacteria and regulate the gut microbiome to treat sepsis, it is important to note that their effects are heavily influenced by dietary habits and individual differences. More extensive clinical data are required to substantiate their efficacy.

## Fecal Microbial Transplantation (FMT)

FMT is typically performed through methods such as enemas or oral capsules, in which processed fecal suspensions from healthy individuals are transplanted into the patient's gut to rebuild the intestinal microbiome.[158] Several animal studies have demonstrated that FMT offers numerous benefits for septic mice, including a reduction in incidence and mortality, restoration of the gut microbiome, and improvement in barrier function.[159–161] In a study by Li et al,[162] animal models of SAE were treated with four different interventions—probiotics, prebiotics, synbiotics, and FMT—to modulate the gut microbiome in septic rats. The results showed that FMT was most effective in restoring gut microbial diversity and exhibited strong neuroprotective effects in SAE. Clinical reports also reveal that, over time, most patients who underwent FMT experienced corresponding changes. Specifically, improvements in organ function, regression of sepsis and its complications, and increased survival rates were observed. For example, in one study on septic patients, those who received FMT showed significant improvement in gut microbial communities, which effectively alleviated sepsis-induced MODS and diarrhea symptoms.[163] A 44-year-old female patient who developed septic shock and severe diarrhea after vagotomy, unresponsive to antibiotic treatment, underwent FMT due to dysbiosis. Post-treatment, the patient's septic symptoms and diarrhea were controlled, and beneficial changes in the microbiome were noted.[164]

When extrapolating animal experimental results to clinical applications, it is essential to maintain a highly cautious approach. This translation process involves numerous complex factors that are difficult to predict with precision, including but not limited to the potential risks of various complications during treatment, the optimal timing for drug interventions, the precise dosing regimen, and the overall safety of the drug in clinical use. Previous mouse models have often failed to translate into effective clinical therapies. For instance, Kim et al[161] constructed a mouse model of sepsis induced by human pathogens and subsequently performed FMT. Their study found that FMT restored the microbiome of

**Table 2** Published Studies on the Effect of Probiotics/Prebiotics/Synbiotics on Sepsis

| Interventions | Research Target | Changes in the Microbiome Caused | Therapeutic Effect | Results | Citations |
|---|---|---|---|---|---|
| *Probiotic Clostridium butyricum* | Mice | Improve gut microbiota imbalance | Inhibits microglial overexcitation in SAE mice, increases BDNF levels, regulates gut microbiota | Reduced cognitive impairment and neuronal | [150] |
| *Lactobacillus rhamnosus GG* | Mice | Untested | Reduced ileal mucosal damage, improved intestinal barrier integrity, altered serum metabolic profiles | Significantly reduced mortality in septic mice | [151] |
| Multi-species probiotic (Winclove 607 based on Omnibiotic® 10 AAD) | Patients with early sepsis | Day 7 exhibited significantly higher abundance of *Lactobacillus plantarum, Lactobacillus salivarius* and *Lactobacillus acidophilus* | Functional α Significant increase in diversity and increase in probiotic strains | Regulate the composition and function of the gut microbiota | [152] |
| Probiotics VSL#3 (Danisco-Dupont USA, Madison, WI) | Children with severe sepsis | Untested | On day 7, the levels of pro-inflammatory cytokines decreased significantly, and those of anti-inflammatory cytokines increased | Organ dysfunction gradually decreased, but mortality did not improve significantly Mortality | [153] |
| *Bifidobacterium shortum BBG-001* | Infants born between 23 and 30 weeks of gestational age | Untested | No positive effects found | Sepsis incidence and pre-discharge deaths were similar to the placebo group | [154] |
| *Lactobacillus rhamnosus GG* | Newborns affected by multiple chromosomal disorders | Increase in *Lactobacillus rhamnosus* | Supplementation with *Lactobacillus rhamnosus* rats triggers sepsis | Causes sepsis in high-risk patients | [155] |
| Prebiotics (a non-fermentable fiber) | Mice | Increased relative abundance of the genera Akk and *Lachnospiraceae* | Pro-inflammatory cytokine concentration decreased, liver inflammation alleviated | Increased survival in septic mice | [156] |
| Oral synbiotic preparation (*Lactobacillus plantarum* and oligofructose) | Infants in rural India | Untested | Enhanced local gastrointestinal mucosa, enhanced systemic host immunity | 40% reduction in death and sepsis rates | [157] |
| Synbiotics combining *Bifidobacterium breve* strain Yakult, *Lactobacillus casei* strain Shirota and galactooligosaccharides | Patients with sepsis on mechanical ventilation in the ICU | Elevated numbers of *bifidobacteria* and *lactobacilli* | Increased beneficial bacteria in the gut and higher levels of organic acids | The incidence of enteritis and ventilator-associated pneumonia was significantly reduced | [15] |

septic mice, re-established interferon regulatory factor 3 levels, activated the TLR signaling pathway, and promoted the clearance of systemic pathogens, thereby improving the survival rate of septic mice.

FMT appears to be a promising therapeutic strategy. However, there have been reports of adverse outcomes, including death, following FMT treatment,[12,165] and there is a concern that FMT may transfer potential pathogenic bacteria from the donor's feces to the recipient. Cases of fatal *Escherichia coli* infections following FMT have already been reported,[12] highlighting the need for thorough donor screening. Additionally, many sepsis patients are treated with broad-spectrum antibiotics, which may influence the effectiveness of FMT. Although FMT has been explored for treating sepsis in humans, most studies remain scattered and case-report-based, without forming a systematic, widely recognized, and routine therapeutic approach. There is an urgent need for large-scale, multi-center, prospective clinical studies to provide robust evidence for the application of FMT in septic patients and to promote the scientific use and development of this therapy in clinical practice.

## Selective Digestive Decontamination (SDD)

SDD involves administering non-absorbable antibiotics, such as polymyxin and tobramycin, to the gastrointestinal tract to eliminate potential pathogenic microorganisms while preserving beneficial anaerobic bacteria. This method is used to prevent infections.[166] Several studies have shown that SDD significantly reduces infection rates in critically ill patients, decreases the duration of mechanical ventilation, and shortens hospital stays. For example, SDD effectively inhibits the growth of Gram-negative bacteria in the gut, reducing their colonization in the respiratory tract, and significantly lowers the incidence of respiratory infections in the ICU.[167] A study involving 24,389 ICU patients who required mechanical ventilation showed that, compared to standard care, SDD reduced the mortality rate (RR 0.91), with a 99.3% probability of lowering the risk of death. SDD also reduced the risk of pneumonia and bacteremia.[168] In patients with severe burns, bacterial translocation plays a key role in burn-associated sepsis, and SDD has been shown to reduce this translocation. A study of 30 burn patients found that the treatment group, which received SDD with amikacin, miconazole, and polymyxin sulfate, showed significant effectiveness in controlling infections and multi-organ dysfunction syndrome.[169]

Selective Digestive Decontamination (SDD) remains a topic of ongoing debate in clinical research, as opinions diverge on whether its potential risks of inducing antibiotic resistance outweigh its clinical benefits.[170] In terms of benefits, SDD has been reported as an effective strategy for reducing mortality rates in ICU patients and preventing bacterial translocation in sepsis.[171] Meta-analyses further support these findings, reporting reduced mortality rates in critically ill patients receiving SDD treatment, particularly in environments with higher baseline infection rates.[172] However, the potential to promote the emergence of antibiotic-resistant pathogens is one of the main concerns in the clinical application of SDD, especially considering that the ICU has become a hotspot for antibiotic use and resistance.[173] There is a view that SDD has a potential risk of inducing antibiotic resistance, which may lead to the colonization or increased infection of multi-drug resistant strains.[174] A study found that during SDD, the resistance rates of intestinal Gram-negative bacteria to ceftazidime, tobramycin and ciprofloxacin were 5%, 7% and 7% respectively, and after SDD intervention, the corresponding resistance rates increased to 15%, 13% and 13%.[175] However, this study was a point-in-time prevalence survey, and the research subjects included all ICU patients. Therefore, the level of evidence for this study is not high. At present, a growing body of evidence indicates that the use of SDD does not increase the emergence of drug-resistant bacteria. A longitudinal study conducted over 21 years in an ICU that implemented SDD found no increase in the incidence of resistant microorganisms during this period.[176] Recent studies have also shown that in ICUs where SDD is used, antibiotic resistance levels are no higher than those in ICUs that do not use SDD.[166,177] The primary factor influencing resistance rates appears to be patient characteristics, rather than the use of SDD itself.[178]

The benefits of SDD in reducing the mortality and infection rates of ICU patients are clear, especially in low antibiotic resistance environments. Although evidence from high-resistance regions still needs to be supplemented, long-term application experience and mechanistic research in Europe suggest that the benefit-risk ratio of SDD is acceptable under reasonable management. In the future, it is necessary to strengthen localized research in high-resistance regions and facilitate the transition of SDD from controversy to precise application.

## Exploring Treatment Techniques That Target LPS

LPS, as a fundamental component of the cell wall of Gram-negative bacteria, plays a central driving role in the pathogenesis of sepsis and is a critical trigger for generating uncontrolled inflammatory reactions in the body. In recent years, investigations based around antagonizing LPS for the treatment of sepsis have developed, opening up new options for clinical therapy.

Targeting the LPS transport pathway is a new line of thought for anti-LPS treatments. A novel antibiotic, Zosurabalpin (RG6006), was discovered to prevent the transfer of bacterial LPS from the inner to the outer membrane, and its in vitro antibacterial and pharmacokinetic properties revealed potent in vivo activity in an animal model of infection.[179] Its potential therapeutic efficacy is subject to further validation in clinical trials.

