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Review

The gut microbiota as a key modulator of sepsis: Mechanisms, clinical implications, and therapeutic perspectives

Bartosz Ziółkowski[1], Kamila Gorczyca[2,*], Dorota Siwicka[1] and Wojciech Dąbrowski[1]

[1] First Department of Anesthesiology and Intensive Therapy, Medical University of Lublin, Lublin, Poland
[2] Chair and Department of Obstetrics and Perinatology, Medical University of Lublin, Lublin, Poland

* **Correspondence:** Email: kamilagorczyca2302@gmail.com; Tel: +48783149474.

Abstract: Sepsis is a life-threatening condition characterized by a dysregulated host response to infection, leading to organ dysfunction and high mortality. Increasing evidence indicates that the gut microbiota plays a significant role in the pathophysiology of sepsis, influencing immune homeostasis, intestinal barrier integrity, and systemic inflammation. This review aimed to provide a comprehensive overview of the role of gut microbiota in the development, progression, and clinical outcomes of sepsis, with particular emphasis on underlying mechanisms and potential therapeutic strategies. Intestinal dysbiosis, characterized by reduced microbial diversity, depletion of commensal bacteria, and expansion of opportunistic pathogens, is associated with increased intestinal permeability and bacterial translocation, which may amplify systemic inflammatory responses. Microbiota-derived metabolites, including short-chain fatty acids and tryptophan-derived compounds, play a key role in maintaining epithelial integrity and modulating immune responses. Disruption of these pathways in sepsis leads to impaired barrier function and immune dysregulation. Clinical studies demonstrate that alterations in gut microbiota composition are associated with disease severity, organ dysfunction, and mortality, suggesting its potential utility as a prognostic marker. At the same time, standard therapeutic interventions, particularly broad-spectrum antibiotics, further exacerbate dysbiosis and may negatively affect clinical outcomes. Emerging microbiota-targeted strategies, such as fecal microbiota transplantation, probiotics, prebiotics, and postbiotics, offer promising adjunctive approaches aimed at restoring microbial balance and improving host responses. However, current evidence remains limited and heterogeneous. In conclusion, the gut microbiota represents an important contributor to sepsis pathophysiology and a potential target for innovative therapeutic interventions. Further research is required to establish clinically effective

microbiome-based strategies and to integrate microbiota profiling into personalized approaches to sepsis management.

Keywords: sepsis; gut microbiota; dysbiosis; intestinal barrier; short-chain fatty acids; immune response; microbiota-targeted therapy

1. Introduction

Sepsis is a life-threatening organ dysfunction resulting from a dysregulated host response to infection and represents a major global health burden, placing a substantial burden on healthcare systems [1]. In 2021, an estimated 166 million cases of sepsis were reported worldwide, with 21.4 million resulting in death [2]. Current recommendations for the management of sepsis emphasize early recognition and prompt diagnosis, timely initiation of appropriate antimicrobial therapy, and preservation of organ function through targeted supportive interventions. Comprehensive supportive care also includes glycemic control, prophylaxis of venous thromboembolism, and prevention of stress-related mucosal injury [3]. Increasing evidence highlights a strong association between alterations in the gut microbiota and the pathophysiology of sepsis. Alterations in microbial composition and function have been associated with immune dysregulation, impaired gut barrier integrity, and systemic inflammation. Consequently, modulation of the gut microbiota has emerged as a promising therapeutic strategy with the potential to improve clinical outcomes in patients with sepsis.

This review aims to provide a comprehensive overview of the role of gut microbiota in the pathogenesis, management, and prognosis of sepsis.

2. Materials and methods

2.1. Protocol and reporting

This study was designed as a structured narrative review. To enhance transparency, reproducibility, and methodological rigor, we incorporated key elements of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) framework, including a systematic search strategy, predefined eligibility criteria, and a transparent study selection process. However, because this work represents a narrative mechanistic review rather than a formal systematic review with quantitative synthesis, the protocol was not prospectively registered. The reporting was aligned with current best practices for narrative reviews integrating mechanistic and translational evidence.

2.2. Information sources and search strategy

A comprehensive literature search was performed in PubMed (MEDLINE), Scopus, and Web of Science from database inception to 31 January 2026. The last search was conducted on January 31, 2026. The search covered all records from database inception to the search date.

The search strategy combined controlled vocabulary terms (MeSH) and free-text keywords related to sepsis and gut microbiota. Key terms included “sepsis”, “gut microbiota”, “intestinal

dysbiosis", "microbiome", "short-chain fatty acids", "intestinal barrier", "immune response", "bacterial translocation", and "critical illness".

Boolean operators ("AND", "OR") and database-specific field tags were applied to optimize sensitivity and specificity. Only studies published in English were included. Additionally, the reference lists of relevant articles and reviews were manually screened to identify further eligible studies not captured in the database search (Figure 1).

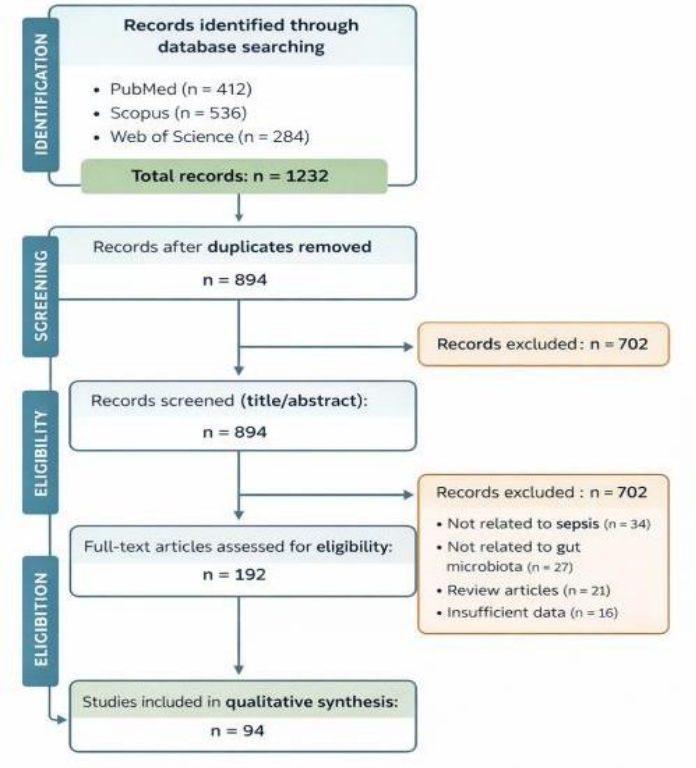


Figure 1. PRISMA 2020 flow diagram of the literature search and study selection process.

2.3. Eligibility criteria

Studies were selected according to predefined inclusion and exclusion criteria.

Inclusion criteria:

- Original peer-reviewed studies (human or animal)
- Experimental, observational, or clinical study designs
- Studies investigating gut microbiota composition, function, or metabolites
- Studies assessing the role of gut microbiota in sepsis pathogenesis, progression, immune response, or clinical outcomes

Exclusion criteria:

- Reviews, meta-analyses, editorials, commentaries, letters, and conference abstracts without full text
- Non-original publications
- Studies not related to sepsis
- Studies not addressing gut microbiota or host–microbiota interactions
- Studies with incomplete or unclear reporting of essential methodology or outcomes

Although narrative reviews, systematic reviews, and clinical guidelines were excluded from the primary study selection (n = 94 original research articles), selected synthesis papers were additionally referenced to provide relevant background and contextual information. Population: Patients with sepsis, critically ill individuals, or relevant animal models of sepsis. Exposure: Alterations in gut microbiota composition (dysbiosis), microbial metabolites (e.g., SCFAs, tryptophan metabolites), or disruption of intestinal barrier integrity. Outcomes: Immune response modulation, inflammatory markers, organ dysfunction, mortality, microbiota composition changes, and clinical outcomes associated with sepsis.

2.4. Study selection

All identified records were screened based on titles and abstracts. Full texts of potentially relevant studies were assessed for eligibility. The selection process was conducted by two reviewers independently. Any discrepancies were resolved through discussion until consensus was reached.

