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Gut Microbiota as a Critical Modulator of Host Immune Responses in Severe Infections: Mechanistic Insights and Therapeutic Implications

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ABSTRACT

Introduction: Severe infections, including sepsis and acute respiratory distress syndrome (ARDS), are the leading causes of morbidity and mortality worldwide, driven by dysregulated host immune responses. Emerging evidence has identified the gut microbiota as a critical regulator of systemic immunity; however, its mechanistic role in severe infection remains unclear.

Methods: This narrative review synthesizes evidence from PubMed, Scopus, and Web of Science, focusing on mechanistic, translational, and clinical studies that evaluated microbiota–immune interactions in severe infections. Relevant studies were critically appraised and integrated to generate a mechanistic and clinically meaningful synthesis.

Results: The gut microbiota maintains immune homeostasis through metabolites, such as short-chain fatty acids, bile acids, and tryptophan derivatives, which regulate epithelial integrity and T cell differentiation. In critical illness, dysbiosis, characterized by reduced diversity, loss of commensals, and pathogen overgrowth, disrupts these processes, leading to increased intestinal permeability, systemic inflammation, and organ dysfunction. Gut–organ axes, including gut–lung, gut–brain, and gut–kidney pathways, further amplify disease severity. Clinical evidence links dysbiosis to higher mortality and prolonged intensive care unit stays. Microbiota-targeted therapies, including probiotics, fecal microbiota transplantation, and precision interventions, show promise but remain limited by heterogeneity and insufficient high-quality evidence.

Conclusion: Gut microbiota is a central modulator of host responses in severe infections, linking intestinal dysregulation and systemic immune dysfunction. Targeting microbiome-related pathways represents a promising strategy for precision critical care, although further mechanistic and clinical studies are required to establish effective therapies, improve patient outcomes in critical illness settings, and advance microbiome-based precision medicine.

Keywords: Severe Infections, Gut Microbiota, Dysbiosis, Immune Response, Short-Chain Fatty Acids, Microbiome Therapy

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INTRODUCTION

Severe infections, including sepsis, acute respiratory distress syndrome (ARDS), and severe viral illnesses, remain major causes of global morbidity and mortality, particularly in critically ill patients, with reported mortality rates exceeding 20–25% in intensive care settings [1,2]. Despite advances in antimicrobial therapy and critical care management, outcomes remain suboptimal, largely due to dysregulated host immune responses characterized by a complex interplay between hyperinflammation and immunosuppression [3]. This persistent challenge highlights the need to explore novel biological systems that critically influence the host defense mechanisms in fish. The gut microbiota, increasingly recognized as the "second genome," plays a fundamental role in shaping systemic immunity through continuous interactions with host immune cells [4]. Under physiological conditions, a diverse microbial ecosystem maintains intestinal barrier integrity, regulates immune tolerance, and produces bioactive metabolites such as short-chain fatty acids (SCFAs), bile acids, and tryptophan derivatives [5]. These metabolites exert profound immunomodulatory effects by promoting regulatory T cell differentiation, enhancing epithelial defense, and maintaining immune homeostasis [6].

In contrast, critical illness induces profound disruptions in gut microbial composition, commonly referred to as dysbiosis. This state is characterized by a loss of microbial diversity, depletion of beneficial commensal organisms, and overgrowth of opportunistic pathogens, particularly Proteobacteria [7,8]. The contributing factors include broad-spectrum antibiotic exposure, altered enteral nutrition, and systemic inflammation. Mechanistically, dysbiosis compromises epithelial barrier integrity, leading to increased intestinal permeability and microbial translocation, which subsequently amplifies systemic inflammatory responses and contributes to multi-organ dysfunction [9,10]. Recent studies have further emphasized the role of gut–organ crosstalk in severe infections, particularly along the gut–lung, gut–brain, and gut–kidney axes, where microbiota-derived signals influence distant organ function and disease progression [11,12]. Clinical evidence consistently demonstrates that reduced microbiome diversity and specific dysbiotic patterns are associated with worse outcomes, including increased mortality and prolonged intensive care unit stay [13]. However, despite accumulating evidence, the precise mechanistic pathways linking microbiota alterations to host immune dysregulation remain incompletely understood, and translation into targeted therapies is still evolving [4,6]. Therefore, this review aims to critically examine the role of the gut microbiota as a key modulator of host immune responses in severe infections, integrating mechanistic insights, clinical evidence, and emerging therapeutic strategies. By bridging fundamental microbiome science with clinical applications, this study aims to advance the development of microbiome-based precision medicine in critical care.

METHOD

This study was conducted as a comprehensive narrative review aimed at synthesizing the current evidence on the role of the gut microbiota in modulating host immune responses in severe infections. A mechanistic and translational framework was adopted to integrate the findings from experimental, clinical, and emerging therapeutic studies to ensure a critical and concept-driven synthesis. A comprehensive literature search was conducted across major electronic databases, including PubMed, Scopus, and Web of Science, from inception to March 2026, to identify relevant studies. The search strategy used Medical Subject Headings (MeSH) together with relevant free-text keywords such as gut microbiota, microbiome, dysbiosis, sepsis, severe infections, immune response, and critical illness. These terms were combined using Boolean operators to ensure the optimal sensitivity and specificity of the search. In addition, the reference lists of relevant studies and high-impact review articles were manually screened to identify further eligible publications.