Gut microbial metabolites reveal unique potential in antagonizing LPS. Butyrate is an essential gut microbial metabolite involved in gut-pulmonary interaction and has immunomodulatory effects. In an animal investigation, septic mice receiving sodium butyrate gavage demonstrated a considerable increase in intestinal barrier integrity, a significant decrease in blood LPS levels, and a significant increase in mouse survival. Thus, butyrate supplementation may be a possible method for treating sepsis by maintaining normal function of the lung-gut axis.[130] In addition, anti-inflammatory LPS produced by some bacteria has been found to aid in the prevention and treatment of LPS-induced inflammatory responses by shifting the balance between anti-inflammatory LPS and pro-inflammatory LPS.[180] A new study has presented an integrated method with both antibacterial and anti-inflammatory actions to reduce sepsis by stopping the cascade of LPS activation. In this work, bacteria were promptly killed and LPS neutralized by bactericidal mucins, and the neutralized LPS was further scavenged by acyl acyl hydrolases, which eliminated secondary fatty chains and detoxified the bacteria in situ. The technique exhibited great therapeutic efficiency in two mouse models of Pseudomonas aeruginosa infection. This technique presents a new intervention strategy for the treatment of sepsis by ameliorating hyperinflammatory-associated infections in the clinic from the standpoint of combination drug delivery.[181]

LPS within the circulation in sepsis interacts with a range of plasma proteins to create diverse biological consequences. Among these, lipopolysaccharide-binding protein (LBP) and bactericidal permeability increasing protein (BPI) are the two most prevalent plasma proteins.[182] During sepsis, plasma LBP can reach more than seven times the normal levels.[183] Early removal of LBP from the body can prevent sepsis-induced acute kidney damage and improve the outcome of critically ill patients.[184] However, the positive and negative effects of LBP combined with LPS-mediated inflammatory response during host infection may be related to the bacterial species, the route of infection, and the concentration of LPS, suggesting that the specific conditions and indications for LBP in the treatment of sepsis need to be thoroughly investigated. BPI has a highly essential role in the clearance of LPS, with bactericidal, anti-inflammatory, and phagocytosis-regulating actions. rBPI23 is a recombinant protein of BPI that is more efficient in the treatment of sepsis. rBPI23 can neutralize LPS, drastically lower the release of inflammatory factors, and diminish the activation of fibrinolytic and coagulant systems after small-dose endotoxin infusion.[185,186] However, the short half-life of BPI in vivo limits the clinical applicability of recombinant BPI. However, a chimeric protein comprised of the N-terminal domain of LBP and the C-terminal domain of BPI overcomes the short half-life and enhances the survival rate of rats with sepsis.[187] More scientific and clinical investigations linked to LBP and BPI are needed to advance its vital role in sepsis management.

## Treatment of Sepsis from Diets

The pathophysiology of sepsis is exceedingly complex, and a number of processes directly or indirectly impact the balance of the intestinal microbiota, which in turn affects the clinical signs and prognosis of sepsis.

Available studies have shown that the use of plant-based diets such as the Mediterranean diet, as a therapeutic dietary intervention, can have a beneficial impact on the host's microbiome, by Shifting the microbiome environment towards the beneficial bacteria Prevotella and Mycobacterium anthropophilum, while away from the thick-walled phylum, helps to reduce inflammation, improve insulin sensitivity and promote optimal energy balance.[188] In patients with sepsis, early enteral nutrition and supplemental parenteral nutrition are beneficial in the presence of intestinal function, while supplementation with pharmacological nutrients such as glutamine, arginine, and omega-3 fatty acids has not been shown to be prognostically beneficial in sepsis.[189]

The western diet is defined as a diet high in fat, high in sugar, and low in fiber. In a sepsis model, mice fed a Western diet generate more severe illness and poor prognosis as compared to mice fed a typical fiber-rich diet. Importantly, the Western diet dependent increase in sepsis severity and increased morbidity and mortality were independent of the microbiome, suggesting that food may directly affect the innate immune system through an undiscovered mechanism.[190]

Ketogenic diets, with their low-carbohydrate, high-fat characteristics, have shown potential in a range of health areas in recent years. A team of researchers recently randomized septic patients in the ICU to a ketogenic diet or a standard high-carbohydrate diet in a clinical experiment. There was no significant difference in survival between the two groups, but notably, the patients on the ketogenic diet did not experience any side effects. In-depth study found that these patients had lower production of inflammatory chemicals by T cells, suggesting that the ketogenic diet may offset the immunological imbalance in sepsis by modifying the immune system.[191] With additional investigations, the ketogenic diet may become an important supplement to enhance the prognosis of sepsis patients, giving fresh inspiration and options to overcome this medical obstacle.[192]

Recently, the SINFONI program evaluated the impact of a multifunctional dietary strategy integrating diverse bioactive components on inflammation, gut microbiota regulation, and cardiometabolic profile. In this randomized crossover controlled study, the multifunctional intervention reduced intestinal inflammation and fasting LPS levels but did not alter systemic inflammation levels compared to controls.[193] Although this technique was only successful for low-grade inflammation, it may be a useful strategy to learn from in the treatment of sepsis in the future when optimized.

Admittedly, dietary strategies still face challenges in the application of sepsis treatment. Dietary compliance is difficult to control, especially under long-term special dietary patterns, where patients tend to give up halfway. Precise nutritional programs are costly, slow to promote, and hard to reach primary care. Different dietary components are complex with synergistic and dynamic interactions, and their underlying logic needs further exploration. However, looking to the future, with the integration of multiple disciplines, the empowerment of big data, and the improvement of public health awareness, nutrition is expected to become a crucial tool in sepsis treatment, rewriting patients' prognosis trajectories from the source.

## AI-Based Analysis of Gut Microbiota-Related Data for Sepsis Treatment

AI plays a significant role in personalized sepsis management. Recently, a new sepsis screening tool named qSepsis has been reported. This tool is based on machine learning algorithms such as logistic regression, random forest, and extreme gradient boosting, and uses 12 non-laboratory data including patients' vital signs and symptoms for modeling. It can quickly assess the risk of sepsis without relying on laboratory test results.[194] Additionally, the TOPSIS-based classification fusion model integrates 7 classic machine learning models such as decision tree and random forest, and uses clinical data from 4872 ICU patients with septic shock for modeling and validation. It can effectively predict the 28-day mortality risk of septic shock patients in the ICU, providing a reliable early warning auxiliary tool for clinicians.[195] At present, some models are still in the preclinical or small-sample validation stage and require larger-scale trials for verification.

The integration of multi-omics technologies and AI is reshaping sepsis clinical practice via a comprehensive approach encompassing molecular typing, target identification, and dynamic monitoring. For example, a study based on transcriptomics constructed a "benefit score" model, successfully identifying a subgroup of septic shock that is sensitive to restrictive fluid strategies, providing the first cross-modal clinical decision-making tool for septic shock fluid management.[196] Another study combined serum exosomal miRNA sequencing with single-cell transcriptome analysis, screened out miR-125a-5p and miR-221-3p as therapeutic targets. Through the delivery of miRNA mimics/inhibitors by macrophage membrane biomimetic nanovesicles, it significantly reduced lung injury in mice, providing a new strategy for targeted intervention.[197] Moreover, by systematically integrating multimodal data from mouse models and clinical samples, the research comprehensively revealed the metabolic change characteristics in the early stage of sepsis-induced acute kidney injury (SA-AKI), identified 5 core metabolites, and constructed a diagnostic model IC3, with an early detection efficacy of Area Under the ROC Curve = 0.90 for SA-AKI, providing a foundation for subsequent clinical targeted therapy trials.[198]

Understanding alterations in the gut microbiota is a key topic in critical care. One study determined the taxonomic composition of gut microbiota by 16S rRNA gene sequencing and constructed a machine learning classifier for differentiating sepsis with an AUC value of 81.25%; although further validation is needed, it suggests that the composition of gut microbiota has some potential for the diagnosis of sepsis.[199] Antibiotics are currently the mainstay in the treatment of sepsis; however, the timing of antibiotic administration is difficult to accurately manage in the clinic. A recent study has developed a unique approach (named T4) to quantify the influence of time-to-treatment antibiotic administration in sepsis treatment. It was able to accurately determine the appropriate timing of treatment in sepsis patients and explain the expected results by displaying crucial time points and factors, which further lowered patient mortality.[200] Fluid treatment is crucial in the management of septic patients. Reinforcement learning has been employed to design a fluid treatment balancing method for patients with viral shock in the ICU. Machine learning and reinforcement learning techniques have the potential to optimize fluid management in sepsis patients, not only to assist in anticipating fluid overload and response but also to improve treatment results through tailored solutions.[201] In the treatment of sepsis associated with neocoronavirus infection, multi-omics data indicated changes in high-density lipoprotein function, which guided the individualized use of recombinant high-density lipoprotein, considerably improving clinical outcomes for patients.[202]

Multi-omics technologies, such as genomics, proteomics and metabolomics, along with combined AI, enable us to develop innovative tools to deeply study the heterogeneity of sepsis and achieve precise treatment. By integrating modern technologies with traditional medicine, the treatment of sepsis is moving towards higher precision and efficiency.