2.5. Data extraction

Data extraction was performed using a structured approach. The following information was collected:

- Author and year of publication
- Study design and population
- Characteristics of microbiota alterations
- Assessed microbial metabolites (e.g., SCFAs, indole derivatives)
- Evaluated immune or clinical outcomes
- Key findings and proposed mechanisms

Any discrepancies were resolved through discussion and re-evaluation of the original publications. The complete baseline characteristics, experimental designs, microbiome profiling methodologies, and primary outcomes of all 94 included primary studies are systematically tabulated in Supplementary Table S1.

2.6. Critical appraisal of studies

Given the broad mechanistic scope and heterogeneity of the included literature, encompassing in vitro experiments, animal models, and observational studies, formal quantitative risk-of-bias scoring tools were not systematically applied. Instead, a qualitative critical appraisal was conducted during data extraction. Priority was given to studies with well-defined experimental controls, robust microbiome profiling methodologies, and clear reporting of potential confounding variables, such as antibiotic exposure and disease severity.

2.7. Synthesis of results

Due to substantial heterogeneity in study design, populations, microbiota assessment methods, and reported outcomes, a formal meta-analysis was not feasible.

Therefore, findings were synthesized narratively, focusing on:

- Mechanisms linking gut microbiota and host immune response
- Role of microbial metabolites (e.g., SCFAs, tryptophan derivatives)
- Integrity of the intestinal barrier
- Impact of dysbiosis on sepsis development and outcomes
- Potential therapeutic strategies targeting the microbiome

The synthesis emphasizes biological plausibility, consistency of findings, and translational relevance.

3. Intestinal microbiota and its role in immune homeostasis

3.1. Composition of the intestinal microbiota

The intestinal microbiota comprises a complex and dynamic community of microorganisms, including bacteria, viruses, and fungi, which colonize the gastrointestinal tract. It is estimated that the human large intestine harbors approximately 38 trillion bacteria, a number comparable to the total number of human cells, with a total microbial biomass of approximately 200 g [4]. The composition of the intestinal microbiota begins to develop early in life. Under physiological conditions, the fetus is generally considered sterile, with microbial colonization initiating at birth [5]. The subsequent maturation of the gut microbiota is influenced by multiple factors, including host genetics, age, mode of delivery, infant feeding practices, diet, environmental exposures, and the use of medications, particularly antibiotics [6,7]. In adults, gut microbiota is predominantly composed of commensal bacteria. The dominant phyla are Firmicutes and Bacteroidota, which together account for approximately 90% of the total microbial population. Additional phyla, including Actinobacteria, Proteobacteria, Verrucomicrobia, and Fusobacteria, are also present in smaller proportions [8]. A healthy gut microbiota is characterized by high microbial diversity at both the α- and β-diversity levels, reflecting not only a rich species composition but also significant spatial variability along different regions of the gastrointestinal tract.

3.2. Mechanisms by which the gut microbiota influences host physiology

3.2.1. Short-chain fatty acids

Short-chain fatty acids (SCFAs) are a group of metabolites consisting of 2–6 carbon atoms, produced through the anaerobic fermentation of dietary fiber by the gut microbiota [9]. The predominant SCFAs in the intestine are acetate, propionate, and butyrate, typically present in a relatively stable ratio of approximately 60:20:20 [10]. Acetate is synthesized by the majority of anaerobic bacterial species within the gut microbiota. In contrast, propionate and butyrate are generated by more specialized microbial taxa. Butyrate-producing bacteria are primarily members of the phylum Firmicutes, particularly within the families Lachnospiraceae (e.g., *Roseburia* spp., *Blautia* spp., *Anaerobutyricum hallii*) and Oscillospiraceae (e.g., *Faecalibacterium prausnitzii*) [11]. Propionate production is associated with representatives of Bacteroidota (e.g., *Prevotella* spp.), Negativicutes (e.g., *Veillonella* spp., *Phascolarctobacterium succinatutens*), Lachnospiraceae (e.g., *Coprococcus* spp., *Roseburia inulinivorans*, *Blautia* spp.), and *Akkermansia muciniphila* [11,12].

SCFAs exert their biological effects through two principal mechanisms. First, they act as ligands

for G protein–coupled receptors (GPCRs), including free fatty acid receptors FFAR2 (GPR43) and FFAR3 (GPR41), as well as hydroxycarboxylic acid receptor 2 (HCAR2, also known as GPR109A) [13]. These receptors play a particularly important role in the regulation of immune responses relevant to sepsis. Second, SCFAs regulate gene expression through epigenetic mechanisms. They inhibit histone deacetylases (HDACs), thereby promoting histone acetylation [14,15]. In addition, butyrate undergoes mitochondrial β-oxidation, generating acetyl-CoA, which further enhances histone acetyltransferase (HAT) activity [16]. These processes lead to hyperacetylation of histone proteins, alterations in chromatin structure, and increased transcriptional activity of multiple genes [13].

SCFAs play a central role in maintaining the function and integrity of intestinal epithelial cells (IECs). Butyrate serves as the primary energy source for colonocytes and may also function as an alternative energy substrate for enterocytes [17–19]. Acetate, in turn, can be utilized in lipogenesis within the colonic epithelium [20]. Furthermore, SCFAs regulate key cellular processes, including proliferation, differentiation, and apoptosis of IECs, thereby supporting epithelial renewal and homeostasis [19–23]. Through activation of peroxisome proliferator-activated receptor-γ (PPAR-γ), SCFAs increase oxygen consumption in IECs and stabilize hypoxia-inducible factor (HIF), promoting a hypoxic luminal environment that favors obligate anaerobes and limits the expansion of facultative pathogenic bacteria [24–26]. Stabilization of HIF-1α also contributes to the maintenance of intestinal barrier integrity by enhancing mucin production, antimicrobial peptide secretion, and tight junction assembly [27].

SCFAs exert potent immunomodulatory effects within the gut environment. Activation of GPR43 and GPR109A receptors stimulates the secretion of interleukin-18 (IL-18) by IECs, which plays a key role in epithelial regeneration [28]. Additionally, SCFAs promote immune tolerance by inhibiting Th17 cell differentiation while enhancing regulatory T cell (Treg) function [29]. Under inflammatory conditions, SCFAs reduce the production of proinflammatory cytokines, including TNF-α, IL-1β, IL-6, and IL-8, while simultaneously increasing the expression of anti-inflammatory cytokines such as IL-10 and TGF-β by intestinal epithelial cells [30–32].

In macrophages, butyrate and acetate activate GPR43, leading to the inhibition of proinflammatory cytokine secretion and pyroptosis [33–36]. Through modulation of histone acetylation, these SCFAs promote macrophage polarization toward the anti-inflammatory M2 phenotype [37], which is associated with increased production of antimicrobial peptides [38]. Acetate is a potent activator of neutrophils and, via GPR43 signaling, enhances their chemotaxis, oxidative burst, and phagocytic activity [39]. In contrast, butyrate exerts predominantly inhibitory effects on neutrophil function. Through HDAC-dependent mechanisms, it suppresses the secretion of proinflammatory cytokines (IL-6, TNF-α, IFN-γ, IL-17A, IL-22), reduces the production of antimicrobial proteins (e.g., calprotectin and lipocalin-2 [LCN2]), and limits reactive oxygen species generation, chemotaxis, and the formation of neutrophil extracellular traps (NETs) [40]. Finally, SCFAs also influence lymphocyte differentiation. They promote the expansion of Treg cells, support the generation of memory $CD8^+$ T cells, and enhance plasma cell activity, while simultaneously reducing the differentiation of Th17 cells [41–43]. The principal mechanisms through which SCFAs regulate intestinal barrier integrity and immune homeostasis, as well as the consequences of impaired SCFA signaling during sepsis-associated dysbiosis, are summarized in Figure 2.

