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Gut microbiota: A novel target for sepsis treatment

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Sepsis is a life-threatening condition, primarily triggered by infection, that can rapidly progress to multiple organ dysfunction syndrome (MODS) without timely intervention. The gut has long been recognized as a pivotal driver in the pathogenesis of sepsis and MODS.[1] In severe sepsis and septic shock, the gut is often the first organ to be compromised and the last to recover, predisposing patients to intestinal dysbiosis and dysfunction, which further accelerates septic MODS.[2] Growing evidence highlights the crucial role of the gut microbiota in sepsis pathophysiology, as sepsis-induced disruptions in microbial composition may contribute to organ failure.[1] This interplay suggests a potential vicious cycle between gut microbiota dysregulation and sepsis progression.[3] In this editorial, we explore the gut microbiota's role in sepsis and potential therapeutic interventions.

Interplay between gut microbiota and sepsis. Observational studies consistently reveal profound gut microbiota alterations in septic patients, characterized by a depletion of commensal bacteria and an expansion of pathogenic bacterial species.[4,5] These shifts correlate with poor clinical outcomes, including increased mortality.[5] However, factors such as antibiotic administration and intensive care interventions (e.g., opioid use and proton pump inhibitors) may also contribute to dysbiosis.[3] The relationship between gut microbiota and sepsis is further supported by pre-sepsis microbiome analyses. Prescott *et al*[6] reported a 70% increased risk of severe sepsis following hospitalization for *Clostridioides difficile* infection (CDI), compared to other infections. Similarly, Baggs *et al*[7] found a 65% higher risk of rehospitalization for severe sepsis or septic shock in patients previously exposed to CDI-related antibiotics. These findings implicate CDI and broad-spectrum antibiotic use in gut microbiome disruption, suggesting microbiome dysbiosis as a potential risk factor for sepsis. However, as most evidence is observational, residual confounding limits definitive causal inference.

Recent advancements have introduced novel methodologies to investigate the sepsis–gut microbiota relationship. Mendelian randomization (MR), a powerful epidemiological tool for causal inference, suggests a bidirectional relationship: specific bacterial taxa may causally influence sepsis risk and severity, while sepsis itself exacerbates microbial imbalance.[8,9] However, current MR studies predominantly rely on European cohorts, limiting generalizability across diverse populations. To establish robust causal relationships, large-scale multicenter studies—particularly randomized controlled trials (RCTs)—and complementary experimental evidence are essential.

Mechanisms of gut microbiota in sepsis. Existing mechanisms primarily focus on two key areas: (1) Gut dysbiosis as a systemic vulnerability: Pre-sepsis gut dysbiosis disrupts microbial homeostasis, favoring pathogens over commensals. This imbalance reduces key microbial metabolites—short-chain fatty acids (SCFAs), D-lactate, butyrate, and deoxycholic acid—compromising regulatory T-cell function and triggering inflammatory cascades. The gut barrier integrity are destroyed, enabling bacterial translocation and systemic dissemination of pathogen-associated molecular patterns (PAMPs).[3,10] (2) Sepsis-induced exacerbation of gut dysbiosis and organ injury: Sepsis amplifies gut dysfunction through systemic inflammation. Proinflammatory cytokines disrupt tight junctions, while ischemia–reperfusion injury shifts microbiota composition toward facultative anaerobes. Pathogens and metabolites translocate via the portal vein, activating Kupffer cells and driving hepatic inflammation. This gut–liver axis dysfunction accelerates MODS.[11] The interplay between systemic inflammation and microbial imbalance perpetuates a self-reinforcing cycle of organ damage [Figure 1]. Despite growing insights, mechanistic studies often examine isolated pathways rather than their interconnections. Critical questions—such as the temporal sequence between dysbiosis-induced immunosuppression and barrier disruption—remain unresolved. Additionally, reliance on animal models and observational data limits direct clinical applicability.

Therapeutic strategies targeting gut microbiota in sepsis. Numerous studies have explored gut microbiota-based

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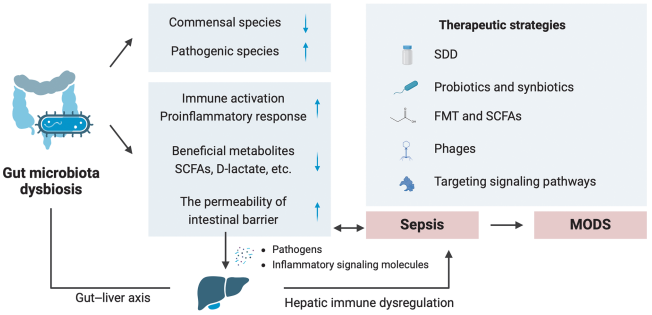

Figure 1: Association between gut dysbiosis and sepsis occurrence. FMT: Fecal microbiota transplantation; MODS: Multiple organ dysfunction syndrome; SCFA: Short-chain fatty acids; SDD: Selective decontamination of the digestive tract.