## Conclusion

To sum up, this review sheds light on the vital role that gut microbiota and its metabolites play in the pathophysiologic process of sepsis, as well as the various therapeutic approaches that go along with it. A symbiotic microbial ecosystem, the gut microbiota of the human body plays a key regulatory function in the pathophysiology of sepsis and is crucial for maintaining internal environment homeostasis. The development of sepsis is at increased risk due to dysbiosis, which includes decreased diversity, attenuation of beneficial commensal bacteria, and growth of dangerous bacteria. Use of antibiotics, infections, and serious illnesses frequently alter the gut microbiota and cause abnormal immune activation, which leads to unchecked inflammation and immunological imbalance and raises the risk of organ failure and death. Good metabolites, on the other hand, such as RKH peptide, butyrate, and HDCA, can stop the production of inflammatory factors, guide the host immune response correctly, and improve sepsis.

Gut microbiota-targeted therapy has garnered a lot of interest lately. Treatments include FMT, SDD, probiotics, prebiotics, synbiotics, anti-LPS medications, and dietary changes that are anticipated to alter the microbial balance, encourage the synthesis of advantageous metabolites, and reduce sepsis. In the meantime, the use of AI and machine learning in the study of gut microbiota data and in the diagnostic and treatment decision-making of sepsis is starting to yield encouraging results. However, a number of obstacles must be addressed before microbiome therapy may be clinically implemented, including the short-term effects of probiotics, the specificity of patient gut microbiota, and the difficulty of standardizing interventions. FMT has been demonstrated in preclinical studies to reduce the mortality rate in animal models of sepsis. For sepsis caused by antibiotic-resistant bacteria, the combination of FMT and SDD holds promise as a potential breakthrough. Metabolite-based therapies are more likely to be translated into clinical practice due to their clear mechanism of action and favorable safety profiles. Future trials should prioritize FMT protocols and metabolite-based therapies, leveraging AI for patient stratification. With standardized systems and refined personalized strategies, microbiota-targeted therapies will synergize with conventional treatments, significantly reducing sepsis mortality and ushering in a new paradigm of restoring health via microbiota balance.

Further investigation into the role of microbial communities and key metabolites in sepsis immunomodulation is necessary to optimize the design of microbial therapies. Modern technologies like metabolomics, spatiotemporal omics, and single-cell RNA sequencing are providing previously unheard-of precision in exposing the intricate web of interactions between host immune cells and gut microbiota.[21,203–205] The immune regulatory mechanisms of important microbial metabolites can be targeted with single-cell RNA sequencing, which can also shed light on the diversity of immune cells during sepsis and the regulation of T-cell, macrophage, and dendritic cell subpopulation differentiation and function by intestinal signals. With the help of systems biology and metagenomics and metabolomics technologies, personalized medicine can be established by precisely identifying the key bacterial strains and their metabolites that impact the sepsis process, investigating possible biomarkers, and building prognostic models.

Even with the remarkable outcomes, there are still issues. The effectiveness and safety of human microbiome therapies must be thoroughly confirmed in extensive randomized clinical trials. The long-term consequences on sepsis survivors are also unknown, as are the best ways to administer probiotics, prebiotics, and fecal microbiota transplants, as well as their dosage and duration. To avoid jeopardizing the effectiveness of microbiome therapy, it is also important to carefully think about how other treatments, such as antibiotics and immunomodulatory medications, may alter the gut microbiota. To sum up, while microbiome therapy is at the vanguard of treating sepsis, more research and clinical validation are required before it can be developed into a sophisticated and successful individualized medicine.

## Abbreviations

FMT, fecal microbiota transplantation; SDD, selective digestive decontamination; ICU, intensive care unit; SCFAs, short-chain fatty acids; MODS, multiple organ dysfunction syndrome; AKK, *Akkermansia muciniphila*; SAE, sepsis-associated encephalopathy; ARDS, acute respiratory distress syndrome; AKI, kidney injury; PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; TLRs, Toll-like receptors; LPS, lipopolysaccharides; NF-κB, nuclear factor-κB; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; FXR, farnesoid X receptor; PXR, pregnane X receptor; HDCA, hyodeoxycholic acid; TDCA, Taurodeoxycholate; IND, Indole; IAA, 3-Indoleacetic acid; IPA, Indole-propionic acid; PPA, Phenylpyruvate; PSA, Polysaccharide A; AhR, aryl hydrocarbon receptor; RKH, Arg-Lys-His; NLRs, Nod-like receptors; IL-1β, interleukin-1β; LBP, lipopolysaccharide-binding protein; BPI, bactericidal permeability increasing protein.

## Funding

There is no funding to report.

## Disclosure

The author declares that they have no competing interests in this work.

---

## References

1. Fleischmann-Struzek C, Mellhammar L, Rose N, et al. Incidence and mortality of hospital- and ICU-treated sepsis: results from an updated and expanded systematic review and meta-analysis. *Intensive Care Med*. 2020;46(8):1552–1562. doi:10.1007/s00134-020-06151-x
2. Giamarellos-Bourboulis EJ, Aschenbrenner AC, Bauer M, et al. The pathophysiology of sepsis and precision-medicine-based immunotherapy. *Nat Immunol*. 2024;25(1):19–28. doi:10.1038/s41590-023-01660-5
3. Wang W, Wang Z, Wang L, et al. Early-onset neonatal sepsis in a Chinese maternal and child healthcare centre, 2017-2023. *Front Pediatr*. 2025;13:1521908. doi:10.3389/fped.2025.1521908
4. Zhu B, Wang X, Li L. Human gut microbiome: the second genome of human body. *Protein Cell*. 2010;1(8):718–725. doi:10.1007/s13238-010-0093-z
5. Cénit MC, Matzaraki V, Tigchelaar EF, Zhernakova A. Rapidly expanding knowledge on the role of the gut microbiome in health and disease. *Biochim Biophys Acta*. 2014;1842(10):1981–1992. doi:10.1016/j.bbadis.2014.05.023
6. Yang W, Cong Y, et al. Gut microbiota-derived metabolites in the regulation of host immune responses and immune-related inflammatory diseases. *Cell Mol Immunol*. 2021;18(4). doi:10.1038/s41423-021-00661-4
7. Sun S, Wang D, Dong D, et al. Altered intestinal microbiome and metabolome correspond to the clinical outcome of sepsis. *Crit Care*. 2023;27(1):127. doi:10.1186/s13054-023-04412-x
8. Tao YL, Wang JR, Liu M, et al. Progress in the study of the correlation between sepsis and intestinal microecology. *Front Cell Infect Microbiol*. 2024;14:1357178. doi:10.3389/fcimb.2024.1357178
9. Adelman MW, Woodworth MH, Langelier C, et al. The gut microbiome's role in the development, maintenance, and outcomes of sepsis. *Crit Care*. 2020;24(1):278. doi:10.1186/s13054-020-02989-1
10. Dickson RP. The microbiome and critical illness. *Lancet Respir Med*. 2016;4(1):59–72. doi:10.1016/s2213-2600(15)00427-0
11. Wang Y, Wen J, Almoiliqy M, et al. Sesamin Protects against and Ameliorates Rat Intestinal Ischemia/Reperfusion Injury with Involvement of Activating Nrf2/HO-1/NQO1 Signaling Pathway. *Oxid Med Cell Longev*. 2021;2021:5147069. doi:10.1155/2021/5147069
12. DeFilipp Z, Bloom PP, Torres Soto M, et al. Drug-resistant E. coli bacteremia transmitted by fecal microbiota transplant. *N Engl J Med*. 2019;381(21):2043–2050. doi:10.1056/NEJMoa1910437
13. Oostdijk EAN, Kesecioglu J, Schultz MJ, et al. Effects of decontamination of the oropharynx and intestinal tract on antibiotic resistance in ICUs: a randomized clinical trial. *JAMA*. 2014;312(14):1429–1437. doi:10.1001/jama.2014.7247
14. Myburgh JA, Seppelt IM, Goodman F, et al. Effect of selective decontamination of the digestive tract on hospital mortality in critically ill patients receiving mechanical ventilation: a randomized clinical trial. *JAMA*. 2022;328(19):1911–1921. doi:10.1001/jama.2022.17927