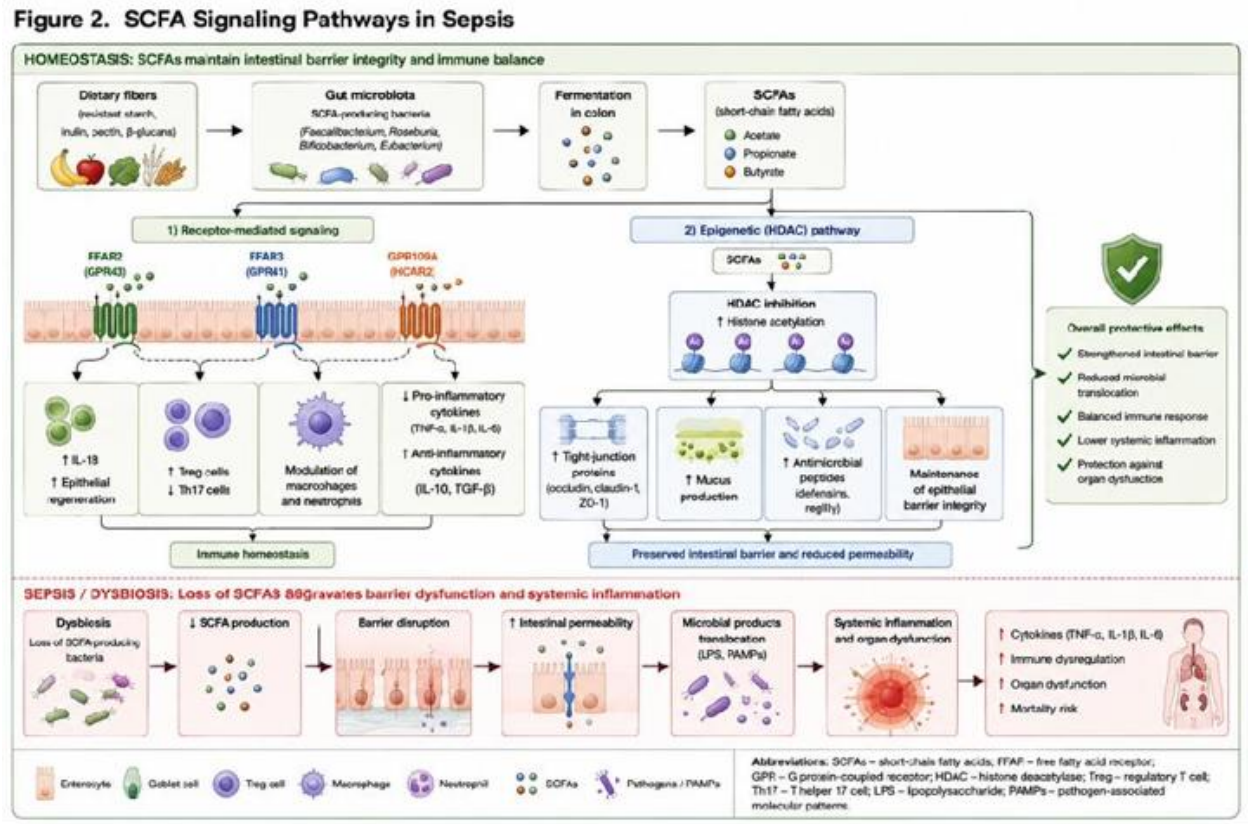


Figure 2. SCFA signaling pathways in sepsis.

3.2.2. Tryptophan metabolites

Tryptophan is an essential amino acid, primarily metabolized in the human body via the kynurenine pathway. More than 95% of tryptophan is converted to kynurenine in reactions catalyzed by indoleamine 2,3-dioxygenases (IDO1 and IDO2), whose activity is upregulated by proinflammatory cytokines such as TNF-α and IFN-γ [44]. A key metabolite of this pathway is kynurenic acid (KYNA), which exhibits potent anti-inflammatory properties. KYNA inhibits the secretion of TNF-α, HMGB1, IL-23, and human neutrophil peptide-1 (HNP-1), reduces Th17 lymphocyte activity, and functions as a free radical scavenger [45–47]. A smaller fraction of tryptophan is metabolized by commensal bacteria, particularly from the genera *Bacteroides* and *Bifidobacterium*, into indole derivatives such as indole-3-acetic acid (IAA), indole-3-propionic acid (IPA), and indole-3-aldehyde (IAld). Certain *Lactobacillus* species, including *Lactobacillus reuteri*, additionally produce indole-3-lactic acid (ILA) [48]. Indole derivatives act as ligands for the aryl hydrocarbon receptor (AhR), a cytosolic receptor expressed in various host cells [49]. Activation of AhR mediates multiple immunomodulatory effects, including inhibition of the NF-κB pathway, promotion of TLR4 ubiquitination, and reduction of proinflammatory cytokine secretion (TNF-α, IL-1β, IL-6). Furthermore, these compounds promote the differentiation of regulatory T (Treg) cells and $CD4^+CD8\alpha\alpha^+$ T cells, enhance macrophage phagocytic activity, and inhibit Th17 cell maturation [50–54]. Indole metabolites also contribute to the maintenance of intestinal barrier integrity by increasing mucus and lysozyme secretion and promoting tight

junction formation in intestinal epithelial cells (IECs) [55,56]. In addition, they modulate the composition of the gut microbiota, increasing the abundance of Akkermansiaceae and Bifidobacteriaceae while reducing Bacteroidaceae and Enterobacteriaceae [57]. Beyond host-directed effects, indole derivatives influence microbial behavior by modulating virulence factor expression, biofilm formation, and sporulation, as well as exerting direct bactericidal activity. These effects contribute to the inhibition of pathogens such as *Escherichia coli* and *Staphylococcus aureus* [58–62]. Moreover, indole metabolites stimulate IL-22 production by type 3 innate lymphoid cells (ILC3), enhancing host defense against *Candida albicans,* and can directly induce calcium-dependent apoptosis in this pathogen [63–65]. The major host- and microbiota-derived pathways of tryptophan metabolism and their downstream effects on AhR signaling, mucosal immunity, and intestinal barrier integrity in the context of sepsis are summarized in Figure 3.

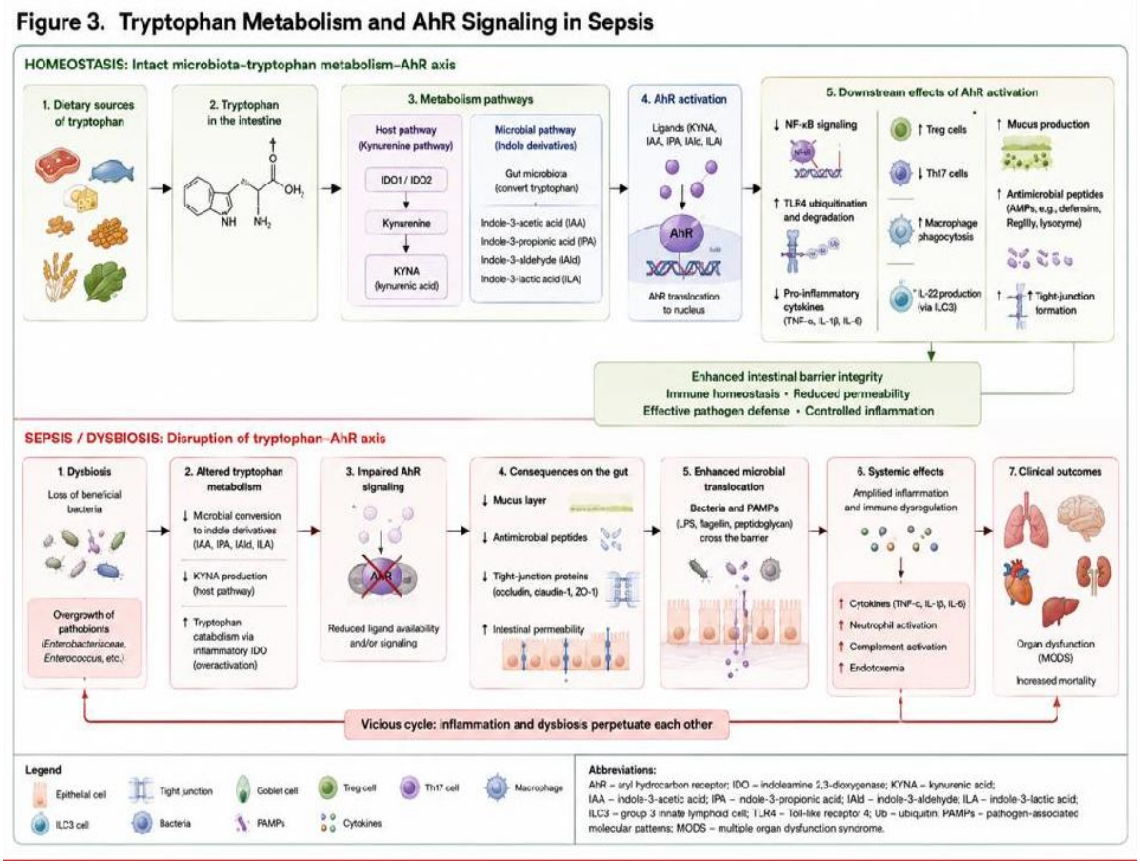


Figure 3. Tryptophan metabolism and AhR signaling in sepsis.

