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Relationship between gut microbiota and immunity: reducing complications in critically ill patients

Relación entre la microbiota intestinal y la inmunidad: reducción de las complicaciones en pacientes críticamente enfermos

Relação entre a microbiota intestinal e a imunidade: redução de complicações em pacientes críticos

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ABSTRACT

This analysis addresses the interaction between gut microbiota and immunity in critically ill patients, emphasizing the importance of maintaining a healthy microbiome in these cases. It's crucial to understand the functions of the microbiota and its relationship with immunity, identify key studies on the topic, and point out strategies to reduce complications in ICU patients. It's observed that an imbalance in the gut microbiota, characterized by a decrease in bacterial diversity, promotes colonization by pathogenic bacteria. This state of dysbiosis can lead to bacterial translocation, where microorganisms and toxins cross the intestinal barrier, causing systemic inflammation. Furthermore, dysbiosis affects neurotransmitter production, impairing the immune response and worsening the clinical condition of patients. Modulating the gut microbiota through the use of probiotics, prebiotics, and other interventions can be a promising strategy to improve immunity and reduce complications in critically ill patients. These approaches have shown potential in restoring microbial diversity and promoting a more balanced immune state. However, more research is needed to deepen the understanding of this relationship and develop effective therapeutic interventions that can be implemented in clinical practice. Thus, understanding the gut microbiota can significantly contribute to improving the care of critically ill patients.

Keywords: bacteria; therapy; dysbiosis; modulation; intestine; illness; severity.

RESUMEN

Este análisis aborda la interacción entre la microbiota intestinal y la inmunidad en pacientes críticamente enfermos, enfatizando la importancia de mantener un microbioma saludable en estos casos. Es fundamental comprender las funciones de la microbiota y su relación con la inmunidad, identificar los principales estudios sobre el tema y señalar estrategias para reducir las complicaciones en los pacientes ingresados en unidades de cuidados intensivos. Se observa que un desequilibrio en la microbiota intestinal, caracterizado por una disminución de la diversidad bacteriana, favorece la colonización por bacterias patógenas. Este estado de disbiosis puede conducir a la translocación bacteriana, en la que microorganismos y toxinas atraviesan la barrera intestinal, provocando inflamación sistémica. Además, la disbiosis afecta la producción de neurotransmisores, comprometiendo la respuesta inmunitaria y agravando el estado clínico de los pacientes. La modulación de la microbiota intestinal mediante el uso de probióticos, prebióticos y otras intervenciones puede constituir una estrategia prometedora para mejorar la inmunidad y reducir las complicaciones en pacientes críticamente enfermos. Estos enfoques han demostrado potencial para restaurar la diversidad microbiana y promover un estado inmunitario más equilibrado. Sin embargo, se requieren más investigaciones para profundizar la comprensión de esta relación y desarrollar intervenciones terapéuticas eficaces que puedan implementarse en la práctica clínica. Así, el conocimiento de la microbiota intestinal puede contribuir significativamente a mejorar la atención de los pacientes críticamente enfermos.

Palabras clave: bacterias; terapia; disbiosis; modulación; intestino; enfermedad; gravedad.

RESUMO

Esta análise aborda a interação entre a microbiota intestinal e a imunidade em pacientes criticamente enfermos, enfatizando a importância da manutenção de um microbioma saudável nesses casos. É fundamental compreender as funções da microbiota e sua relação com a imunidade, identificar os principais estudos sobre o tema e apontar estratégias para reduzir complicações em pacientes internados em unidades de terapia intensiva. Observa-se que um desequilíbrio da microbiota intestinal, caracterizado pela diminuição da diversidade bacteriana, favorece a colonização por bactérias patogênicas. Esse estado de disbiose pode levar à translocação bacteriana, na qual microrganismos e toxinas atravessam a barreira intestinal, provocando inflamação sistêmica. Além disso, a disbiose afeta a produção de neurotransmissores, comprometendo a resposta imunológica e agravando o quadro clínico dos pacientes. A modulação da microbiota intestinal por meio do uso de probióticos, prebióticos e outras intervenções pode representar uma estratégia promissora para melhorar a imunidade e reduzir complicações em pacientes criticamente enfermos. Essas abordagens têm demonstrado potencial para restaurar a diversidade microbiana e promover um estado imunológico mais equilibrado. Entretanto, são necessárias mais pesquisas para aprofundar a compreensão dessa relação e desenvolver intervenções terapêuticas eficazes que possam ser implementadas na prática clínica. Assim, o conhecimento acerca da microbiota intestinal pode contribuir significativamente para a melhoria da assistência aos pacientes criticamente enfermos.