15. Shimizu K, Yamada T, Ogura H, et al. Synbiotics modulate gut microbiota and reduce enteritis and ventilator-associated pneumonia in patients with sepsis: a randomized controlled trial. *Crit Care*. 2018;22(1):239. doi:10.1186/s13054-018-2167-x
16. Theodorakopoulou M, Perros E, Giamarellos-Bourboulis EJ, Dimopoulos G. Controversies in the management of the critically ill: the role of probiotics. *Int J Antimicrob Agents*. 2013;42 Suppl:S41–4. doi:10.1016/j.ijantimicag.2013.04.010
17. Johnstone J, Meade M, Lauzier F, et al. Effect of probiotics on incident ventilator-associated pneumonia in critically ill patients: a randomized clinical trial. *JAMA*. 2021;326(11):1024–1033. doi:10.1001/jama.2021.13355
18. Zheng D, Liwinski T, Elinav E. Interaction between microbiota and immunity in health and disease. *Cell Res*. 2020;30(6):492–506. doi:10.1038/s41422-020-0332-7
19. Li D, Wang P, Wang P, Hu X, Chen F. The gut microbiota: a treasure for human health. *Biotechnol Adv*. 2016;34(7):1210–1224. doi:10.1016/j.biotechadv.2016.08.003
20. Adak A, Khan MR. An insight into gut microbiota and its functionalities. *Cell Mol Life Sci*. 2019;76(3):473–493. doi:10.1007/s00018-018-2943-4
21. Yang S, Guo J, Kong Z, et al. Causal effects of gut microbiota on sepsis and sepsis-related death: insights from genome-wide Mendelian randomization, single-cell RNA, bulk RNA sequencing, and network pharmacology. *J Transl Med*. 2024;22(1):10. doi:10.1186/s12967-023-04835-8
22. Assimakopoulos SF, Triantos C, Thomopoulos K, et al. Gut-origin sepsis in the critically ill patient: pathophysiology and treatment. *Infection*. 2018;46(6):751–760. doi:10.1007/s15010-018-1178-5
23. MacFie J, O'Boyle C, Mitchell CJ, Buckley PM, Johnstone D, Sudworth P. Gut origin of sepsis: a prospective study investigating associations between bacterial translocation, gastric microflora, and septic morbidity. *Gut*. 1999;45(2):223–228. doi:10.1136/gut.45.2.223
24. Gomaa EZ. Human gut microbiota/microbiome in health and diseases: a review. *Antonie van Leeuwenhoek*. 2020;113(12):2019–2040. doi:10.1007/s10482-020-01474-7
25. Pancu DF, Scurtu A, Macasoi IG, et al. Antibiotics: conventional therapy and natural compounds with antibacterial activity-a pharmaco-toxicological screening. *Antibiotics*. 2021;10(4). doi:10.3390/antibiotics10040401
26. Ramirez J, Guarner F, Bustos Fernandez L, Maruy A, Sdepanian VL, Cohen H. Antibiotics as major disruptors of gut microbiota. *Front Cell Infect Microbiol*. 2020;10:572912. doi:10.3389/fcimb.2020.572912
27. Lange K, Buerger M, Stallmach A, Bruns T. Effects of Antibiotics on gut microbiota. *Dig Dis*. 2016;34(3):260–268. doi:10.1159/000443360
28. de la Fuente-Nunez C, Cesaro A, Hancock REW. Antibiotic failure: beyond antimicrobial resistance. *Drug Resist Updat*. 2023;71:101012. doi:10.1016/j.drup.2023.101012
29. Murray CJ, Ikuta KS, Sharara F, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet*. 2022;399(10325):629–655. doi:10.1016/s0140-6736(21)02724-0
30. Haak BW, Wiersinga WJ. The role of the gut microbiota in sepsis. *Lancet Gastroenterol Hepatol*. 2017;2(2):135–143. doi:10.1016/s2468-1253(16)30119-4
31. Kuppala VS, Meinzen-Derr J, Morrow AL, Schibler KR. Prolonged initial empirical antibiotic treatment is associated with adverse outcomes in premature infants. *J Pediatr*. 2011;159(5):720–725. doi:10.1016/j.jpeds.2011.05.033
32. Baggs J, Jernigan JA, Halpin AL, Epstein L, Hatfield KM, McDonald LC. Risk of subsequent sepsis within 90 days after a hospital stay by type of antibiotic exposure. *Clin Infect Dis*. 2018;66(7):1004–1012. doi:10.1093/cid/cix947
33. Agudelo-Ochoa GM, Valdés-Duque BE, Giraldo-Giraldo NA, et al. Gut microbiota profiles in critically ill patients, potential biomarkers and risk variables for sepsis. *Gut Microbes*. 2020;12(1):1707610. doi:10.1080/19490976.2019.1707610
34. Lankelma JM, van Vught LA, Belzer C, et al. Critically ill patients demonstrate large interpersonal variation in intestinal microbiota dysregulation: a pilot study. *Intensive Care Med*. 2017;43(1):59–68. doi:10.1007/s00134-016-4613-z
35. Graspeuntner S, Künzel S, Waschina S, et al. Gut dysbiosis with bacilli dominance and accumulation of fermentation products precedes late-onset sepsis in preterm infants. *Clin Infect Dis*. 2019;69(2):268–277. doi:10.1093/cid/ciy882
36. Fay KT, Klingensmith NJ, Chen CW, et al. The gut microbiome alters immunophenotype and survival from sepsis. *FASEB J*. 2019;33(10):11258–11269. doi:10.1096/fj.201802188R
37. Victoria M, Elena VB, Amparo GN, et al. Gut microbiota alterations in critically ill older patients: a multicenter study. *BMC Geriatr*. 2022;22(1):373. doi:10.1186/s12877-022-02981-0
38. Takiishi T, Fenero CIM, Câmara NOS. Intestinal barrier and gut microbiota: shaping our immune responses throughout life. *Tissue Barriers*. 2017;5(4):e1373208. doi:10.1080/21688370.2017.1373208
39. Yuan Y, Liu S, Ding X, et al. Early intestinal microbiota changes in aged and adult mice with sepsis. *Front Cell Infect Microbiol*. 2022;12:1061444. doi:10.3389/fcimb.2022.1061444
40. Ma X, Jia X, Peng Y, Li X, Wang C, Yu K. Gut microbiota disruption during sepsis and the influence of innate metabolites on sepsis prognosis. *Int Microbiol*. 2023;26(4):929–938. doi:10.1007/s10123-023-00349-x
41. Schirmer M, Smeekens SP, Vlamakis H, et al. Linking the human gut microbiome to inflammatory cytokine production capacity. *Cell*. 2016;167(4):1125–1136.e8. doi:10.1016/j.cell.2016.10.020
42. Wilmore JR, Gaudette BT, Gomez Atria D, et al. Commensal microbes induce serum iga responses that protect against polymicrobial sepsis. *Cell Host Microbe*. 2018;23(3):302–311.e3. doi:10.1016/j.chom.2018.01.005
43. Singer JR, Blosser EG, Zindl CL, et al. Preventing dysbiosis of the neonatal mouse intestinal microbiome protects against late-onset sepsis. *Nat Med*. 2019;25(11):1772–1782. doi:10.1038/s41591-019-0640-y
44. Fusco W, Lorenzo MB, Cintoni M, et al. Short-chain fatty-acid-producing bacteria: key components of the human gut microbiota. *Nutrients*. 2023;15(9). doi:10.3390/nu15092211
45. Macfarlane S, Macfarlane GT. Regulation of short-chain fatty acid production. *Proc Nutr Soc*. 2003;62(1):67–72. doi:10.1079/pns2002207
46. Knysh IT. Proĭdennye étapy i dal'neishie puti razvitiia sokhrannykh operatsiĭ v kostnoĭ onkologii. [Past stages and future prospects in the development of conservative operations in bone oncology]. *Vestn Khir Im I I Grek*. 1983;131(11):117–120.
47. Mai V, Torrazza RM, Ukhanova M, et al. Distortions in development of intestinal microbiota associated with late onset sepsis in preterm infants. *PLoS One*. 2013;8(1):e52876. doi:10.1371/journal.pone.0052876