3.2.3. Pathogen-associated molecular patterns

Pathogen-associated molecular patterns (PAMPs) are conserved microbial structures, including lipopolysaccharide (LPS), peptidoglycan (PGN), and flagellin (FliC), that are recognized by pattern recognition receptors (PRRs) expressed on immune cells and intestinal epithelial cells, thereby triggering inflammatory responses. LPS, a major component of the outer membrane of Gram-negative bacteria, is one of the most extensively studied PAMPs. It is recognized by Toll-like receptor 4 (TLR4) expressed on monocytes, macrophages, dendritic cells,

and neutrophils, leading to the activation of innate immunity and increased production of proinflammatory cytokines (TNF-α, IL-1β, IL-6) as well as type I interferons [66]. Flagellin (FliC), a structural protein of bacterial flagella, is recognized by TLR5 expressed on monocytes, immature macrophages, dendritic cells, and IECs. TLR5 activation promotes the secretion of proinflammatory cytokines and RegIIIγ, activates ILC3, enhances plasma cell and Th17 cell differentiation, and inhibits Treg cell maturation [67]. Peptidoglycan (PGN) is recognized by multiple receptors, including TLR1/2, TLR2/6, nucleotide-binding oligomerization domain-like receptors (NOD1 and NOD2), and peptidoglycan recognition proteins (PGRPs). Activation of TLR and NOD pathways induces inflammatory signaling and increases the expression of proinflammatory cytokines and interferon-β (IFN-β) [68,69]. In contrast, PGRPs exhibit direct bactericidal and bacteriostatic activity, contribute to inflammatory signaling, and facilitate the degradation of circulating PGN [70–75].

Polysaccharide A (PSA), a capsular component of *Bacteroides fragilis*, represents a unique example of a PAMP with immunoregulatory properties and is often described as a prototypical symbiosis factor. PSA is recognized by TLR2 on dendritic cells and subsequently presented via major histocompatibility complex (MHC) class II molecules. Recognition of PSA by the T cell receptor (TCR) promotes the differentiation of naïve $CD4^+$ T cells into IL-10-producing regulatory T (Treg) cells and inhibits Th17 cell maturation. Additionally, PSA contributes to maintaining immune homeostasis by balancing Th1 and Th2 responses [76].

3.3. Intestinal barrier dysfunction in sepsis

The intestinal barrier is a critical structure mediating communication between the gut microbiota and the host. Its integrity ensures the physiological separation between microorganisms residing in the intestinal lumen and host tissues. This function is maintained through multiple mechanisms, including the secretion of mucus and antimicrobial peptides, as well as the presence of tight junctions between intestinal epithelial cells (IECs). Disruption of intestinal barrier integrity in sepsis is considered a key mechanism contributing to bacterial translocation and the development of multiple organ failure [77]. Mucus produced by goblet cells protects the deeper layers of the intestinal wall from mechanical, chemical (e.g., extreme pH or digestive enzymes), and biological insults, including pathogenic microorganisms and their toxins [78]. The mucus layer contains numerous antimicrobial components, such as α-defensins, lysozyme, immunoglobulin A (IgA), and regenerating islet-derived protein IIIγ (RegIIIγ) [79–81]. Together, these elements constitute the first line of defense, preventing bacterial translocation from the intestinal lumen into host tissues. In addition, antimicrobial peptides attenuate local inflammation by inhibiting Toll-like receptor 4 (TLR4)-dependent signaling pathways [82]. As detailed in Section 3.2.1, SCFAs, particularly butyrate and propionate, play a critical role in preserving intestinal barrier integrity by upregulating key tight junction proteins (including claudin-1, ZO-1, and occludin), stimulating antimicrobial protein secretion, and suppressing myeloperoxidase-mediated oxidative stress. In the context of sepsis, the depletion of SCFA-producing taxa directly compromises the protective network, facilitating hyperpermeability and systemic pathogen translocation [39,83–89]. Through mechanisms involving G protein–coupled receptors GPR43 and GPR109A, as well as inhibition of histone deacetylase (HDAC) activity, SCFAs stimulate IECs and macrophages to produce antimicrobial molecules, including α- and β-defensins, lysozyme, RegIIIγ, S100 proteins,

and ficolin-1 [39,81–86]. Moreover, SCFAs regulate the expression of genes encoding tight junction proteins, such as claudin-1, claudin-7, zonula occludens-1 (ZO-1), zonula occludens-2 (ZO-2), occludin, and junctional adhesion molecule A (JAM-A) [87,88]. In addition, SCFAs reduce myeloperoxidase (MPO) activity and enhance the activity of antioxidant enzymes, including superoxide dismutase and catalase [89]. The intestinal microbiota and the mucus layer covering the intestinal wall are functionally interdependent and jointly determine the integrity of the intestinal barrier. Proper secretion of mucin 2 (MUC2), the principal glycoprotein of intestinal mucus, requires the activity of meprin β, a protease responsible for cleaving MUC2 from the goblet cell membrane. The activity of this enzyme is stimulated by commensal bacteria [90]. Additionally, butyrate has been shown to upregulate the expression of genes encoding mucins, whereas pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide (LPS) and peptidoglycan (PGN), can enhance mucus secretion into the intestinal lumen [57,91]. Mucus also shapes the composition of the microbiota in close proximity to the epithelium. The outer mucus layer of the colon is colonized by specialized mucin-degrading bacteria, including *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Bifidobacterium bifidum*, *Akkermansia muciniphila*, and *Ruminococcus gnavus*. These microorganisms contribute to intestinal homeostasis by stimulating mucus production and competing with potential pathobionts for available resources [92–94]. Sepsis is characterized by an excessive systemic inflammatory response, including elevated levels of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), and interleukin-17 (IL-17). These mediators disrupt intestinal barrier integrity by altering the expression and organization of tight junction proteins [77,95–97]. In addition, epithelial damage is exacerbated by intestinal ischemia resulting from vasodilation, endothelial dysfunction, microthrombus formation, and impaired microcirculation [98]. The combination of cytokine storm and ischemia–reperfusion injury leads to enterocyte apoptosis, villus shortening, and disturbances in the composition and function of the mucus layer and antimicrobial proteins [99–101]. Consequently, intestinal barrier integrity is compromised, facilitating bacterial translocation into the systemic circulation. These processes are further aggravated by dysbiosis, particularly reduced SCFA production, as well as oxidative stress and excessive neutrophil activation [102,103].

3.4. Gut dysbiosis in sepsis and clinical outcomes

3.4.1. Dysbiosis in sepsis

Intestinal dysbiosis is defined as a disruption in the balance, diversity, and functional capacity of the gut microbiota, leading to secondary alterations in its composition, disease progression, and/or the development of clinical symptoms [104]. In the context of sepsis, dysbiosis is closely associated with the ongoing amplification and perpetuation of the systemic inflammatory response. Alterations in microbiota composition facilitate the translocation of bacteria and their products into systemic circulation, thereby exacerbating organ dysfunction and worsening patient outcomes. A dysbiotic profile characterized by reduced microbial diversity, depletion of commensal bacteria, and overgrowth of potentially pathogenic microorganisms, such as *Escherichia coli*, *Clostridioides difficile*, *Enterococcus*, and *Staphylococcus*, predisposes individuals to the development of sepsis. These alterations are accompanied by impaired metabolic activity of the microbiota and disruption of intestinal barrier integrity [105].