Palavras-chave: bactérias; terapia; disbiose; modulação; intestino; doença; gravidade.

1. INTRODUCTION

The gut microbiota, which is made up of a vast array of microorganisms in the gastrointestinal tract, plays a fundamental role in maintaining health. It's become an increasing focus of research, especially concerning critically ill patients. Individuals admitted to intensive care units (ICUs) often face conditions of dysbiosis, an imbalance in the microbiota frequently caused by antimicrobial use, invasive procedures, and compromised immune systems. This imbalance can further worsen their clinical state, increasing the risk of infections and other complications.

Understanding the complex relationship between the microbiota and immunity is crucial for developing effective strategies to help regulate the immune system and improve clinical outcomes in these patients. The interaction between the gut microbiota and the host not only influences immune function but also impacts metabolism and resistance to pathogens.

Intestinal bacteria perform essential functions, such as aiding digestion, producing vitamins, and protecting the gut against pathogenic microorganisms, thereby promoting overall body health and contributing to recovery in critical situations. Understanding changes in the gut microbiota in critically ill patients is essential for improving their clinical management. Microbiotic alterations in these cases can directly influence prognosis and recovery, but the exact mechanisms are still under study.

This field of research not only expands the understanding of intestinal physiology but also opens doors for the development of innovative and personalized therapeutic interventions aimed at restoring microbiotic balance. Approaching this topic, focusing on the symbiosis of microorganisms and their impact on human health, has the potential to positively influence clinical practice in hospital settings, contributing to better clinical outcomes. Furthermore, understanding these interactions can help educate and raise community awareness about the crucial role of gut microbiota in immunity and overall health.

Thus, it's clear that the gut microbiota plays a crucial role in its relationship with immunity, especially in critically ill patients, impacting health both directly and indirectly. This interaction highlights the importance of disseminating and implementing measures that can be developed into care protocols, not only for those with severe illness but also for healthy individuals. A deep understanding of how the gut microbiota reacts in different health states is fundamental to promoting the health and care needed to maintain a healthy microbiome. These protocols can include guidelines on proper nutrition, responsible antibiotic use, and the incorporation of probiotics and prebiotics into the diet, focusing on the patient as unique in the process. By validating the need to care for the gut microbiota, we can encourage health promotion and disease prevention, providing more effective and personalized care to patients in different health conditions, thereby contributing to better clinical outcomes.

2. DEVELOPMENT

2.1 Methodology

This systematic, qualitative, and descriptive literature review aimed to analyze the intricate relationship between gut microbiota and immunity in critically ill patients. We meticulously searched PubMed/Medline, SciELO, Embase, and Web of Science databases using a comprehensive Boolean strategy: ("gut microbiota" OR "intestinal microbiota" OR "microbiome" OR "microbiota") AND ("immunity" OR "immune system" OR "immune response" OR "immunomodulation") AND ("critically ill" OR "severely ill" OR "ICU patients" OR "gravemente enfermos"). Our search was filtered for articles published between 2003 and 2024, in English, Portuguese, or Spanish, specifically focusing on scientific articles, systematic reviews, and meta-analyses. We included studies that linked gut microbiota and immune response in critical patients, research on microbiota interventions (probiotics, prebiotics, fecal transplantation) impacting immunity, and relevant experimental or clinical designs (randomized trials, cohorts, case-control studies). Studies on animal models without direct clinical application, articles outside our specified timeframe, and publications without peer review or of low methodological quality were excluded.

Our screening process began with an initial identification of 70 articles, followed by a thorough filtering based on titles and abstracts, which narrowed the selection to 37 full-text articles. These selected articles underwent a thematic analysis to categorize key findings. The data analysis employed a descriptive approach, focusing on highlighting alterations in microbiota

in critically ill patients, the mechanisms of microbiota-immunity interaction, and therapeutic strategies based on microbial modulation. This process culminated in a critical synthesis of the evidence, emphasizing existing gaps in knowledge and outlining future research perspectives.

2.2 Key Factors in Gut Microbiota Imbalance

The hypothesis that a compromised intestinal barrier can increase intestinal permeability and inflammatory response suggests that "leaky gut syndrome" and "dysbiosis" are interconnected. Both are involved in the pathogenesis of various gastrointestinal and systemic disorders. In conditions of gut microbiota imbalance, known as dysbiosis, clinical complications can arise. Dysbiosis may be associated with inflammatory bowel diseases, irritable bowel syndrome, and other chronic conditions.