48. Zhao Y, Chen F, Wu W, et al. GPR43 mediates microbiota metabolite SCFA regulation of antimicrobial peptide expression in intestinal epithelial cells via activation of mTOR and STAT3. *Mucosal Immunol*. 2018;11(3):752–762. doi:10.1038/mi.2017.118
49. Yatsunenko T, Rey FE, Manary MJ, et al. Human gut microbiome viewed across age and geography. *Nature*. 2012;486(7402):222–227. doi:10.1038/nature11053
50. Niu M, Chen P. Crosstalk between gut microbiota and sepsis. *Burns Trauma*. 2021;9:tkab036. doi:10.1093/burnst/tkab036
51. Prescott HC, Dickson RP, Rogers MA, Langa KM, Iwashyna TJ. Hospitalization type and subsequent severe sepsis. *Am J Respir Crit Care Med*. 2015;192(5):581–588. doi:10.1164/rccm.201503-0483OC
52. Xu Y, Kong X, Zhu Y, et al. Contribution of gut microbiota toward renal function in sepsis. *Front Microbiol*. 2022;13:985283. doi:10.3389/fmicb.2022.985283
53. Paone P, Cani PD. Mucus barrier, mucins and gut microbiota: the expected slimy partners? *Gut*. 2020;69(12):2232–2243. doi:10.1136/gutjnl-2020-322260
54. Wang C, Li Q, Ren J. Microbiota-Immune interaction in the pathogenesis of gut-derived infection. *Front Immunol*. 2019;10:1873. doi:10.3389/fimmu.2019.01873
55. Luo Y, Song Y. Mechanism of antimicrobial peptides: antimicrobial, anti-inflammatory and antibiofilm activities. *Int J Mol Sci*. 2021;22(21). doi:10.3390/ijms222111401
56. Niu X, Daniel S, Kumar D, et al. Transient neonatal antibiotic exposure increases susceptibility to late-onset sepsis driven by microbiota-dependent suppression of type 3 innate lymphoid cells. *Sci Rep*. 2020;10(1):12974. doi:10.1038/s41598-020-69797-z
57. Hornik CP, Fort P, Clark RH, et al. Early and late onset sepsis in very-low-birth-weight infants from a large group of neonatal intensive care units. *Early Hum Dev*. 2012;88 Suppl 2(Suppl 2):S69–74. doi:10.1016/s0378-3782(12)70019-1
58. Cernada M, Pinilla-González A, Kuligowski J, et al. Transcriptome profiles discriminate between Gram-positive and Gram-negative sepsis in preterm neonates. *Pediatr Res*. 2022;91(3):637–645. doi:10.1038/s41390-021-01444-3
59. El Manouni El Hassani S, Niemarkt HJ, Berkhout DJC, et al. Profound pathogen-specific alterations in intestinal microbiota composition precede late-onset sepsis in preterm infants: a longitudinal, multicenter, case-control study. *Clin Infect Dis*. 2021;73(1):e224–e232. doi:10.1093/cid/ciaa1635
60. Liao C, Huang X, Wang Q, Yao D, Lu W. Virulence factors of pseudomonas aeruginosa and antivirulence strategies to combat its drug resistance. *Front Cell Infect Microbiol*. 2022;12:926758. doi:10.3389/fcimb.2022.926758
61. Marzhoseyni Z, Mousavi MJ, Saffari M, Ghotloo S. Immune escape strategies of Pseudomonas aeruginosa to establish chronic infection. *Cytokine*. 2023;163:156135. doi:10.1016/j.cyto.2023.156135
62. Colbert JF, Kirsch JM, Erzen CL, et al. Aging-associated augmentation of gut microbiome virulence capability drives sepsis severity. *mBio*. 2023;14(3):e0005223. doi:10.1128/mbio.00052-23
63. Huang XQ, Qiu JK, Wang CH, et al. Sepsis secondary to multifocal Enterococcus faecium infection: a case report. *Medicin*. 2020;99(27):e19811. doi:10.1097/md.0000000000019811
64. Kullberg RFJ, Wiersinga WJ, Haak BW. Gut microbiota and sepsis: from pathogenesis to novel treatments. *Curr Opin Gastroenterol*. 2021;37(6):578–585. doi:10.1097/mog.0000000000000781
65. Delano MJ, Ward PA. The immune system's role in sepsis progression, resolution, and long-term outcome. *Immunol Rev*. 2016;274(1):330–353. doi:10.1111/imr.12499
66. Yuan JJ, Chang XN, Li M, Yuan QX, Yang XL. Clinical utility of characterizing intestinal flora in septic kidney injury. *Chin Med J*. 2020;133(7):842–846. doi:10.1097/cm9.0000000000000724
67. Morrison DJ, Preston T. Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. *Gut Microbes*. 2016;7(3):189–200. doi:10.1080/19490976.2015.1134082
68. Liu Z, Li N, Fang H, et al. Enteric dysbiosis is associated with sepsis in patients. *FASEB J*. 2019;33(11):12299–12310. doi:10.1096/fj.201900398RR
69. Shimizu K, Ogura H, Hamasaki T, et al. Altered gut flora are associated with septic complications and death in critically ill patients with systemic inflammatory response syndrome. *Dig Dis Sci*. 2011;56(4):1171–1177. doi:10.1007/s10620-010-1418-8
70. Cabrera-Perez J, Badovinac VP, Griffith TS. Enteric immunity, the gut microbiome, and sepsis: rethinking the germ theory of disease. *Exp Biol Med*. 2017;242(2):127–139. doi:10.1177/1535370216669610
71. Han C, Guo N, Bu Y, et al. Intestinal microbiota and antibiotic-associated acute gastrointestinal injury in sepsis mice. *Aging*. 2021;13(7):10099–10111. doi:10.18632/aging.202768
72. Freedberg DE, Zhou MJ, Cohen ME, et al. Pathogen colonization of the gastrointestinal microbiome at intensive care unit admission and risk for subsequent death or infection. *Intensive Care Med*. 2018;44(8):1203–1211. doi:10.1007/s00134-018-5268-8
73. Wolochow H, Hildebrand GJ, Lamanna C. Translocation of microorganisms across the intestinal wall of the rat: effect of microbial size and concentration. *J Infect Dis*. 1966;116(4):523–528. doi:10.1093/infdis/116.4.523
74. Berg RD, Garlington AW. Translocation of certain indigenous bacteria from the gastrointestinal tract to the mesenteric lymph nodes and other organs in a gnotobiotic mouse model. *Infect Immun*. 1979;23(2):403–411. doi:10.1128/iai.23.2.403-411.1979
75. Baker JW, Deitch EA, Li M, Berg RD, Specian RD. Hemorrhagic shock induces bacterial translocation from the gut. *J Trauma*. 1988;28(7):896–906. doi:10.1097/00005373-198807000-00002
76. Saydjari R, Beerthuizen GI, Townsend CM Jr, Herndon DN, Thompson JC. Bacterial translocation and its relationship to visceral blood flow, gut mucosal ornithine decarboxylase activity, and DNA in pigs. *J Trauma*. 1991;31(5):639–43;discussion643–4. doi:10.1097/00005373-199105000-00007
77. Pastores SM, Katz DP, Kvetan V. Splanchnic ischemia and gut mucosal injury in sepsis and the multiple organ dysfunction syndrome. *Am J Gastroenterol*. 1996;91(9):1697–1710.
78. Singer BH, Dickson RP, Denstaedt SJ, et al. Bacterial dissemination to the brain in sepsis. *Am J Respir Crit Care Med*. 2018;197(6):747–756. doi:10.1164/rccm.201708-1559OC
79. Druml W. Systemic consequences of acute kidney injury. *Curr Opin Crit Care*. 2014;20(6):613–619. doi:10.1097/mcc.0000000000000150
80. Li J, Moturi KR, Wang L, Zhang K, Yu C. Gut derived-endotoxin contributes to inflammation in severe ischemic acute kidney injury. *BMC Nephrol*. 2019;20(1):16. doi:10.1186/s12882-018-1199-4

81. Shi H, Ge X, Ma X, et al. A fiber-deprived diet causes cognitive impairment and hippocampal microglia-mediated synaptic loss through the gut microbiota and metabolites. *Microbiome*. 2021;9(1):223. doi:10.1186/s40168-021-01172-0
82. Li S, Lv J, Li J, et al. Intestinal microbiota impact sepsis associated encephalopathy via the vagus nerve. *Neurosci Lett*. 2018;662:98–104. doi:10.1016/j.neulet.2017.10.008
83. Bailey MT, Cryan JF. The microbiome as a key regulator of brain, behavior and immunity: commentary on the 2017 named series. *Brain Behav Immun*. 2017;66:18–22. doi:10.1016/j.bbi.2017.08.017
84. Yuan Y, Adam A, Zhao C, Chen H. Recent advancements in the mechanisms underlying resistance to PD-1/PD-L1 blockade immunotherapy. *Cancers*. 2021;13(4). doi:10.3390/cancers13040663
85. Mu S, Xiang H, Wang Y, et al. The pathogens of secondary infection in septic patients share a similar genotype to those that predominate in the gut. *Crit Care*. 2022;26(1):68. doi:10.1186/s13054-022-03943-z
86. Long X, Mu S, Zhang J, et al. Global signatures of the microbiome and metabolome during hospitalization of septic patients. *Shock*. 2023;59(5):716–724. doi:10.1097/shk.0000000000002117
87. Zhou X, Liao Y. Gut-lung crosstalk in sepsis-induced acute lung injury. *Front Microbiol*. 2021;12:779620. doi:10.3389/fmicb.2021.779620
88. Dickson RP, Singer BH, Newstead MW, et al. Enrichment of the lung microbiome with gut bacteria in sepsis and the acute respiratory distress syndrome. *Nat Microbiol*. 2016;1(10):16113. doi:10.1038/nmicrobiol.2016.113
89. Zhang P, Liu B, Zheng W, et al. Pulmonary microbial composition in sepsis-induced acute respiratory distress syndrome. *Front Mol Biosci*. 2022;9:862570. doi:10.3389/fmolb.2022.862570
90. Pérez-Hernández EG, Delgado-Coello B, Luna-Reyes I, Mas-Oliva J. New insights into lipopolysaccharide inactivation mechanisms in sepsis. *Biomed Pharmacother*. 2021;141:111890. doi:10.1016/j.biopha.2021.111890
91. Zhang X, Liu H, Hashimoto K, Yuan S, Zhang J. The gut-liver axis in sepsis: interaction mechanisms and therapeutic potential. *Crit Care*. 2022;26(1):213. doi:10.1186/s13054-022-04090-1
92. Zhang J, Ankawi G, Sun J, et al. Gut-kidney crosstalk in septic acute kidney injury. *Crit Care*. 2018;22(1):117. doi:10.1186/s13054-018-2040-y
93. Mankowski RT, Laitano O, Darden D, et al. Sepsis-induced myopathy and gut microbiome dysbiosis: mechanistic links and therapeutic targets. *Shock*. 2022;57(1):15–23. doi:10.1097/shk.0000000000001843
94. Chen G, Huang B, Fu S, et al. G protein-coupled receptor 109A and host microbiota modulate intestinal epithelial integrity during sepsis. *Front Immunol*. 2018;9:2079. doi:10.3389/fimmu.2018.02079
95. Emal D, Rampanelli E, Stroo I, et al. Depletion of Gut microbiota protects against renal ischemia-reperfusion injury. *J Am Soc Nephrol*. 2017;28(5):1450–1461. doi:10.1681/asn.2016030255
96. Gong S, Yan Z, Liu Z, et al. Intestinal microbiota mediates the susceptibility to polymicrobial sepsis-induced liver injury by granisetron generation in mice. *Hepatology*. 2019;69(4):1751–1767. doi:10.1002/hep.30361
97. Sasabe J, Miyoshi Y, Rakoff-Nahoum S, et al. Interplay between microbial d-amino acids and host d-amino acid oxidase modifies murine mucosal defence and gut microbiota. *Nat Microbiol*. 2016;1(10):16125. doi:10.1038/nmicrobiol.2016.125
98. Nakade Y, Iwata Y, Furuichi K, et al. Gut microbiota-derived D-serine protects against acute kidney injury. *JCI Insight*. 2018;3(20). doi:10.1172/jci.insight.97957
99. Al-Harbi NO, Nadeem A, Ahmad SF, et al. Short chain fatty acid, acetate ameliorates sepsis-induced acute kidney injury by inhibition of NADPH oxidase signaling in T cells. *Int Immunopharmacol*. 2018;58:24–31. doi:10.1016/j.intimp.2018.02.023
100. Andrade-Oliveira V, Amano MT, Correa-Costa M, et al. Gut bacteria products prevent AKI induced by ischemia-reperfusion. *J Am Soc Nephrol*. 2015;26(8):1877–1888. doi:10.1681/asn.2014030288
101. Hotchkiss RS, Monneret G, Payen D. Immunosuppression in sepsis: a novel understanding of the disorder and a new therapeutic approach. *Lancet Infect Dis*. 2013;13(3):260–268. doi:10.1016/s1473-3099(13)70001-x
102. Cani PD, Depommier C, Derrien M, Everard A, de Vos WM. Akkermansia muciniphila: paradigm for next-generation beneficial microorganisms. *Nat Rev Gastroenterol Hepatol*. 2022;19(10):625–637. doi:10.1038/s41575-022-00631-9
103. Ghosh TS, Shanahan F, O'Toole PW. The gut microbiome as a modulator of healthy ageing. *Nat Rev Gastroenterol Hepatol*. 2022;19(9):565–584. doi:10.1038/s41575-022-00605-x
104. Lin X, Hu T, Wu Z, et al. Isolation of potentially novel species expands the genomic and functional diversity of Lachnospiraceae. *Imeta*. 2024;3(2):e174. doi:10.1002/imt2.174
105. Krag-Olsen B, Wolthers OD, Storm K. Mitralinsufficiens og Marfan's syndrom hos børn. [Mitral insufficiency and Marfan syndrome in children]. *Ugeskr Laeger*. 1988;150(46):2825–2827.
106. Brown EM, Clardy J, Xavier RJ. Gut microbiome lipid metabolism and its impact on host physiology. *Cell Host Microbe*. 2023;31(2):173–186. doi:10.1016/j.chom.2023.01.009
107. Tang WH, Kitai T, Hazen SL. Gut microbiota in cardiovascular health and disease. *Circ Res*. 2017;120(7):1183–1196. doi:10.1161/circresaha.117.309715
108. Wong CC, Yu J. Gut microbiota in colorectal cancer development and therapy. *Nat Rev Clin Oncol*. 2023;20(7):429–452. doi:10.1038/s41571-023-00766-x
109. Gruda MC, Ruggeberg KG, O'Sullivan P, et al. Broad adsorption of sepsis-related PAMP and DAMP molecules, mycotoxins, and cytokines from whole blood using CytoSorb® sorbent porous polymer beads. *PLoS One*. 2018;13(1):e0191676. doi:10.1371/journal.pone.0191676
110. Akira S, Takeda K, Kaisho T. Toll-like receptors: critical proteins linking innate and acquired immunity. *Nat Immunol*. 2001;2(8):675–680. doi:10.1038/90609
111. Salomão R, Martins PS, Brunialti MK, et al. TLR signaling pathway in patients with sepsis. *Shock*. 2008;30 Suppl 1:73–77. doi:10.1097/SHK.0b013e318181af2a
112. Carneiro AB, Iaciura BM, Nohara LL, et al. Lysophosphatidylcholine triggers TLR2- and TLR4-mediated signaling pathways but counteracts LPS-induced NO synthesis in peritoneal macrophages by inhibiting NF-κB translocation and MAPK/ERK phosphorylation. *PLoS One*. 2013;8(9):e76233. doi:10.1371/journal.pone.0076233
113. Wang S, Jiang D, Huang F, et al. Therapeutic effect of Echinococcus granulosus cyst fluid on bacterial sepsis in mice. *Parasit Vectors*. 2023;16(1):450. doi:10.1186/s13071-023-06021-7