Importantly, sepsis itself further alters the composition and function of the gut microbiota, as demonstrated in treatment-naïve animal models [106,107]. In patients with sepsis, stool samples are characterized by reduced α-diversity and altered β-diversity (reflecting shifts in overall community composition) [106–109]. Dysbiosis is primarily associated with shifts in the relative abundance of existing microbial species rather than the emergence of new taxa [110]. Although findings at higher taxonomic levels remain partially inconsistent, the most commonly reported pattern includes an increased abundance of Proteobacteria, alongside a reduction in Firmicutes, the latter being a major source of short-chain fatty acids (SCFAs) [106–109]. At the genus level, sepsis-associated dysbiosis is characterized by a decrease in beneficial bacteria with probiotic potential, such as *Lactobacillus*, *Bifidobacterium*, and *Blautia*, and a concomitant increase in opportunistic pathogens, including *Escherichia-Shigella* and *Enterococcus* [107,108]. An additional noteworthy observation is the increased abundance of *Akkermansia* in the small intestine [107]. While this bacterium typically exerts beneficial effects by supporting intestinal barrier integrity in healthy individuals, in the context of sepsis, it may paradoxically contribute to epithelial damage, potentially through excessive degradation of the mucus layer [107,111,112].

Overall, sepsis induces profound alterations in the composition and function of the gut microbiota, leading to reduced diversity, loss of commensal bacteria, and expansion of pathobionts, particularly Proteobacteria. These changes contribute to intestinal barrier disruption and amplification of systemic inflammation, representing a key pathophysiological component of sepsis. Growing evidence indicates that the composition of the gut microbiota is strongly correlated with disease severity and clinical outcomes in patients with sepsis. Intestinal dysbiosis has been shown to correlate with multiple clinical parameters, including heart rate, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, circulating endotoxin levels, cardiac troponin I (cTnI), interleukin-6 (IL-6), and procalcitonin (PCT) [108].

While higher α-diversity is generally associated with more favorable clinical outcomes, the prognostic utility of the Firmicutes/Bacteroidota ratio remains controversial. Although some studies link an increased ratio to better survival, findings across the literature are highly inconsistent due to clinical confounders such as antibiotic exposure and sampling timing. In contrast, increased abundances of *Oscillospira*, Rikenellaceae, and *Akkermansia muciniphila* have been linked to poorer treatment outcomes [113,114]. Moreover, *Enterococcus* abundance positively correlates with the risk of in-hospital mortality, secondary infections, and prolonged intensive care unit (ICU) stay [115]. Depletion of *Bifidobacterium* in critically ill patients is associated with increased mortality risk and represents an independent prognostic factor beyond SOFA and APACHE II scores [116]. Recently, the Microbiome Mortality Index (MMI) has been proposed as a novel prognostic tool. This index, based on the relative abundance of *Anaerococcus*, Enterobacteriaceae, *Parasutterella*, and *Campylobacter*, enables the prediction of 28-day mortality independently of acute respiratory distress syndrome (ARDS) and APACHE II score [117]. The composition of the gut microbiota also plays a critical role in the development of multiorgan failure in critically ill patients [118]. Broad-spectrum antibiotic-induced gastrointestinal decontamination has been shown to exacerbate lung injury and increase mortality in sepsis. Moreover, disruption of the intestinal barrier permits the translocation of microbiota-derived components, which can be detected in the bronchoalveolar lavage fluid of patients with ARDS [119,120]. Consistent with the critical role of the gut–lung axis in septic organ failure, targeted restoration of gut microbiota

homeostasis—characterized by the suppression of pathogenic Chlamydiaceae (e.g., *Chlamydia abortus*) and enrichment of commensal Lactobacillaceae—has been shown to mitigate pulmonary inflammation and restore endothelial–epithelial barrier integrity in sepsis-associated acute lung injury [121]. The development of sepsis-associated encephalopathy (SAE) is associated with increased abundances of Firmicutes, Proteobacteria, *Neisseria*, *Haemophilus*, *Lautropia*, *Enterococcus*, and *Parabacteroides*, alongside a reduction in Bacteroidota, *Fusobacterium*, *Phocaeicola*, *Bacteroides*, *Flavonifactor*, *Lactobacillus*, and *Anaerotignum* [122,123]. Patients with sepsis-induced cardiomyopathy (SICM) exhibit decreased β-diversity, increased abundances of Proteobacteria, Enterobacteriaceae, *Thiorhodovibrio*, *Escherichia virus HK022*, and *Klebsiella variicola*, and reduced abundances of Bacteroidota, Bacteroidaceae, *Bacteroides vulgatus*, *Cystobacter*, and *Fusarium oxysporum* [124,125]. Notably, *Klebsiella variicola* abundance positively correlates with high-sensitivity cardiac troponin I (hs-cTnI) and negatively with left ventricular ejection fraction (LVEF), whereas *Bacteroides vulgatus* shows a positive correlation with LVEF [124]. Additionally, increased abundances of *Cronobacter* and *Cronobacter phage* are strongly associated with SOFA scores and demonstrate predictive potential for SICM and ventricular arrhythmias [125].

Intestinal dysbiosis also contributes to the development of sepsis-associated acute kidney injury (SA-AKI) by disrupting intestinal barrier integrity, promoting bacterial and endotoxin translocation, and amplifying systemic inflammation. In turn, SA-AKI further impairs barrier function, creating a vicious cycle [126]. Microbial urea metabolism leads to the formation of ammonium hydroxide, which disrupts tight junction integrity in the intestinal epithelium [127]. In SA-AKI, increased α-diversity and dominance of Proteobacteria, *Enterococcus avium*, *Bacteroides caccae*, and *Campylobacter hominis* have been observed, with the latter two positively correlating with markers of kidney injury [128]. Emerging nanomedicine-based adjunctive strategies targeting oxidative stress and inflammatory cascades show significant promise in mitigating SA-AKI. For instance, naturally derived bio-carbon dots have been shown to protect renal tubular integrity and attenuate systemic inflammation by scavenging reactive oxygen species and inhibiting the NF-κB pathway [129]. Translocation of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) through the compromised intestinal barrier facilitates their entry into the portal circulation and subsequent delivery to the liver. There, activation of pattern recognition receptors (PRRs) promotes polarization of Kupffer cells toward a proinflammatory M1 phenotype, exacerbating sepsis-associated liver injury (SLI) [130–132]. The severity of SLI is further increased by expansion of pathobionts, such as *Escherichia/Shigella* and *Parasutterella*, whereas metabolites produced by commensal bacteria, such as Granisetron, may exert hepatoprotective effects [133,134]. Similarly, systemic translocation of gut-derived endotoxins (such as LPS) significantly impairs hepatic function along the gut–liver axis; recent findings demonstrate that novel nanozymes, such as *Glycyrrhiza*-derived carbon dots with SOD-mimicking activity, can attenuate sepsis-induced liver injury (SILI) by co-regulating the Keap1/Nrf2 antioxidant defense and suppressing NF-κB-driven hepatic inflammation [135].

3.5. Microbiota-targeted therapeutic strategies in sepsis

Intestinal dysbiosis in sepsis is multifactorial and arises from both disease-related

mechanisms and therapeutic interventions. The principal contributors include pharmacotherapy, endogenous catecholamine release, intestinal ischemia–reperfusion injury, and parenteral nutrition. The interplay of these factors promotes the persistence of dysbiosis and further aggravates the course of sepsis. Broad-spectrum antibiotic therapy remains a cornerstone of sepsis management; however, its use requires a nuanced approach consistent with current international guidelines [3]. Immediate antimicrobial administration, ideally within one hour of recognition, is strongly recommended for patients with septic shock or a high likelihood of sepsis. In contrast, in patients with possible sepsis without shock, current management frameworks recommend rapid diagnostic evaluation and clinical assessment within a 3-h window before antimicrobial therapy is initiated, allowing non-infectious causes to be considered. This diagnostic stratification is an important component of antimicrobial stewardship, which aims to balance timely pathogen eradication with minimizing unnecessary disruption of the gut microbiota. Despite its essential role in infection control, broad-spectrum antibiotic therapy can profoundly disrupt the intestinal microbiota. Antibiotics reduce microbial abundance, alter species composition, decrease microbial diversity, and impair the regenerative capacity of the gut microbiome. Unnecessary or empirical broad-spectrum antibiotic coverage in unconfirmed infections may cause substantial collateral damage to the gut microbiota, including depletion of commensal bacteria [136–140]. Depletion of commensal bacteria leads to reduced production of short-chain fatty acids (SCFAs) [141]. Antibiotic exposure also compromises intestinal barrier integrity by downregulating tight junction protein expression, increasing intestinal epithelial cell (IEC) shedding, and promoting inflammatory cell infiltration [142,143]. Additionally, antibiotics reduce mucus layer thickness, disrupt its structure, and alter the composition of mucus-associated microbiota, thereby facilitating the translocation of pathobionts [144–154]. Importantly, intestinal barrier dysfunction may occur both indirectly, through microbiota disruption, and directly, via the effects of antibiotics on intestinal epithelial cells [142]. Therefore, active antimicrobial stewardship emphasizing daily clinical re-evaluation, culture-guided de-escalation, and prompt treatment cessation when infection is ruled out is essential to mitigate dysbiosis while maintaining therapeutic efficacy (Table 1).