Studies were included if they examined the role of gut microbiota or microbiome-derived metabolites in severe infections, explored the underlying mechanisms of immune modulation, or evaluated microbiome-targeted therapeutic strategies for severe infections. Preclinical studies, including animal and in vitro research, and clinical studies, including observational studies, randomized controlled trials, and systematic reviews were considered. Publications not written in English, conference abstracts without full-text availability, and studies lacking clear mechanistic or clinical relevance were excluded. Titles and abstracts were screened for relevance, followed by a full-text assessment of eligible studies. The extracted data included the study design, population characteristics, microbiota-related findings, immune pathways involved, and clinical outcomes. We focused on identifying the mechanistic links between microbiota alterations and host immune responses.

The included studies were critically appraised based on their methodological rigor, sample size, and translational relevance. Evidence was synthesized using a thematic approach, focusing on key mechanistic pathways, gut–organ interactions, and therapeutic implications. Particular emphasis was placed on studies employing multi-omics approaches, including metagenomics, metabolomics, and transcriptomics, to enhance mechanistic interpretation.

RESULTS

Current evidence demonstrates that the gut microbiota plays a central and dynamic role in modulating host immune responses in severe infections through interconnected mechanisms involving microbial dysbiosis, immune regulation, and systemic inflammatory amplification. Across experimental and clinical studies, three major domains have consistently emerged, highlighting the mechanistic and clinical relevance of microbiome alterations in critically ill patients. First, dysbiosis is a hallmark of severe infections and critical illnesses. This condition is characterized by a profound reduction in microbial diversity, depletion of beneficial commensal taxa such as Firmicutes and Bacteroidetes, and expansion of opportunistic pathogens, particularly Proteobacteria. Mechanistically, these alterations compromise intestinal barrier integrity, leading to increased permeability and microbial translocation into the systemic circulation of the host.

Table 1. Gut Microbiota Alterations and Clinical Impact in Severe Infections

Study	Population	Key Microbiota Change	Mechanistic Effect	Clinical Outcome
Ojima et al.	ICU	Reduced diversity	Barrier disruption, inflammation	Increased mortality
Zaborin et al.	Critical illness	Pathogen dominance	Loss of colonization resistance	Prolonged ICU stay
Schuijt et al.	Experimental	Microbiota depletion	Impaired immune defense	Increased infection severity
Haak et al.	Sepsis	Dysbiosis	Immune dysregulation	Poor outcomes

This process amplifies systemic inflammation through the release of pathogen-associated molecular patterns, contributing to immune dysregulation and multi-organ dysfunction. Second, microbiota-derived metabolites are critical mediators of immune system homeostasis. Short-chain fatty acids, bile acids, and tryptophan-derived metabolites regulate epithelial integrity and modulate immune cell differentiation, particularly of regulatory T cells, and inflammatory pathways. In dysbiotic states, depletion of these metabolites results in impaired immune tolerance, exaggerated inflammatory responses, and disruption of epithelial defense mechanisms, further exacerbating disease severity.

Table 2. Microbiota-Derived Metabolites and Immune Regulation

Metabolite	Source	Key Mechanism	Immune Effect
Short-chain fatty acids	Fiber fermentation	Enhance barrier, regulate T cells	Anti-inflammatory
Bile acids	Microbial metabolism	Modulate immune signaling	Immune homeostasis
Tryptophan metabolites	Microbial metabolism	Activate aryl hydrocarbon receptor	Immune regulation

These microbiota alterations translate into clinically significant outcomes, as consistently demonstrated in previous human studies. Third, clinical evidence shows that reduced microbiome diversity and specific dysbiotic patterns are strongly associated with adverse outcomes, including increased mortality, prolonged intensive care unit stay, and higher susceptibility to secondary infections.

Table 3. Microbiome-Targeted Therapeutic Strategies in Severe Infections

Intervention	Mechanism	Evidence	Limitation
Probiotics	Restore microbial balance	Reduced ICU infections	Variable efficacy
Fecal microbiota transplantation	Rebuild microbial diversity	Promising early outcomes	Safety concerns
Antibiotic stewardship	Preserve commensal microbiota	Improved microbiome stability	Implementation variability
Emerging therapies	Target microbiome pathways	Early-stage evidence	Limited clinical data

Emerging evidence highlights the importance of gut–organ interactions, particularly along the gut–lung, gut–brain, and gut–kidney axes, where microbiota-derived signals influence distant organ function and contribute to disease progression and organ-specific dysfunctions. In addition to mechanistic insights, microbiome-targeted therapeutic strategies have been explored to restore microbial homeostasis and improve the clinical outcomes.