Dysbiosis can also affect the host's immune response. Studies show that dysbiosis is linked to increased intestinal permeability and systemic inflammation, which can lead to an inadequate immune response. An altered microbial composition, termed dysbiosis, has been implicated in mucosal barrier dysfunction and inflammatory responses, predisposing host animals to systemic diseases (e.g., inflammatory bowel disease, celiac disease, food allergy, obesity, and autoimmune diseases) (Levy, 2017).

Clostridioides difficile (CD) is the most common pathogen in hospital-acquired gastrointestinal infections, accounting for 25% of antibiotic-associated diarrheas. This gram-positive bacillus, challenging to culture, is the leading cause of hospital diarrhea, with incidence and morbidity/mortality increasing in recent years. Key risk factors include antibiotic use, advanced age, and prolonged hospitalization. The combination of multiple antibiotics significantly raises the risk of CD infection and recurrent diarrhea. The gut microbiota, comprising hundreds of species of bacteria, fungi, viruses, and archaea, plays essential roles in the human body's immunological, metabolic, structural, and neurological spheres. Recent studies show that the microbiota is fundamental for health, regulating the inflammatory response, preventing pathogen colonization, and promoting immune tolerance. Furthermore, it modulates the activity of immune cells, directly influencing the immune response and playing a crucial role in host defense (Adak & Khan, 2019).

Antibiotic use increases the risk of gut microbiota degradation, with Clostridioides difficile (CD) infection being one of the main consequences. An effective alternative for restoring gut microbiota in patients with recurrent CD infection is Fecal Microbiota Transplantation (FMT). This technique involves introducing microbiota from a healthy donor into the patient, demonstrating proven efficacy, low cost compared to conventional treatment, and few adverse effects. The relationship between intestinal microbiota transplantation and *Clostridium difficile* discusses its indication and laboratory diagnosis, highlighting its effectiveness in restoring healthy intestinal microbiota and reducing CD-related complications, with one of the main advantages being the normalization of the intestinal microbiota (Silveira *et al.*, 2024).

In this context, fecal microbiota transplantation (FMT) is understood as an emerging therapeutic strategy used to treat intestinal dysbiosis. The procedure involves transferring gut microbiota from a healthy donor to a critically ill patient with the goal of restoring the host's intestinal microbiota.

Studies conducted on germ-free mice have shown that the absence of gut microbiota compromises gastrointestinal development. These findings confirm previous research, highlighting the significant influence of the microbiota on the host's immune system health and functionality, demonstrating its importance for mucosal immunity and gastrointestinal homeostasis (Hooper *et al.*, 2012; Samuelson *et al.*, 2015).