The role of endogenous catecholamines in the pathogenesis of sepsis is well established. Norepinephrine (NE) levels increase early in the course of the disease, and experimental studies suggest that the gastrointestinal tract constitutes its primary source during the initial hours of sepsis [155]. NE production is predominantly mediated by the enteric nervous system and Paneth cells [156,157].

Norepinephrine and epinephrine play a key role in host–microorganism interactions by modulating bacterial growth, virulence, and biofilm formation. These effects have been demonstrated in several pathogenic species, including *Escherichia coli*, *Salmonella typhimurium*, *Campylobacter jejuni*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. The underlying mechanisms involve activation of bacterial signaling pathways, particularly sensor kinases such as QseC and QseE/F/G [158–160]. The effect of NE on *Escherichia coli* is especially well characterized; it enhances the expression of genes associated with stress adaptation and virulence and promotes chemotaxis and biofilm formation [161–163]. Catecholamines also exert significant systemic effects. Through activation of α2-adrenergic receptors, they stimulate Kupffer cells, increase the production of proinflammatory cytokines, and contribute to organ dysfunction, including hepatic injury and exacerbation of renal ischemic damage in septic shock [155,157,161–164]. Intestinal ischemia–reperfusion injury (IRI) represents a key component of sepsis pathophysiology and contributes substantially to intestinal barrier

disruption. It also alters the composition and function of the gut microbiota, thereby promoting dysbiosis. These changes include increased overall bacterial load and diversity, depletion of beneficial taxa such as *Verrucomicrobiota*, *Lachnospiraceae*, and *Lactobacillus*, and overgrowth of Firmicutes, Bacteroidota (particularly *Bacteroides vulgatus*, *Parabacteroides distasonis*, and *Prevotella oralis*), and Proteobacteria, including *Escherichia coli* [165–167]. Parenteral nutrition is another crucial factor influencing the gut microbiota in critically ill patients. It deprives enterocytes of luminal trophic stimuli, leading to Treg cell dysfunction, reduced secretion of antimicrobial peptides and immunoglobulin A (IgA), and impairment of intestinal barrier integrity [168,169]. Consequently, it promotes dysbiosis, characterized by reduced total bacterial load, decreased α-diversity, and altered β-diversity. Compositional changes include a decline in Bacteroides, *Faecalibacterium*, *Ruminococcus*, and *Lactobacillus*, alongside an increased abundance of Proteobacteria, Verrucomicrobiota (notably the genus *Akkermansia*), *Escherichia–Shigella*, *Cronobacter*, *Staphylococcus*, and Bifidobacteriaceae [168–171]. These alterations are associated with reduced production of short-chain fatty acids (SCFAs) and increased lactate levels [172] (Figure 4).

Table 1. Effects of selected medications on the intestinal microbiota.

Medication	Intestinal microbiota	References
Ceftriaxone, piperacillin/tazobactam	↑ Firmicutes, Proteobacteria, Enterobacteriaceae, *MDR E. coli* and *K. pneumoniae* ↓ *Bacteroides*	[137] [138]*† [145]
Meropenem	↓ *Lachnospiraceae NK4A136*, *Prevotellaceae UCG001*, *Oscillibacter*, *Anaerotruncus*, *Helicobacter* ↑ *Clostridia Vadin BB60*, *Enterococcus*, *Lachnoclostridium*, *Roseburia* ↑ *Candida albicans*	[147]*
Vancomycin	↓ *Roseburia*, *Coprococcus*, *Dorea*, *Ruminococcus*, *Faecalibacterium*, *Fuscobacterium*, *Oscillospira*, *Bacteroides fragilis* ↑ *Bilophila*, *Pseudoramibacter*, *Eubacterium*, *Cloacibacillus*, *Lactobacillus*	[148]†
Hydrocortisone (short-term)	↓ *Clostridium*, *Lachnospira*, *Anaerotignum*, *Dysosmobacter*, *Sutterella*, *Staphylococcus* ↑ *Blautia*, *Collinsella*	[149]†
Hydrocortisone (long-term)	↓ Proteobacteria, *Faecalibacterium*, *Bifidobacterium*, *Prevotella*, *Akkermansia* ↑ Firmicutes, *Streptococcus*, *Parabacteroides*, *Collinsella* ↑ Firmicutes/*Bacteroides* ↓ *SCFAs*	[150]†
Proton pump inhibitors	↓ Ruminococcaceae, Lachnospiraceae	[151]
Opioids	↓ Firmicutes, Ruminococcaceae, Lachnospiraceae, *Bifidobacterium* ↑ Proteobacteria, *Escherichia-Shigella*	[152]
Propofol	↑ *Enterococcus*, *Escherichia-Shigella*	[153]*†
Dexmedetomidine	↑ *Faecalibacterium*, *Bifidobacterium*	[154]

Note: Evidence regarding the effects of specific pharmacological agents is derived primarily from preclinical animal studies or small human cohorts. * Animal study; † study conducted in a small cohort.

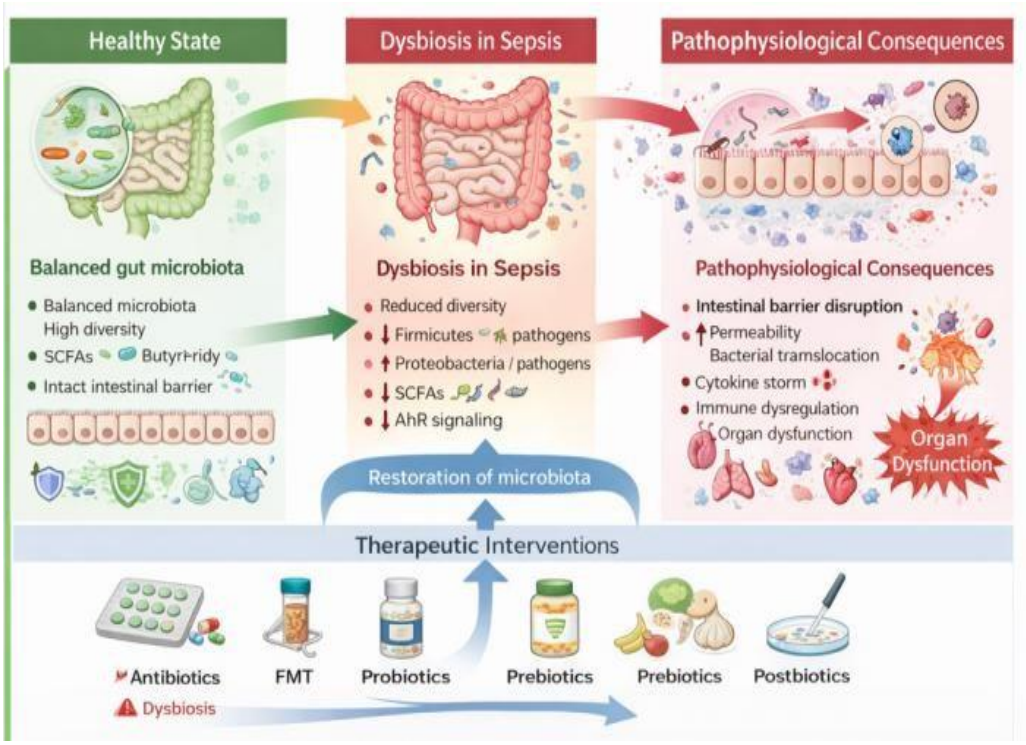


Figure 4. The role of the gut microbiota in the pathophysiology and therapeutic modulation of sepsis.

