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Gut Microbiota–Driven Modulation of Host Immune Responses in Severe Infections: Mechanistic Insights and Translational Implications

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ABSTRACT

Introduction: Severe infections, particularly sepsis and ICU-acquired infections, remain leading causes of global morbidity and mortality, primarily driven by dysregulated host immune responses. Increasing evidence positions the gut microbiota as a critical regulator of systemic immunity through bidirectional host–microbiome interactions, functioning not merely as a passive microbial reservoir but also as an active determinant of disease progression and clinical outcomes.

Methods: A structured narrative synthesis was conducted using literature retrieved from PubMed, Embase, and Cochrane Library. Priority was given to high-quality randomized controlled trials, large observational cohorts, and mechanistic preclinical studies published within the past 10–15 years. Evidence was systematically appraised using standardized risk-of-bias frameworks, including Cochrane tools, and integrated into a translational model linking microbiome alterations with host immune dynamics.

Results: Severe infections were consistently associated with rapid-onset gut dysbiosis, characterized by reduced microbial diversity and expansion of opportunistic pathogens. Five principal mechanistic domains were identified: immune system modulation, disruption of epithelial barrier integrity, altered microbial metabolite signaling, systemic microbial translocation, and antibiotic-induced ecological imbalance. Although observational data demonstrate strong associations between dysbiosis and adverse outcomes, interventional studies targeting the microbiome have reported heterogeneous efficacy, reflecting the underlying biological complexity and current therapeutic limitations.

Conclusion: Gut microbiotas represent a dynamic and potentially modifiable regulator of host immune responses during severe infections. Future research should emphasize causal inference, precision microbiome-based interventions, and the integration of multi-omics approaches to develop mechanism-based therapeutic strategies and clinically actionable biomarkers to improve outcomes in critically ill patients.

Keywords

Gut Microbiota, Sepsis, Immune Modulation, Dysbiosis, Critical Illness, Microbiome Therapy

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INTRODUCTION

Severe infections, particularly sepsis and ICU-acquired infections, are among the leading causes of global morbidity and mortality, accounting for a substantial proportion of the healthcare burden worldwide [1]. Sepsis is defined as life-threatening organ dysfunction resulting from a dysregulated host response to infection, emphasizing that disease severity is not solely determined by pathogen virulence but also by the host's immune response [2]. Despite advances in antimicrobial therapy and critical care, mortality remains unacceptably high, largely because of persistent immune dysregulation characterized by a complex interplay between

hyperinflammation and immunosuppression [3]. In this context, increasing attention has been directed toward the gut microbiota as a critical regulator of systemic immunity. The gut microbiome, often conceptualized as a functional organ, plays a fundamental role in maintaining immune homeostasis, epithelial barrier integrity, and resistance to pathogen colonization [4]. However, critical illness is associated with rapid and profound alterations in gut microbial composition, commonly referred to as dysbiosis. This state is characterized by a loss of microbial diversity, depletion of beneficial commensals, and overgrowth of opportunistic pathogens, collectively termed pathogen domination [5]. These alterations have been consistently associated with adverse clinical outcomes, including secondary infections, organ dysfunction, and increased mortality [6].

Mechanistically, gut microbiota modulate host responses through multiple interconnected pathways, including immune priming and regulation, maintenance of epithelial barrier integrity, microbial metabolite signaling, systemic microbial translocation, and antibiotic-driven ecological disruption [7]. These pathways highlight the dynamic and bidirectional nature of host–microbiome interactions, positioning gut microbiota as a central determinant of immune competence during severe infections rather than a passive bystander. However, despite strong biological plausibility and consistent observational associations, significant gaps remain. First, establishing causal relationships between microbiome alterations and clinical outcomes is challenging because of confounding factors, including antibiotic exposure, nutritional status, and illness severity [8]. Second, the translation of mechanistic insights into effective clinical interventions has been limited, with microbiome-targeted therapies, such as probiotics, demonstrating heterogeneous efficacy and potential safety concerns in critically ill populations [9]. Third, methodological limitations, including reliance on low-resolution sequencing techniques and lack of multi-omics integration, hinder a comprehensive understanding of microbiome–host interactions [10].

Therefore, a comprehensive and mechanistically grounded synthesis is required to bridge these gaps. This study aimed to integrate the current evidence on the role of gut microbiota in modulating host immune responses in severe infections, critically evaluate existing clinical and preclinical data, and outline future directions for precision microbiome-based therapeutic strategies.