114. Li C, Qi X, Xu L, et al. Preventive effect of the total polyphenols from nymphaea candida on sepsis-induced acute lung injury in mice via gut microbiota and NLRP3, TLR-4/NF-κB pathway. *Int J Mol Sci*. 2024;25(8). doi:10.3390/ijms25084276
115. Chang YL, Chen TH, Wu YH, et al. A novel TLR2-triggered signalling crosstalk synergistically intensifies TNF-mediated IL-6 induction. *J Cell Mol Med*. 2014;18(7):1344–1357. doi:10.1111/jcmm.12294
116. Lee EP, Lin MJ, Wu HP. Time-serial expression of toll-like receptor 4 signaling during polymicrobial sepsis in rats. *Int J Immunopathol Pharmacol*. 2022;36:3946320221090021. doi:10.1177/03946320221090021
117. Li H, Liu S, Chen H, et al. Gut dysbiosis contributes to SCFAs reduction-associated adipose tissue macrophage polarization in gestational diabetes mellitus. *Life Sci*. 2024;350:122744. doi:10.1016/j.lfs.2024.122744
118. Keller SA, Paxian M, Ashburn JH, Clemens MG, Huynh T. Kupffer cell ablation improves hepatic microcirculation after trauma and sepsis. *J Trauma*. 2005;58(4):740–9;discussion749–51. doi:10.1097/01.ta.0000158246.74816.18
119. Shen JC, Qi Q, Han D, et al. Moxibustion improves experimental colitis in rats with Crohn's disease by regulating bile acid enterohepatic circulation and intestinal farnesoid X receptor. *J Integr Med*. 2023;21(2):194–204. doi:10.1016/j.joim.2023.01.001
120. Li J, Chen Y, Li R, et al. Gut microbial metabolite hyodeoxycholic acid targets the TLR4/MD2 complex to attenuate inflammation and protect against sepsis. *Mol Ther*. 2023;31(4):1017–1032. doi:10.1016/j.ymthe.2023.01.018
121. Sondermann NC, Faßbender S, Hartung F, et al. Functions of the aryl hydrocarbon receptor (AHR) beyond the canonical AHR/ARNT signaling pathway. *Biochem. Pharmacol*. 2023;208:115371. doi:10.1016/j.bcp.2022.115371
122. Jakkampudi A, Sarkar P, Unnisa M, et al. Kynurenine pathway alteration in acute pancreatitis and its role as a biomarker of infected necrosis. *Pancreatology*. 2023;23(6):589–600. doi:10.1016/j.pan.2023.07.003
123. Xie S, Li J, Lyu F, et al. Novel tripeptide RKH derived from Akkermansia muciniphila protects against lethal sepsis. *Gut*. 2023;73(1):78–91. doi:10.1136/gutjnl-2023-329996
124. Fu J, Han Z, Wu Z, et al. GABA regulates IL-1β production in macrophages. *Cell Rep*. 2022;41(10):111770. doi:10.1016/j.celrep.2022.111770
125. Wang W, Dernst A, Martin B, et al. Butyrate and propionate are microbial danger signals that activate the NLRP3 inflammasome in human macrophages upon TLR stimulation. *Cell Rep*. 2024;43(9):114736. doi:10.1016/j.celrep.2024.114736
126. Hao H, Cao L, Jiang C, et al. Farnesoid X receptor regulation of the NLRP3 inflammasome underlies cholestasis-associated sepsis. *Cell Metab*. 2017;25(4):856–867.e5. doi:10.1016/j.cmet.2017.03.007
127. Yang F, Mao C, Guo L, et al. Structural basis of GPBAR activation and bile acid recognition. *Nature*. 2020;587(7834):499–504. doi:10.1038/s41586-020-2569-1
128. Jin P, Deng S, Tian M, et al. INT-777 prevents cognitive impairment by activating Takeda G protein-coupled receptor 5 (TGR5) and attenuating neuroinflammation via cAMP/ PKA/ CREB signaling axis in a rat model of sepsis. *Exp Neurol*. 2021;335:113504. doi:10.1016/j.expneurol.2020.113504
129. Singh N, Gurav A, Sivaprakasam S, et al. Activation of Gpr109a, receptor for niacin and the commensal metabolite butyrate, suppresses colonic inflammation and carcinogenesis. *Immunity*. 2014;40(1):128–139. doi:10.1016/j.immuni.2013.12.007
130. Wei Y, Li T, Zhao D, et al. Sodium butyrate ameliorates sepsis-associated lung injury by enhancing gut and lung barrier function in combination with modulation of CD4(+)Foxp3(+) regulatory T cells. *Eur J Pharmacol*. 2024;963:176219. doi:10.1016/j.ejphar.2023.176219
131. Chang S, Kim YH, Kim YJ, et al. Taurodeoxycholate increases the number of myeloid-derived suppressor cells that ameliorate sepsis in mice. *Front Immunol*. 2018;9:1984. doi:10.3389/fimmu.2018.01984
132. Jiang L, Hao Y, Han D, et al. Gut microbiota dysbiosis deteriorates immunoregulatory effects of tryptophan via colonic indole and LBP/HTR2B-mediated macrophage function. *Isme J*. 2024;18(1). doi:10.1093/ismejo/wrae166
133. Huang ZB, Zhang GP, Lu CX, et al. Gut microbiota-derived 3-indoleacetic acid confers a protection against sepsis-associated encephalopathy through microglial aryl hydrocarbon receptors. *Exp Neurol*. 2025;384:115055. doi:10.1016/j.expneurol.2024.115055
134. Huang ZB, Hu Z, Lu CX, et al. Gut microbiota-derived indole 3-propionic acid partially activates aryl hydrocarbon receptor to promote macrophage phagocytosis and attenuate septic injury. *Front Cell Infect Microbiol*. 2022;12:1015386. doi:10.3389/fcimb.2022.1015386
135. Gu P, Liu R, Yang Q, et al. A metabolite from commensal Candida albicans enhances the bactericidal activity of macrophages and protects against sepsis. *Cell Mol Immunol*. 2023;20(10):1156–1170. doi:10.1038/s41423-023-01070-5
136. Deng F, Hu JJ, Lin ZB, et al. Gut microbe-derived milnacipran enhances tolerance to gut ischemia/reperfusion injury. *Cell Rep Med*. 2023;4(3):100979. doi:10.1016/j.xcrm.2023.100979
137. Carasso S, Zaatry R, Hajjo H, et al. Inflammation and bacteriophages affect DNA inversion states and functionality of the gut microbiota. *Cell Host Microbe*. 2024;32(3):322–334.e9. doi:10.1016/j.chom.2024.02.003
138. Bengmark S. Pro- and synbiotics to prevent sepsis in major surgery and severe emergencies. *Nutrients*. 2012;4(2):91–111. doi:10.3390/nu4020091
139. Sun J, Marwah G, Westgarth M, Buys N, Ellwood D, Gray PH. Effects of probiotics on necrotizing enterocolitis, sepsis, intraventricular hemorrhage, mortality, length of hospital stay, and weight gain in very preterm infants: a meta-analysis. *Adv Nutr*. 2017;8(5):749–763. doi:10.3945/an.116.014605
140. Conca N. Probióticos y sepsis tardía en prematuros: un meta-análisis. [Probiotic supplementation and late-onset sepsis in preterm infants: a meta-analysis]. *Rev Chilena Infectol*. 2016;33(2):239. doi:10.4067/s0716-10182016000200016
141. Li JY, He ZX, Wang WM, Lin C. Efficacy of probiotics in preventing late-onset sepsis in very low birth weight infants: a Meta analysis. *Zhongguo Dang Dai Er Ke Za Zhi*. 2021;23(6):599–607. doi:10.7499/j.issn.1008-8830.2012014
142. Xie H, Cai M, Zhang Y. Influence of early enteral nutrition plus probiotics on intestinal function of senile patients with sepsis. *Am J Transl Res*. 2023;15(1):445–451.
143. Kochan P, Chmielarczyk A, Szymaniak L, et al. Lactobacillus rhamnosus administration causes sepsis in a cardiosurgical patient--is the time right to revise probiotic safety guidelines? *Clin Microbiol Infect*. 2011;17(10):1589–1592. doi:10.1111/j.1469-0691.2011.03614.x
144. Kumar R, Tripathi AS, Sharma N, Singh G, Mohapatra L. Is regular probiotic practice safe for management of sepsis? *Chin J Integr Med*. 2022;28(2):185–192. doi:10.1007/s11655-021-3334-5
145. Alander M, Satokari R, Korpela R, et al. Persistence of colonization of human colonic mucosa by a probiotic strain, Lactobacillus rhamnosus GG, after oral consumption. *Appl Environ Microbiol*. 1999;65(1):351–354. doi:10.1128/aem.65.1.351-354.1999