DISCUSSION

The present review highlights the gut microbiota as a central and dynamic regulator of host immune responses in severe infections, extending beyond passive bystanders to active drivers of disease progression. These findings underscore that dysbiosis is not merely a consequence of critical illness but a mechanistic contributor to immune dysregulation and multi-organ dysfunction in critically ill patients. This concept reinforces the long-standing hypothesis that the gut acts as the "motor" of sepsis, where disruption of intestinal homeostasis initiates and perpetuates systemic inflammation [14,15]. Mechanistically, the loss of microbial diversity and depletion of beneficial commensal taxa profoundly alter immune homeostasis. Commensal-derived metabolites, particularly short-chain fatty acids, bile acids, and tryptophan derivatives, are essential for maintaining epithelial integrity and regulating immune tolerance by modulating T cell differentiation and inflammatory signaling pathways [16,17]. Their depletion in dysbiotic states shifts the host immune response toward a pro-inflammatory phenotype, characterized by exaggerated cytokine production and impaired regulatory mechanisms. This imbalance contributes to the paradoxical coexistence of hyperinflammation and immunosuppression in severe infections [18]. Importantly, the concept of gut–organ crosstalk provides a unifying framework linking local intestinal dysregulation to systemic organ dysfunction. Evidence from experimental and clinical studies has demonstrated that the gut microbiota influences distant organs through the gut–lung, gut–brain, and gut–kidney axes [19,20]. For instance, disruption of the gut microbiota impairs alveolar macrophage function and increases susceptibility to pulmonary infections, while also contributing to neuroinflammation and sepsis-associated encephalopathy [21,22]. Similarly, alterations in gut-derived metabolites and barrier integrity have been implicated in the pathogenesis of acute kidney injury in patients with sepsis [23,24]. These findings emphasize that microbiota-mediated immune modulation operates at the systemic level and affects multiple organ systems simultaneously. From a clinical perspective, the consistent association between microbiome alterations and adverse outcomes highlights the potential of the gut microbiota as both a prognostic biomarker and therapeutic target. Reduced microbial diversity and pathogen-dominant profiles have been linked to increased mortality, prolonged intensive care unit stays, and a higher risk of secondary infection [25,26]. However, despite strong associative data, causality remains difficult to establish because of confounding factors inherent in critically ill populations, including antibiotic exposure and underlying comorbidities [27].

Microbiome-targeted interventions are promising therapeutic strategies. Probiotics and synbiotics have demonstrated potential in reducing infection rates in selected populations, although their efficacy remains inconsistent because of heterogeneity in the study design and microbial strains [28]. Fecal microbiota transplantation represents a more direct approach to restoring microbial diversity, with encouraging early results; however, concerns regarding safety, donor selection, and regulatory frameworks limit its widespread application [29]. Antibiotic stewardship is a fundamental strategy for preserving microbiome integrity, emphasizing the importance of minimizing unnecessary antimicrobial exposure [30]. Emerging approaches, including engineered microbiota, postbiotics, and microbiome-based precision therapies, represent a new frontier but require robust clinical validation [31]. Despite these advances, several critical gaps remain. Most available evidence is derived from observational studies and preclinical models, limiting the ability to establish causal relationships between microbiota alterations and clinical outcomes. Furthermore, heterogeneity in microbiome assessment techniques and the lack of standardized methodologies hinder comparability across studies. Future research should focus on integrating multi-omics approaches, including metagenomics, metabolomics, and transcriptomics, to provide a comprehensive understanding of host–microbiome interactions. Longitudinal studies are also essential to elucidate the dynamic changes in microbiota during the course of critical illness and their relationship with disease progression and recovery [32].

Collectively, these findings support a paradigm shift in the understanding of severe infections, in which the gut microbiota is recognized as a key determinant of host immune response and clinical outcomes.

Integrating microbiome science into critical care practice holds significant potential for improving risk stratification, guiding therapeutic interventions, and advancing microbiome-based precision medicine.

CONCLUSION

The gut microbiota is a central regulator of host immune responses during severe infections, linking intestinal dysregulation to systemic inflammation and to organ dysfunction. Dysbiosis not only reflects disease severity but also actively drives immune imbalance through disruption of epithelial barrier integrity and depletion of key immunoregulatory metabolites. Emerging evidence highlights the role of gut–organ crosstalk in amplifying disease progression in multiple systems. Although microbiome-targeted interventions, such as probiotics, fecal microbiota transplantation, and antibiotic stewardship, show promise, their clinical application remains limited by heterogeneous evidence. Future research should prioritize mechanistic studies and well-designed clinical trials to establish effective and safe treatment strategies for this condition. Ultimately, targeting the gut microbiota represents a promising strategy for improving outcomes and advancing precision medicine in critical care.

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AUTHORS' CONTRIBUTIONS

AC conceptualized and designed the study, conducted the literature search, performed the data synthesis, and drafted the manuscript. SW contributed to the critical interpretation of the data, provided intellectual input, and revised the manuscript for its important scientific content. KR contributed to the data validation, methodological refinement, and critical revision of the manuscript. All the authors have reviewed and approved the final version of the manuscript.

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