METHODS

This study was conducted as a structured narrative synthesis aimed at integrating current evidence on the role of the gut microbiota in modulating host immune responses during severe infections. The methodological approach was designed to balance comprehensiveness and conceptual clarity, allowing for the critical evaluation of both mechanistic and clinical evidence within a translational framework. A systematic literature search was performed across major biomedical databases, including PubMed/MEDLINE, Embase, and the Cochrane Library. The search strategy incorporated combinations of keywords related to gut microbiota, sepsis, critical illness, immune response, and microbiome-targeted therapies. To ensure both relevance and scientific rigor, emphasis was placed on studies published within the past decade, while landmark studies were included to support foundational concepts. Additional articles were identified through manual screening of the reference lists and relevant clinical trial registries. Eligible studies included randomized controlled trials, observational cohort studies, and preclinical mechanistic investigations that examined the relationship between gut microbiota and host immune function in the context of severe infections. Studies were selected based on their ability to provide meaningful insights into microbiome–host interactions, particularly those incorporating clinical outcomes, immune profiling, or mechanistic pathways. Purely descriptive microbiome studies without translational or clinical relevance were not prioritized in this synthesis. Data extraction focused on key domains, including study design, patient population, microbiome assessment techniques, immunological parameters, and reported clinical outcomes. The synthesis was conducted using a narrative-integrative approach, with particular attention to identifying consistent mechanistic patterns, areas of heterogeneity, and translational implications. A conceptual model was developed to link microbiome alterations with host immune dysregulation and the clinical trajectories of severe infections.

The methodological quality of the included studies was critically appraised, with particular attention paid to the sources of bias commonly encountered in microbiome research, incling antibiotic exposure,

nutritional variability, disease severity, and sampling heterogeneity. Evidence was interpreted cautiously, emphasizing the distinction between association and causation and highlighting the limitations of current clinical and experimental data. Given the complexity of microbiome–host interactions, the analysis adopted a system-level perspective, integrating microbial composition, metabolite signaling, and host immune responses. Longitudinal dynamics and context-dependent effects were prioritized over static associations to reflect the evolving nature of the microbiome during critical illnesses. As this study synthesized previously published data, formal ethical approval was not required. However, all included studies were assumed to have adhered to established ethical standards for human and animal research, and particular consideration was given to the safety profile of microbiome-targeted interventions in critically ill populations.