146. Chi C, Buys N, Li C, Sun J, Yin C. Effects of prebiotics on sepsis, necrotizing enterocolitis, mortality, feeding intolerance, time to full enteral feeding, length of hospital stay, and stool frequency in preterm infants: a meta-analysis. *Eur J Clin Nutr*. 2019;73(5):657–670. doi:10.1038/s41430-018-0377-6
147. Klingensmith NJ, Coopersmith CM. Gut Microbiome in Sepsis. *Surg Infect*. 2023;24(3):250–257. doi:10.1089/sur.2022.420
148. Shimizu K, Ogura H, Asahara T, et al. Probiotic/synbiotic therapy for treating critically ill patients from a gut microbiota perspective. *Dig Dis Sci*. 2013;58(1):23–32. doi:10.1007/s10620-012-2334-x
149. Shimizu K, Ogura H, Goto M, et al. Synbiotics decrease the incidence of septic complications in patients with severe SIRS: a preliminary report. *Dig Dis Sci*. 2009;54(5):1071–1078. doi:10.1007/s10620-008-0460-2
150. Liu J, Jin Y, Li H, et al. Probiotics exert protective effect against sepsis-induced cognitive impairment by reversing gut microbiota abnormalities. *J Agric Food Chem*. 2020;68(50):14874–14883. doi:10.1021/acs.jafc.0c06332
151. Chen L, Xu K, Gui Q, Chen Y, Chen D, Yang Y. Probiotic pre-administration reduces mortality in a mouse model of cecal ligation and puncture-induced sepsis. *Exp Ther Med*. 2016;12(3):1836–1842. doi:10.3892/etm.2016.3534
152. Stadlbauer V, Horvath A, Komarova I, et al. Dysbiosis in early sepsis can be modulated by a multispecies probiotic: a randomised controlled pilot trial. *Benef Microbes*. 2019;10(3):265–278. doi:10.3920/bm2018.0067
153. Angurana SK, Bansal A, Singhi S, et al. Evaluation of effect of probiotics on cytokine levels in critically ill children with severe sepsis: a double-blind, placebo-controlled trial. *Crit Care Med*. 2018;46(10):1656–1664. doi:10.1097/ccm.0000000000003279
154. Costeloe K, Hardy P, Juszczak E, Wilks M, Millar MR. Bifidobacterium breve BBG-001 in very preterm infants: a randomised controlled Phase 3 trial. *Lancet*. 2016;387(10019):649–660. doi:10.1016/s0140-6736(15)01027-2
155. Dani C, Coviello CC, Corsini II, Arena F, Antonelli A, Rossolini GM. Lactobacillus sepsis and probiotic therapy in newborns: two new cases and literature review. *AJP Rep*. 2016;6(1):e25–9. doi:10.1055/s-0035-1566312
156. Morowitz MJ, Di Caro V, Pang D, et al. Dietary supplementation with nonfermentable fiber alters the gut microbiota and confers protection in murine models of sepsis. *Crit Care Med*. 2017;45(5):e516–e523. doi:10.1097/ccm.0000000000002291
157. Panigrahi P, Parida S, Nanda NC, et al. A randomized synbiotic trial to prevent sepsis among infants in rural India. *Nature*. 2017;548(7668):407–412. doi:10.1038/nature23480
158. Cammarota G, Ianiro G, Tilg H, et al. European consensus conference on faecal microbiota transplantation in clinical practice. *Gut*. 2017;66(4):569–580. doi:10.1136/gutjnl-2016-313017
159. Gai X, Wang H, Li Y, et al. Fecal microbiota transplantation protects the intestinal mucosal barrier by reconstructing the gut microbiota in a murine model of sepsis. *Front Cell Infect Microbiol*. 2021;11:736204. doi:10.3389/fcimb.2021.736204
160. Assimakopoulos SF, Papadopoulou I, Bantouna D, et al. Fecal microbiota transplantation and hydrocortisone ameliorate intestinal barrier dysfunction and improve survival in a rat model of cecal ligation and puncture-induced sepsis. *Shock*. 2021;55(5):666–675. doi:10.1097/shk.0000000000001566
161. Kim SM, DeFazio JR, Hyoju SK, et al. Fecal microbiota transplant rescues mice from human pathogen mediated sepsis by restoring systemic immunity. *Nat Commun*. 2020;11(1):2354. doi:10.1038/s41467-020-15545-w
162. Li S, Guo H, Xu X, et al. Therapeutic methods for gut microbiota modification in lipopolysaccharide-associated encephalopathy. *Shock*. 2021;56(5):824–831. doi:10.1097/shk.0000000000001758
163. Wei Y, Yang J, Wang J, et al. Successful treatment with fecal microbiota transplantation in patients with multiple organ dysfunction syndrome and diarrhea following severe sepsis. *Crit Care*. 2016;20(1):332. doi:10.1186/s13054-016-1491-2
164. Li Q, Wang C, Tang C, et al. Successful treatment of severe sepsis and diarrhea after vagotomy utilizing fecal microbiota transplantation: a case report. *Crit Care*. 2015;19(1):37. doi:10.1186/s13054-015-0738-7
165. Gopalsamy SN, Sherman A, Woodworth MH, Lutgring JD, Kraft CS. Fecal microbiota transplant for multidrug-resistant organism decolonization administered during septic shock. *Infect Control Hosp Epidemiol*. 2018;39(4):490–492. doi:10.1017/ice.2017.300
166. Tejerina-álvarez EE, de la Cal López M. Selective decontamination of the digestive tract: concept and application. *Med Intensiva*. 2023;47(10):603–615. doi:10.1016/j.medine.2023.05.018
167. Oostdijk EA, de Smet AM, Kesecioglu J, Bonten MJ. The role of intestinal colonization with gram-negative bacteria as a source for intensive care unit-acquired bacteremia. *Crit Care Med*. 2011;39(5):961–966. doi:10.1097/CCM.0b013e318208ee26
168. Hammond NE, Myburgh J, Seppelt I, et al. Association between selective decontamination of the digestive tract and in-hospital mortality in intensive care unit patients receiving mechanical ventilation: a systematic review and meta-analysis. *JAMA*. 2022;328(19):1922–1934. doi:10.1001/jama.2022.19709
169. Aboelatta YA, Abd-Elsalam AM, Omar AH, Abdelaal MM, Farid AM. Selective digestive decontamination (SDD) as a tool in the management of bacterial translocation following major burns. *Ann Burns Fire Disasters*. 2013;26(4):182–188.
170. Potruch A, Schwartz A, Ilan Y. The role of bacterial translocation in sepsis: a new target for therapy. *Therap Adv Gastroenterol*. 2022;15:17562848221094214. doi:10.1177/17562848221094214
171. Hurley JC. Selective digestive decontamination is neither safe nor efficacious for critically ill patients. *Crit Care Med*. 2020;48(5):732–735. doi:10.1097/ccm.0000000000004047
172. Minozzi S, Pifferi S, Brazzi L, Pecoraro V, Montrucchio G, D'Amico R. Topical antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving mechanical ventilation. *Cochrane Database Syst Rev*. 2021;1(1):Cd000022. doi:10.1002/14651858.CD000022.pub4
173. Vincent JL, Jacobs F. Effect of selective decontamination on antibiotic resistance. *Lancet Infect Dis*. 2011;11(5):337–338. doi:10.1016/s1473-3099(11)70067-6
174. Mibelli N, Oehme F, Radulova-Mauersberger O, et al. Bacterial shift and resistance pattern in pancreatic head resections after selective decontamination of the digestive tract - a propensity score-matched analysis. *J Gastrointest Surg*. 2024;28(11):1844–1852. doi:10.1016/j.gassur.2024.08.030
175. Oostdijk EA, de Smet AM, Blok HE, et al. Ecological effects of selective decontamination on resistant gram-negative bacterial colonization. *Am J Respir Crit Care Med*. 2010;181(5):452–457. doi:10.1164/rccm.200908-1210OC
176. Buitinck S, Jansen R, Rijkenberg S, et al. The ecological effects of selective decontamination of the digestive tract (SDD) on antimicrobial resistance: a 21-year longitudinal single-centre study. *Crit Care*. 2019;23(1):208. doi:10.1186/s13054-019-2480-z