3.5.1. Microbiota-targeted therapeutic strategies in sepsis

Modulation of the gut microbiota represents a promising adjunctive strategy in the management of sepsis. Potential approaches include fecal microbiota transplantation (FMT), as well as the use of probiotics, prebiotics, and postbiotics. FMT involves the transfer of microbiota from a healthy donor to restore a balanced intestinal ecosystem in the recipient. In preclinical animal models of sepsis, FMT has been shown to reduce mortality, restore microbial composition, limit the expansion of opportunistic and multidrug-resistant pathogens, and facilitate the clearance of translocated bacteria [173]. Preclinical evidence indicates that FMT also modulates host immune responses by regulating inflammatory pathways and restoring immune homeostasis [174]. Furthermore, FMT attenuates sepsis-associated organ damage through distinct physiological mechanisms. In murine models, FMT improves intestinal barrier integrity by inhibiting intestinal epithelial cell (IEC) apoptosis, enhancing mucus secretion, suppressing pattern recognition receptor (PRR)-mediated inflammatory responses, and promoting tight junction formation [175], which aligns with translational clinical observations in human cohorts [176]. In preclinical rodent models of lipopolysaccharide (LPS)-induced acute respiratory distress syndrome (ARDS), FMT improves pulmonary function, as evidenced by increased arterial oxygen tension (PaO_2) and decreased carbon dioxide tension ($PaCO_2$) [177]. Preclinical studies demonstrate that FMT exerts neuroprotective effects in sepsis-associated encephalopathy (SAE), improving cognitive function, reducing microglial activation and neuroinflammation, and decreasing epileptiform activity in electroencephalography (EEG) recordings [178]. These effects are partly mediated through activation of receptors such as the aryl hydrocarbon receptor (AhR) and G protein-coupled

receptor 109A (GPR109A), as well as modulation of the gut–brain axis [178–181]. Additionally, FMT demonstrates hepatoprotective properties [134]. The evaluation of probiotics in sepsis spans both clinical and preclinical domains. In human clinical research, a double-blinded, randomized controlled trial (RCT) demonstrated that probiotic supplementation was associated with a lower incidence of nosocomial infections, shorter duration of antibiotic therapy and intensive care unit stay, and partial restoration of gut microbiota composition [182,183]. Complementary preclinical mouse studies confirm these protective pathways. Specific probiotic strains such as *Lactobacillus rhamnosus* GC reduce mortality, downregulate proinflammatory cytokines (Il-7, IL-17, G-CSF, MCP-1), preserve mucosal barrier integrity, limit lung injury, and exert neuroprotective effects [184,185]. Similarly, in murine sepsis models, *Lactobacillus rhamnosus* L34 mitigates sepsis severity, bacteremia, and systemic inflammation while improving intestinal barrier function [186]. *Lactobacillus johnsonii* 6094 increases survival, reduces IL-1β, IL-6, and TNF-α levels, and alleviates organ damage in the lungs, liver, kidneys, and intestines [187].

Preclinical evidence in murine models demonstrates that multi-strain probiotic formulations and specific commensal isolates exhibit broad physiological benefits during sepsis and endotoxemia. For instance, *Lactobacillus rhamnosus*, *Lactobacillus casei*, and *Lactobacillus acidophilus* reduce oxidative stress associated with endotoxemia [188]. Similarly, mouse studies show that *Bifidobacterium longum* BL-10 modulates immune responses by reducing proinflammatory cytokines (TNF-α, IFN-γ, IL-2, IL-12, IL-17, and IL-22), increasing $CD4^+$ T lymphocytes and IgA-producing plasma cells, and restoring Th1/Th2 and Th17/Treg balance [189,190]. Furthermore, *Bifidobacterium bifidum* E3 and *Bifidobacterium infantis* E4 enhance intestinal barrier integrity by increasing villus length, upregulating tight junction proteins and MUC2 expression, and promoting IgA secretion, alongside expansion of dendritic cells and T lymphocyte populations [191]. In murine models, *Clostridium butyricum* exhibits neuroprotective and cardioprotective effects, partly by inhibiting microglial activation, reducing proinflammatory cytokine levels, and promoting regulatory T cell (Treg) differentiation [192,193], while the probiotic mixture VSL#3 reduces mortality, suppresses systemic inflammation, decreases biochemical markers of renal and hepatic injury, and attenuates renal ischemia–reperfusion injury in sepsis [184,194,195]. However, the results of clinical trials evaluating probiotics in sepsis remain inconsistent. Although a recent meta-analysis reported potential reductions in sepsis incidence and intensive care unit (ICU) length of stay, these findings must be interpreted with significant caution. Most included clinical trials exhibited a high risk of bias, substantial methodological heterogeneity, and marked variability in strain-specific efficacy. Consequently, current evidence remains insufficient to support the routine clinical use of probiotics in patients with sepsis [196].

Importantly, safety concerns in critically ill populations warrant strong emphasis. Probiotic administration carries a risk of iatrogenic infectious complications. Cases of bacteremia and sepsis caused by *Lactobacillus* and *Bifidobacterium* species have been reported. These complications occur most frequently in vulnerable populations, including extremely premature infants, patients with extremely low birth weight, short bowel syndrome, critically ill pediatric patients, and children with hematological disorders or congenital heart defects. In adults, such infections are typically associated with immunosuppression or the perinatal period. Notably, probiotic-associated bacteremia is generally linked to favorable treatment outcomes and low mortality [197,198]. Impaired metabolic activity of the gut microbiota has been associated with worse outcomes in sepsis [199]. Specific microbiota-derived metabolites represent a promising therapeutic approach.

Among these, short-chain fatty acids (SCFAs) are of particular importance, as their systemic and fecal levels are markedly reduced during septic illness, as demonstrated in observational human cohorts [200] and preclinical mouse models [173]. SCFAs have been shown to improve survival and enhance bacterial clearance. In preclinical rodent studies, SCFA administration improves survival and enhances bacterial clearance while mitigating organ damage in the lungs, heart, brain, kidneys, and liver [102] (reviewed in [201]), which correlates with observational findings regarding barrier restoration in patients with sepsis [176]. Nevertheless, potential adverse effects of SCFAs should be considered. Experimental mouse models indicate that in early sepsis, SCFAs may impair mitochondrial aerobic respiration. Additionally, they may exert unfavorable hemodynamic effects, including reductions in cardiac output, heart rate, and mean arterial pressure [202,203].

Prebiotics, particularly dietary fiber, may also beneficially influence sepsis outcomes through modulation of the gut microbiota and enhancement of SCFA production, as suggested by a meta-analysis of studies conducted in human preterm infants [204]. In preclinical murine models, diets rich in insoluble fiber have been associated with reduced risk of sepsis development and mortality, accelerated recovery, and attenuation of oxidative stress, systemic inflammation, and organ damage, including injury to the intestines, lungs, and liver [205,206], while promoting β-diversity and enrichment of Lachnospiraceae and *Akkermansia* [207]. Similarly, in a piglet model of sepsis, fiber supplementation enhanced endogenous SCFA production [208].

However, preclinical mouse studies demonstrate that concurrent broad-spectrum antibiotic therapy attenuates these beneficial effects [209], and in specific inflammatory settings such as peritonitis, fiber exposure may exacerbate IL-1β-mediated inflammation [208].

Among specific prebiotics, inulin has been shown to reduce myeloperoxidase activity, oxidative tissue damage, inducible nitric oxide synthase (iNOS) activity, and proinflammatory cytokine levels (IL-6 and TNF-α) in the kidneys, suggesting a potential role in preventing sepsis-associated acute kidney injury (SA-AKI) in rodent models of sepsis [209]. However, a randomized phase II trial demonstrated no significant effect of inulin supplementation on gut microbiota composition, function, or mortality in sepsis. Fructooligosaccharides reduce intestinal oxidative stress and myeloperoxidase activity, but do not significantly affect proinflammatory cytokine levels [188]. In contrast, galactooligosaccharides preserve intestinal barrier integrity by increasing villus length, enhancing tight junction protein expression, stimulating SCFA production, and inhibiting TLR4/NF-κB signaling and proinflammatory cytokine secretion in macrophages (Table 2).

In summary, while preclinical models provide encouraging mechanistic rationale for modulation of gut microbiota as a promising adjunctive strategy in sepsis management, translating these findings into clinical practice faces major hurdles. Microbiota-targeted therapies currently remain investigational interventions rather than established sepsis treatments. The clinical literature is characterized by high risk of bias, lack of strain standardization, variable dosing schedules, and serious safety risks regarding strain translocation in vulnerable patients. Until large-scale, high-quality, strain-specific randomized controlled trials establish clear efficacy and safety profiles, routine implementation of these strategies cannot be recommended as a part of standard supportive care in sepsis.