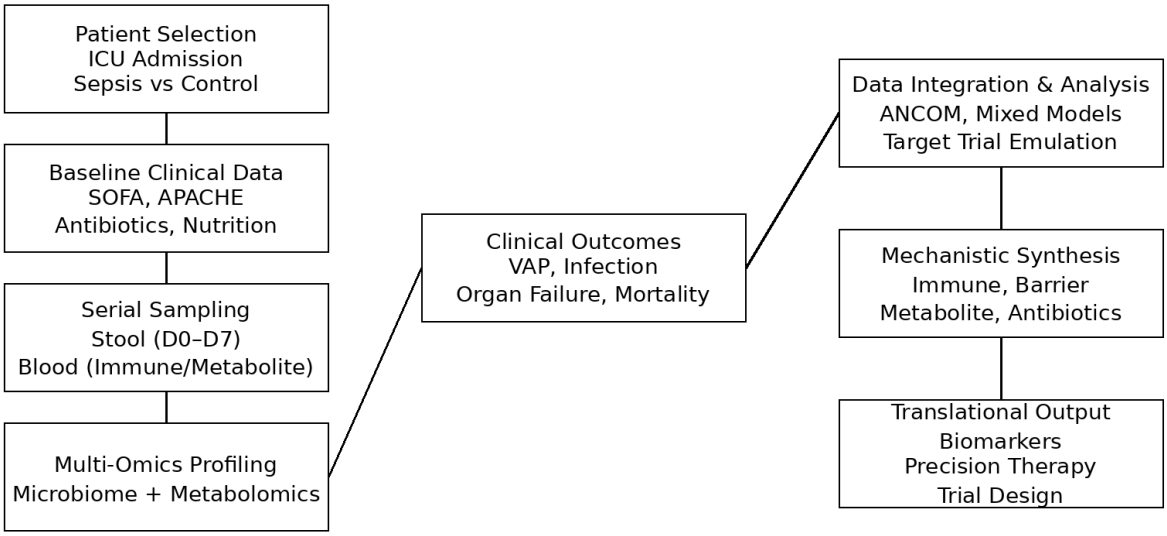

Figure 1. Integrated Study Workflow and Mechanistic Evidence Synthesis Framework

RESULTS

The synthesized evidence reveals a consistent pattern linking gut microbiota alterations with host immune dysregulation and clinical deterioration in severe infections. The synthesis of available evidence demonstrates a consistent and biologically coherent pattern in which severe infections profoundly alter the gut microbial ecosystem. Across clinical and experimental studies, critical illness is associated with a rapid transition from a diverse and functionally stable microbiota toward a low-diversity, pathogen-dominated state. These alterations are not merely descriptive but are closely linked to impaired host immune responses, increased susceptibility to secondary infections, and progression of organ dysfunction. Gut dysbiosis appears early in the course of critical illness, often within the first 48–72 h following ICU admission. This process is characterized by the depletion of obligate anaerobic commensals and expansion of opportunistic pathogens, particularly Enterobacteriaceae and Enterococcus species. In prolonged illness, this disruption may progress to extreme ecological collapse, in which microbial diversity is markedly reduced and a limited number of pathogenic taxa dominate the intestinal environment. Such microbial patterns have been consistently associated with adverse clinical outcomes, including ventilator-associated pneumonia, bloodstream infections, and increased mortality.

Mechanistically, the interaction between gut microbiota and host response is mediated through several interconnected pathways. Microbial signals contribute to immune modulation by shaping both innate and adaptive immune responses and influencing neutrophil function and systemic antimicrobial defense. Simultaneously, disruption of epithelial barrier integrity facilitates the translocation of microbial products, thereby amplifying systemic inflammation. Alterations in microbial metabolite production, particularly reductions in short-chain fatty acids, further impair immune regulation and mucosal homeostasis. In addition, microbial translocation and gut-to-organ trafficking—especially along the gut-lung axis—provide a mechanistic basis for the dissemination of gut-derived signals to distant organs. These processes are further

exacerbated by antibiotic-driven ecological disruption, which weakens colonization resistance and promotes pathogen overgrowth, thereby establishing a self-reinforcing cycle of dysbiosis and immune dysfunction. These mechanisms are illustrated in (Figure 2).

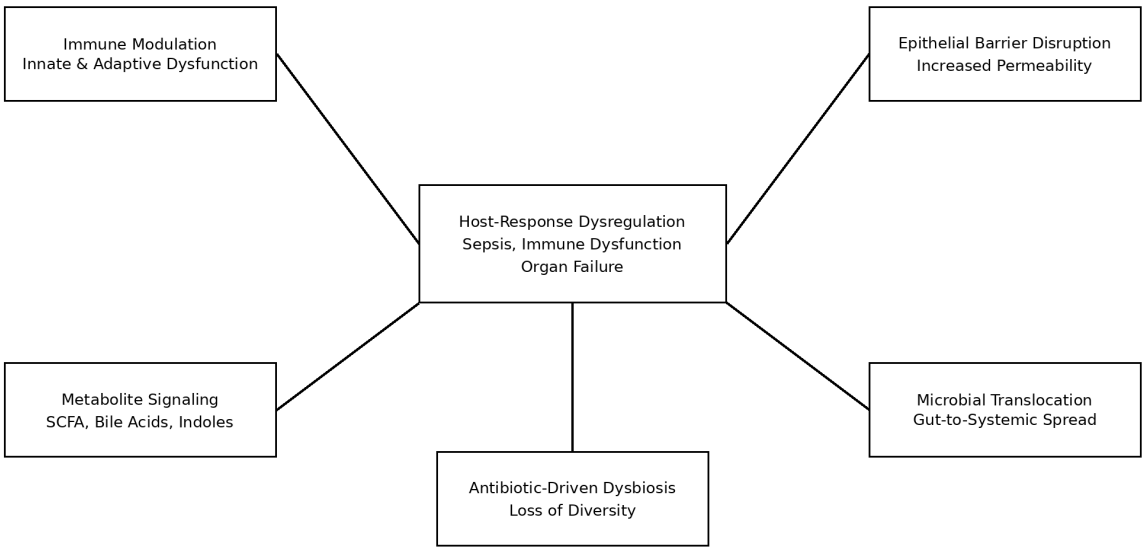

Figure 2. Mechanistic Integration of Microbiome–Host Interactions Driving Immune Dysregulation in Severe Infections

Clinical evidence supports these mechanistic insights, although with varying levels of consistency. Observational studies have demonstrated strong associations between microbial disruption and impaired immune effector function, including neutrophil dysfunction and an increased risk of nosocomial infections. Integrative analyses further suggest that pathogen-dominated microbial microbiota profiles are linked to adverse clinical trajectories in critically ill patients. However, interventional studies have yielded heterogeneous findings. Large randomized controlled trials evaluating probiotics in critically ill populations have not demonstrated significant improvements in major clinical outcomes and have raised safety concerns, including the detection of probiotic organisms at sterile sites. In contrast, smaller and more targeted studies have suggested that synbiotic interventions may reduce specific complications, such as ventilator-associated pneumonia, in selected sepsis populations. These findings indicate that therapeutic efficacy is likely dependent on patient selection, microbial composition, and intervention specificity. An integrated overview of clinical evidence is presented in Figure 3.