177. Wittekamp BHJ, Oostdijk EAN, Cuthbertson BH, Brun-Buisson C, Bonten MJM. Selective decontamination of the digestive tract (SDD) in critically ill patients: a narrative review. *Intensive Care Med*. 2020;46(2):343–349. doi:10.1007/s00134-019-05883-9
178. Rodríguez-Gascón A, Lloréns-Villar Y, Solinís M, Barrasa H, Canut-Blasco A. Does selective digestive decontamination (SDD) increase antibiotic resistance? Long-term comparison of two intensive care units (with and without SDD) of the same tertiary hospital. *Eur J Clin Microbiol Infect Dis*. 2024;43(5):885–893. doi:10.1007/s10096-024-04792-0
179. Zampaloni C, Mattei P, Bleicher K, et al. A novel antibiotic class targeting the lipopolysaccharide transporter. *Nature*. 2024;625(7995):566–571. doi:10.1038/s41586-023-06873-0
180. Lin TL, Shu CC, Chen YM, et al. Like cures like: pharmacological activity of anti-inflammatory lipopolysaccharides from gut microbiome. *Front Pharmacol*. 2020;11:554. doi:10.3389/fphar.2020.00554
181. Li X, Qu S, Song X, Wu C, Shen J, Zhu K. In situ neutralization and detoxification of lps to attenuate hyperinflammation. *Adv Sci*. 2023;10(26): e2302950. doi:10.1002/advs.202302950
182. Balakrishnan A, Marathe SA, Joglekar M, Chakravortty D. Bactericidal/permeability increasing protein: a multifaceted protein with functions beyond LPS neutralization. *Innate Immun*. 2013;19(4):339–347. doi:10.1177/1753425912465098
183. Chen KF, Chaou CH, Jiang JY, et al. Diagnostic accuracy of lipopolysaccharide-binding protein as biomarker for sepsis in adult patients: a systematic review and meta-analysis. *PLoS One*. 2016;11(4):e0153188. doi:10.1371/journal.pone.0153188
184. Stasi A, Intini A, Divella C, et al. Emerging role of Lipopolysaccharide binding protein in sepsis-induced acute kidney injury. *Nephrol Dial Transplant*. 2017;32(1):24–31. doi:10.1093/ndt/gfw250
185. Schultz H, Hume J, Zhang DS, Gioannini TL, Weiss JP. A novel role for the bactericidal/permeability increasing protein in interactions of gram-negative bacterial outer membrane blebs with dendritic cells. *J Immunol*. 2007;179(4):2477–2484. doi:10.4049/jimmunol.179.4.2477
186. Jellema WT, Veerman DP, De Winter RJ, et al. In vivo interaction of endotoxin and recombinant bactericidal/permeability-increasing protein (rBPI23): hemodynamic effects in a human endotoxemia model. *J Lab Clin Med*. 2002;140(4):228–235. doi:10.1067/mlc.2002.127170
187. Opal SM, Palardy JE, Jhung JW, et al. Activity of lipopolysaccharide-binding protein-bactericidal/permeability-increasing protein fusion peptide in an experimental model of Pseudomonas sepsis. *Antimicrob Agents Chemother*. 1995;39(12):2813–2815. doi:10.1128/aac.39.12.2813
188. Beam A, Clinger E, Hao L. Effect of diet and dietary components on the composition of the gut microbiota. *Nutrients*. 2021;13(8). doi:10.3390/nu13082795
189. Reignier J, Boisramé-Helms J, Brisard L, et al. Enteral versus parenteral early nutrition in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2). *Lancet*. 2018;391(10116):133–143. doi:10.1016/s0140-6736(17)32146-3
190. Li J, Lin S, Vanhoutte PM, Woo CW, Xu A. Akkermansia Muciniphila protects against atherosclerosis by preventing metabolic endotoxemia-induced inflammation in apoe-/- mice. *Circulation*. 2016;133(24):2434–2446. doi:10.1161/circulationaha.115.019645
191. Rahmel T, Effinger D, Bracht T, et al. An open-label, randomized controlled trial to assess a ketogenic diet in critically ill patients with sepsis. *Sci Transl Med*. 2024;16(755):eadn9285. doi:10.1126/scitranslmed.adn9285
192. Sugimoto T, Ritter C, Slatopolsky E, Morrissey J. Effect of 1,25-dihydroxyvitamin D3 on phospholipid metabolism in cultured bovine parathyroid cells. *Endocrinology*. 1988;122(6):2387–2392. doi:10.1210/endo-122-6-2387
193. Hornero-Ramirez H, Morisette A, Marcotte B, et al. Multifunctional dietary approach reduces intestinal inflammation in relation with changes in gut microbiota composition in subjects at cardiometabolic risk: the SINFONI project. *Gut Microbes*. 2025;17(1):2438823. doi:10.1080/19490976.2024.2438823
194. Jiang S, Dai S, Li Y, et al. Development and validation of a screening tool for sepsis without laboratory results in the emergency department: a machine learning study. *EClinicalMedicine*. 2025;80:103048. doi:10.1016/j.eclinm.2024.103048
195. Wang S, Liu X, Yuan S, Bian Y, Wu H, Ye Q. Artificial intelligence based multispecialty mortality prediction models for septic shock in a multicenter retrospective study. *NPJ Digit Med*. 2025;8(1):228. doi:10.1038/s41746-025-01643-w
196. Zhang Z, Chen L, Sun B, et al. Identifying septic shock subgroups to tailor fluid strategies through multi-omics integration. *Nat Commun*. 2024;15(1):9028. doi:10.1038/s41467-024-53239-9
197. Wang G, Ma X, Huang W, et al. Macrophage biomimetic nanoparticle-targeted functional extracellular vesicle micro-RNAs revealed via multiomics analysis alleviate sepsis-induced acute lung injury. *J Nanobiotechnol*. 2024;22(1):362. doi:10.1186/s12951-024-02597-z
198. Huang P, Liu Y, Li Y, et al. Metabolomics- and proteomics-based multi-omics integration reveals early metabolite alterations in sepsis-associated acute kidney injury. *BMC Med*. 2025;23(1):79. doi:10.1186/s12916-025-03920-7
199. Liu J, Wang M, Chen W, et al. Altered gut microbiota taxonomic compositions of patients with sepsis in a pediatric intensive care unit. *Front Pediatr*. 2021;9:645060. doi:10.3389/fped.2021.645060
200. Liu R, Hunold KM, Caterino JM, Zhang P. Estimating treatment effects for time-to-treatment antibiotic stewardship in sepsis. *Nat Mach Intell*. 2023;5(4):421–431. doi:10.1038/s42256-023-00638-0
201. Su L, Li Y, Liu S, et al. Establishment and implementation of potential fluid therapy balance strategies for ICU sepsis patients based on reinforcement learning. *Front Med*. 2022;9:766447. doi:10.3389/fmed.2022.766447
202. Tanaka S, Begue F, Veeren B, et al. First recombinant high-density lipoprotein particles administration in a severe ICU COVID-19 patient, a MULTI-OMICS EXPLORATORY INVESTIGATIOn. *Biomedicines*. 2022;10(4). doi:10.3390/biomedicines10040754
203. Krautkramer KA, Fan J, Bäckhed F. Gut microbial metabolites as multi-kingdom intermediates. *Nat Rev Microbiol*. 2021;19(2):77–94. doi:10.1038/s41579-020-0438-4
204. Shalon D, Culver RN, Grembi JA, et al. Profiling the human intestinal environment under physiological conditions. *Nature*. 2023;617(7961):581–591. doi:10.1038/s41586-023-05989-7
205. Liu L, Chen A, Li Y, Mulder J, Heyn H, Xu X. Spatiotemporal omics for biology and medicine. *Cell*. 2024;187(17):4488–4519. doi:10.1016/j.cell.2024.07.040