interventions for sepsis. Here, we summarize current evidence. (1) Selective decontamination of the digestive tract. A meta-analysis of 32 RCTs published in 2022 showed that selective decontamination of the digestive tract (SDD) was associated with reduced in-hospital mortality compared with standard care or placebo in mechanically ventilated intensive care unit (ICU) patients. However, the quality of evidence regarding SDD's impact on antimicrobial resistance remains extremely low.[12] Notably, an RCT published in the same year reported no statistically significant mortality reduction with SDD compared with the standard care in critically ill ventilated patients.[13] These conflicting findings, coupled with concerns that SDD may promote antibiotic resistance, have hindered its routine clinical adoption worldwide. Further research is needed to develop personalized strategies that mitigate resistance risks while optimizing clinical efficacy. (2) Probiotics and synbiotics. Probiotics are live microorganisms that, when consumed in adequate amounts, confer health benefits to the host. Synbiotics, in contrast, are a combination of probiotics and prebiotics, which serve as substrates that promote the growth and activity of beneficial microbes.[14] A meta-analysis by Lou *et al*[15] included 33 studies of 4065 patients receiving probiotics or synbiotics and 3821 control patients found that these supplements reduced sepsis incidence, shortened ICU stays and lowered mortality in critically ill patients. However, variations in probiotic and synbiotic strains, dosages, and treatment durations among studies may have influenced these findings.[16] The clinical utility of probiotics remains controversial, particularly in critically ill populations. Their administration has been linked to an increased risk of bacteremia in ICU patients due to microbial translocation into the bloodstream.[17] Moreover, some evidence suggests that probiotics may exacerbate bacterial translocation in individuals with organ failure, raising concerns about their safety in this subgroup.[18] Currently, there is insufficient direct evidence supporting the use of postbiotics—defined as preparations of inactivated microorganisms and/or their components—for sepsis prevention or treatment.[16] Further research is needed to determine the efficacy, safety, and mechanisms of action of probiotics and related interventions across diverse patient populations and disease conditions. (3) Fecal microbiota transplantation (FMT) and SCFAs. FMT involves transferring fecal material, containing diverse microbial communities, from a healthy donor to a patient to restore gut microbial balance. FMT has been successfully used in cases of refractory sepsis and diarrhea.[19] However, a study reported two fatal cases of bacteremia resulting from the transmission of extended-spectrum beta-lactamase-producing *Escherichia coli* through FMT in 2019, highlighting the substantial risk of multidrug-resistant organism transmission.[20] These findings underscore the need for rigorous donor screening, comprehensive pathogen testing, and standardized safety protocols to mitigate such risks. Emerging research suggests that combining FMT with SCFAs may improve survival in sepsis models, potentially offering a microbe-associated therapeutic benefit.[21] However, excessive SCFA levels could exert cytotoxic effects on pathogens and contribute to MODS, necessitating further investigation into the balance between therapeutic benefit and potential harm.[22] (4) Phage. Phage therapy, which leverages bacteriophages—viruses that infect bacteria and archaea—has demonstrated both immunomodulatory and anti-inflammatory properties in preclinical models of sepsis.[23] Animal studies have highlighted its efficacy,[24] and a clinical trial of the phage AB-SA01 (AmpliPhi Biosciences, San Diego, USA) showed a favorable safety profile in treating septic shock caused by *Staphylococcus aureus*.[25] However, viral therapies pose potential risks that require thorough investigation. Comprehensive safety assessments are crucial to ensuring the viability of phage therapy as a treatment option for sepsis. (5) Others. Emerging therapies targeting gut microbiota-associated pathways hold promise for sepsis management. Preclinical studies suggest that high-density lipoprotein (HDL) infusion mitigates organ damage by neutralizing bacterial toxins (lipopolysaccharide) and modulating immune responses. Inhibiting miR-155 suppresses nuclear factor κB (NF-κB) signaling, thereby reducing inflammation and preserving intestinal barrier integrity. Adsorbent materials targeting the gut–liver axis further impede sepsis progression by sequestering toxins and inflammatory mediators. To counteract antibiotic-induced microbiome disruption, innovative approaches include oral beta-lactamases (ribaxamase) for beta-lactam antibiotics and adsorbents (DAV132; DaVolterra, Paris, France) for broad-spectrum agents. While still experimental, these pathway-specific interventions underscore the potential for precision sepsis therapies.[11]

Summary and prospects. Despite their promise, microbiota-targeted therapies face critical challenges. First, heterogeneity in SDD, probiotic strains, and FMT protocols highlights the urgent need for standardization. Additionally, the long-term risks of these treatments require thorough evaluation. Second, MR studies implicate specific gut microbes in sepsis but are largely based on European cohorts, necessitating broader population studies to establish causality. Integrating microbiota modulation with gut barrier-enhancing strategies, such as combining SCFAs with HDL therapy, may offer synergistic benefits. To translate these therapies into clinical practice, large-scale RCTs and comprehensive mechanistic studies are essential to bridge knowledge gaps and optimize therapeutic efficacy.

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Conflicts of interest

None.

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