Table 2. Summary of microbiota-targeted therapeutic strategies in sepsis, contrasting preclinical rationale, human clinical evidence, safety considerations, and translational status.

Therapeutic strategy	Preclinical evidence (*in vivo*/*in vitro*)	Human clinical evidence (observational & RCTs)	Safety concerns and limitations	Translational status
Fecal microbiota transplantation (FMT)	Restores microbial diversity, clears MDR pathogens, enhances mucosal barrier integrity, and attenuates lung, liver, and brain damage in murine models [170,172,174,175]	Limited to small observational cohorts and pilot studies showing gut barrier restoration; lacks powered Phase III RCTs in acute sepsis [173].	Risk of donor-derived pathogen transmission, aspiration during enteral delivery, and technical invasiveness in critically ill patients.	Investigational
Probiotics and synbiotics	Downregulates systemic cytokines (TNF-α, IL-6, IL-17), preserves tight junctions, and reduces mortality in rodent sepsis models [181,182,185–190].	Meta-analyses show reduced risk of secondary infections and shorter ICU stays, but no consistent overall mortality benefit; high risk of trial bias [180,191,193].	Non-negligible risk of strain translocation leading to probiotic bacteremia/fungemia in immunocompromised or severely ill ICU patients [194,195].	Investigational/ adjunctive
Prebiotics and dietary fibers	Promotes commensal taxa (Lachnospiraceae, *Akkermansia*), boosts endogenous SCFA levels, and lowers organ injury in rodent and swine models [202–205].	Meta-analysis indicates reduced sepsis in preterm infants [201]; however, a Phase II RCT in adult septic patients showed no clinical or metabolic benefit [208].	Gastrointestinal intolerance, bloating, reduced efficacy during concurrent broad-spectrum antibiotic therapy [207], risk of exacerbating IL-1β in peritonitis [206].	Investigational
Microbial metabolites (SCFAs)	Preserves endothelial–epithelial barrier, attenuates multi-organ dysfunction (SA-ALI, SA-AKI), and enhances bacterial clearance [102,198].	Observational studies confirm marked reduction of circulating and fecal SCFAs in septic patients correlating with worse clinical outcomes [197].	Short biological half-life; high early doses may impair mitochondrial aerobic respiration and induce adverse hemodynamic instability [199,200].	Investigational/ preclinical

4. Discussion

The present review highlights the central role of the gut microbiota as a key regulator of immune homeostasis and a critical determinant of sepsis pathophysiology. The available evidence indicates that intestinal dysbiosis is closely correlated with critical illness and represents a major potential contributor to immune dysregulation, barrier dysfunction, and systemic inflammation. One of the most important findings emerging from this synthesis is the bidirectional relationship between sepsis and gut microbiota alterations. On the one hand, dysbiosis—characterized by reduced microbial diversity, depletion of commensal taxa, and expansion of pathobionts such as Proteobacteria—predisposes individuals to exaggerated inflammatory responses and impaired host defense. Establishing a direct cause-and-effect relationship between gut dysbiosis and sepsis progression in critically ill patients remains highly challenging. Human clinical data are predominantly observational and confounded by multiple variables, including baseline comorbidities, varying degrees of organ failure, aggressive antibiotic regimens, dietary disruptions, and supportive pharmacological interventions (e.g., opioids and proton pump inhibitors). While preclinical animal models provide mechanistic support for a causal role of dysbiosis in amplifying systemic inflammation, current human evidence demonstrates strong correlations rather than definitive

causation. Future prospective studies with standardized sampling and multi-omics integration are required to delineate whether specific microbial alterations actively drive clinical deterioration or primarily reflect disease severity and associated factors, including hypoperfusion, ischemia–reperfusion injury, and extensive degradation of mucin to generate short-chain fatty acids (SCFAs), thereby promoting goblet cell differentiation and strengthening intestinal barrier integrity. However, in the setting of severe sepsis and systemic nutrient deprivation, an overabundance of *A. muciniphila* can lead to excessive consumption of the protective mucus layer. In the absence of adequate dietary fiber, this unchecked mucin degradation thins the mucosal layer, exposing epithelial cells to pathobionts and accelerating systemic translocation. Resolving whether targeted modulation of such mucin-degrading species represents a therapeutic benefit or a clinical risk remains an unresolved critical question.

A major challenge in synthesizing the current evidence is the substantial heterogeneity of clinical cohorts, which significantly limits comparability across studies. Gut microbiota composition in patients with sepsis is influenced by a wide range of potential confounding factors. Baseline patient characteristics, including prior hospitalizations, underlying comorbidities, geographic and ethnic variation, and dietary habits, contribute to distinct premorbid microbial profiles. Upon ICU admission, these baseline differences are further compounded by acute clinical factors, such as disease severity, the route of nutritional support, and extensive multidrug therapy. Because existing clinical studies vary widely in sampling timelines, medication protocols, and control group selection, cross-study comparisons often yield inconsistent or non-reproducible results. Future studies should adopt standardized reporting frameworks that systematically account for these confounding factors, thereby enabling more reliable cross-study comparisons, meta-analyses, and clinically valid conclusions. Further research should include well-designed, large-scale clinical trials evaluating the efficacy and safety of microbiota-targeted interventions, together with studies aimed at identifying specific microbial signatures with potential prognostic or predictive value. The growing recognition of the gut microbiota as a key modulator of host physiology also opens new perspectives for precision medicine in sepsis. Integration of microbiome profiling with clinical, immunological, and metabolomic data may enable the development of personalized therapeutic strategies aimed at restoring microbial homeostasis and improving patient outcomes. Such an approach may complement current pathogen-directed strategies by incorporating the host–microbiota ecosystem into a more comprehensive and personalized framework for sepsis management.

5. Conclusions

The evidence synthesized in this review indicates that the gut microbiota is an important component of sepsis pathophysiology, with potential roles in the regulation of immune homeostasis, intestinal barrier integrity, and systemic inflammatory responses. In critically ill patients, intestinal dysbiosis is strongly associated with disease progression, increased intestinal permeability, bacterial translocation, and adverse clinical outcomes. Although experimental models support biologically plausible causal mechanisms linking microbiota alterations to sepsis progression, current human evidence remains predominantly associative.

A key mechanistic insight is the central role of microbiota-derived metabolites, particularly short-chain fatty acids and tryptophan-derived compounds, in maintaining epithelial and immunological

homeostasis. Disruption of these metabolic pathways in sepsis may contribute to impaired barrier function, altered immune cell differentiation, and a shift toward a sustained proinflammatory phenotype.

Clinical observations further support the translational relevance of these mechanisms. Specific microbiota signatures, including reduced diversity and depletion of commensal taxa, are consistently associated with increased mortality, organ failure, and adverse clinical outcomes. These findings highlight the potential utility of the gut microbiota as a source of biomarkers of disease severity and as a potential target for therapeutic intervention.

Importantly, both sepsis-related pathophysiology and therapeutic interventions can influence the gut microbiota, which should be considered when interpreting microbiome alterations and developing microbiota-targeted strategies.

Microbiota-targeted strategies, including fecal microbiota transplantation, probiotics, prebiotics, and postbiotics, represent a promising adjunctive direction; however, their clinical application remains limited by heterogeneity of available evidence, lack of standardization, and safety concerns in critically ill populations.

Future research should focus on elucidating causal relationships between microbiota alterations and clinical outcomes, identifying robust microbial and metabolomic biomarkers, and conducting well-designed clinical trials to evaluate microbiome-based interventions. Integration of microbiome science with clinical and immunological data may enable the development of precision medicine approaches in sepsis.

In this context, the gut microbiota represents a promising source of biomarkers and a potential therapeutic target; however, further clinical validation is required before microbiota-based approaches can be incorporated into routine sepsis management.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: B.Z.; K.G.; Methodology: B.Z.; K.G.; Literature search: B.Z; Data curation: B.Z.; K.G.; Writing—original draft preparation: B.Z.; K.G.; Writing—review and editing: B.Z.; K.G.; Supervision: W.D.; D.S. All authors have read and agreed to the published version of the manuscript.

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