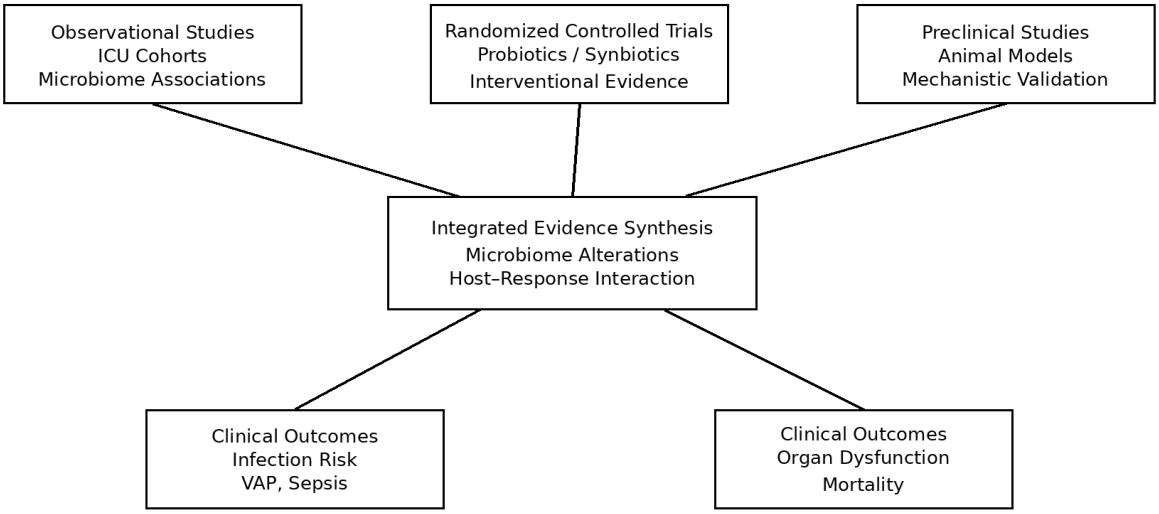

Figure 3. Integrated Evidence Hierarchy Linking Microbiome Alterations to Clinical Outcomes in Severe Infections

These findings are further supported by preclinical and translational studies that provide important evidence for causality. Experimental models have demonstrated that depletion of the microbiota impairs systemic immune defense, whereas restoration strategies, including microbiota reconstitution and metabolite supplementation, improve survival, enhance epithelial barrier integrity, and modulate inflammatory responses. Emerging evidence also highlights the role of interkingdom interactions, including fungal and viral components, suggesting that microbiome–host interactions extend beyond bacterial communities alone. To contextualize the heterogeneity and strength of the available evidence, a comparative summary of the key clinical and translational studies is presented in Table 1.

Table 1. Key Clinical Evidence Linking Gut Microbiota to Outcomes in Severe Infections

Study	Design & Population	Key Findings	Interpretation
Zaborin et al.	Observational, ICU	Pathogen-dominated low diversity	Ecological collapse in critical illness
McDonald et al.	Observational, ICU	Early severe dysbiosis	Critical early window
Ravi et al.	Prospective ICU cohort	Antibiotic-associated diversity loss	Antibiotic-driven dysbiosis
Ojima et al.	Prospective ICU	Rapid early microbiome shifts	Dynamic microbiome response
Johnstone et al.	RCT, ICU	No VAP reduction; safety concerns	Not supportive for routine use
Shimizu et al.	RCT, sepsis ICU	Reduced complications	Benefit in selected patients
Besselink et al.	RCT, pancreatitis	Increased mortality	Potential harm

DISCUSSION

The present review underscores the central role of the gut microbiota as a dynamic regulator of host immune responses in severe infections, extending beyond associative observations toward mechanistic and translational relevance [11-13]. These findings consistently demonstrate that critical illness induces rapid and profound dysbiosis, characterized by a loss of microbial diversity, depletion of commensal anaerobes, and expansion of opportunistic pathogens. This ecological disruption is closely linked to immune dysregulation, impaired barrier integrity, and increased susceptibility to secondary infections, supporting the concept that the gut microbiota actively shapes the disease trajectory rather than serving as a passive bystander [14,15]. This review provides a unified mechanistic and translational perspective that bridges the existing gaps between microbiome research and clinical application in critical care. A key strength of this review is the integration of mechanistic pathways with clinical observations. The identified domains—immune modulation, epithelial barrier disruption, metabolite signaling, microbial translocation, and antibiotic-driven ecological imbalance—highlight the multidimensional nature of microbiome–host interactions [16-18]. These pathways operate in a highly interconnected manner, forming a feedback loop in which dysbiosis amplifies systemic inflammation while simultaneously impairing immune competence. In particular, the loss of microbiota-derived metabolites, such as short-chain fatty acids, appears to play a critical role in disrupting immune homeostasis and mucosal defense [19,20].

Despite the strong mechanistic plausibility, translation of these findings into clinical practice remains limited. Observational studies consistently demonstrate associations between dysbiosis and adverse outcomes; however, interventional trials have yielded heterogeneous and often inconclusive results [21-23]. Large randomized controlled trials evaluating probiotics in critically ill populations have failed to show significant benefits in reducing major outcomes, such as ventilator-associated pneumonia or mortality, and in some cases, have raised safety concerns [24]. Conversely, smaller studies employing targeted synbiotic strategies have suggested potential benefits in selected populations, indicating that therapeutic efficacy may depend on precision-based patient selection, microbial composition, and the timing of intervention [25]. These findings emphasize the importance of moving beyond empirical microbiome modulation to precision-guided therapeutic strategies. The integration of microbiome profiling with host immune phenotyping and metabolomic data offers a promising avenue for identifying patient-specific endotypes and tailoring interventions accordingly [26,27]. In this context, microbiome-targeted therapies should not be viewed as universally applicable, but rather as context-dependent interventions that require careful stratification and

safety considerations. Several limitations of the current study must be acknowledged. First, most clinical studies are observational and subject to significant confounding factors, particularly those related to antibiotic exposure, nutritional status, and severity of illness [28]. Second, methodological heterogeneity, including variability in sequencing platforms and analytical approaches, limits comparability across studies [29]. Third, the complexity of microbiome–host interactions, including the emerging roles of fungal and viral communities, remains incompletely understood, highlighting the need for integrative multi-omics approaches [30]. Future research should prioritize longitudinal and mechanistically informed study designs capable of establishing causality. The development of standardized biomarkers reflecting microbiome function rather than composition alone is essential to advance clinical translation. Furthermore, emerging strategies such as postbiotic therapy, metabolite supplementation, and precision microbiome engineering warrant rigorous evaluation in well-designed clinical trials. Importantly, antibiotic stewardship should be integrated into microbiome-focused strategies, given its profound and modifiable impact on microbial ecology and host outcomes. From a clinical standpoint, these findings support the early recognition of microbiome disruption and cautious context-specific therapeutic modulation in critically ill patients.

In conclusion, the gut microbiota emerges as a pivotal and potentially modifiable regulator of host immune responses in severe infections, thereby redefining its role from a passive component to a central determinant of disease trajectory. Bridging the gap between mechanistic insights and clinical applications requires a transition toward precision-guided, safety-conscious, and system-level strategies that integrate microbiome, immune, and metabolic profiling. This approach holds significant potential for improving patient outcomes, mitigating secondary complications, and establishing microbiome-targeted interventions as a transformative paradigm in critical care medicine.

CONCLUSION

Gut microbiota has emerged as a central and dynamic regulator of host immune responses in severe infections, fundamentally reshaping our understanding of disease pathophysiology in critical illness. Accumulating evidence demonstrates that dysbiosis is not merely an epiphenomenon, but also a key driver of immune dysregulation, barrier failure, and adverse clinical outcomes. Bridging mechanistic insights with clinical translation requires a paradigm shift toward precision-guided, safety-oriented, and system-based approaches that integrate microbiome, immune, and metabolic profiling. Such strategies hold substantial promise for improving patient outcomes, reducing secondary complications, and advancing microbiome-targeted interventions from experimental concepts to clinically actionable therapies in critical care.

DECLARATIONS

None

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The Authors agree to the publication in the Journal of Society Medicine.

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AUTHORS' CONTRIBUTIONS

FB conceptualized and designed the study, performed the data analysis, and drafted the manuscript. CO contributed to data interpretation, critical revision of the manuscript, and provided scientific oversight. Both authors approved the final version and take responsibility for the content.

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