2.3 Maintaining Gut Microbiota

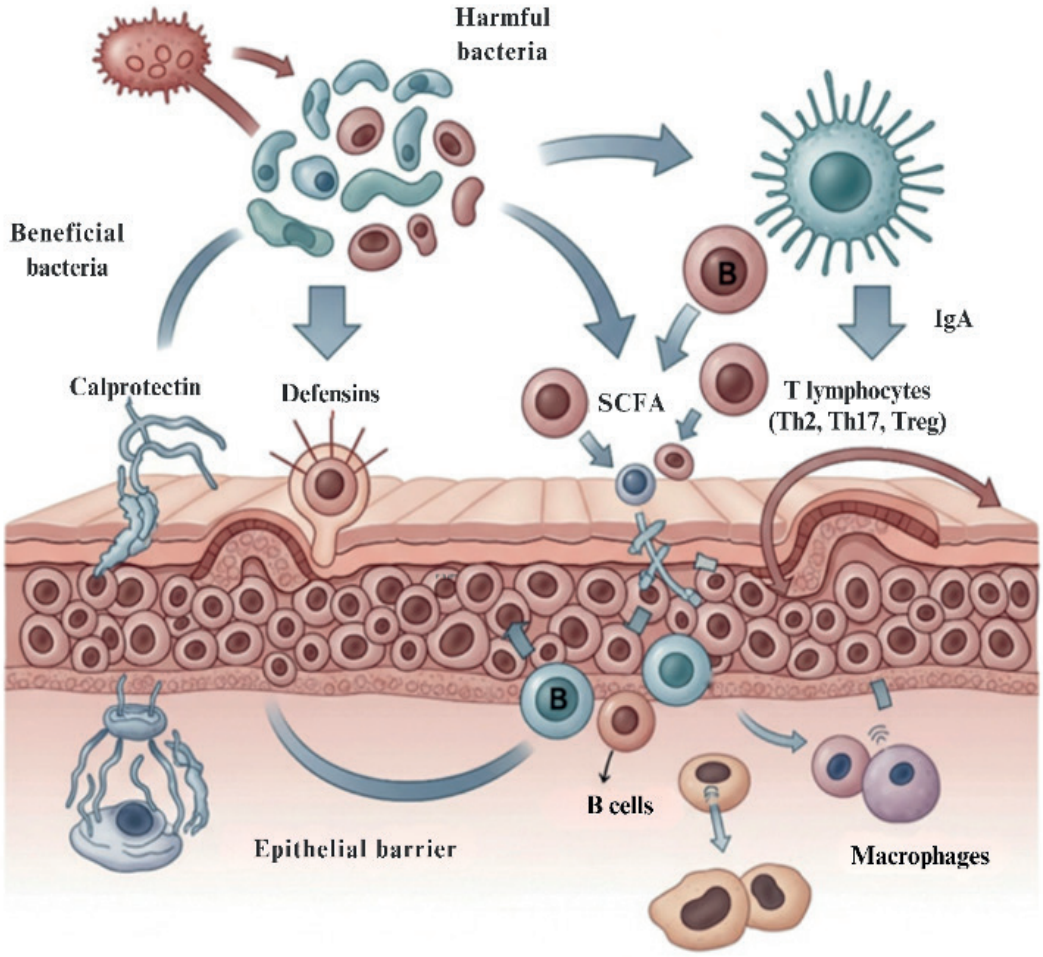
Changes in the gut microbiota impact not only the growth of opportunistic pathogens but also the host's immune status. Studies in germ-free mice demonstrate compromised gastrointestinal development, including smaller Peyer's patches, reduced CD8$\alpha\beta$ intraepithelial lymphocytes, underdeveloped lymphoid follicles, and lower IgA antibody levels. The gut microbiota protects the host by preventing pathogen colonization and by producing antimicrobial substances that control the growth of harmful bacteria, reinforcing its importance for mucosal immunity (Hooper *et al.*, 2012; Samuelson *et al.*, 2015).

The interaction between the gut microbiota, the epithelial barrier, and the immune system is essential for maintaining health and is associated with various diseases, such as inflammatory bowel diseases and allergies. Figure 1 illustrates how the microbiota plays a crucial role in digestion, vitamin production, and immune system modulation. The epithelial barrier, composed of epithelial cells joined by tight junctions and covered by mucus, separates the intestinal lumen from the underlying tissue. The immune system includes cells such as T lymphocytes (Th1, Th2, Th17, Treg), B cells, dendritic cells, macrophages, and NK cells, which work together to protect the body against pathogens and maintain immune tolerance. Key molecules in this process include calprotectin, an antimicrobial protein; defensins, antimicrobial peptides; SCFAs (short-chain fatty acids), which have anti-inflammatory effects and modulate immunity; and IgA, an antibody that lines the intestinal mucosa and neutralizes pathogens, highlighting the importance of microbiota and immunity in maintaining intestinal balance. Other fundamental interactions include: the microbiota influencing epithelial barrier permeability by modulating tight junctions and mucus production; the microbiota interacting with the immune system, affecting cellular development and function; and the epithelial barrier allowing immune response to pathogens while maintaining tolerance to food antigens (Samuelson *et al.*, 2015).

The interaction between the immune system and the gut microbiota is complex and fundamental for host protection. Various immune effectors, such as the mucus layer, epithelial antibacterial proteins, and IgA secreted by lamina propria plasma cells, collaborate to minimize bacterial invasion. Compartmentalization, achieved by unique anatomical adaptations, limits the exposure of commensal bacteria to the immune system. Some bacteria are captured by

intestinal dendritic cells, which traffic to mesenteric lymph nodes without migrating to distal tissues. This allows for the induction of specific immune responses. B cells and T cell subgroups recirculate, and B cells differentiate into IgA-secreting plasma cells, thereby shaping the host's mucosal and systemic immunity, partly due to isolated lymphoid follicles (ILFs) (Samuelson *et al.*, 2015).

Figure 1 - Gut microbiota, barrier, and immunity: an essential interaction for health.



Source: (Adapted). Author, 2025.

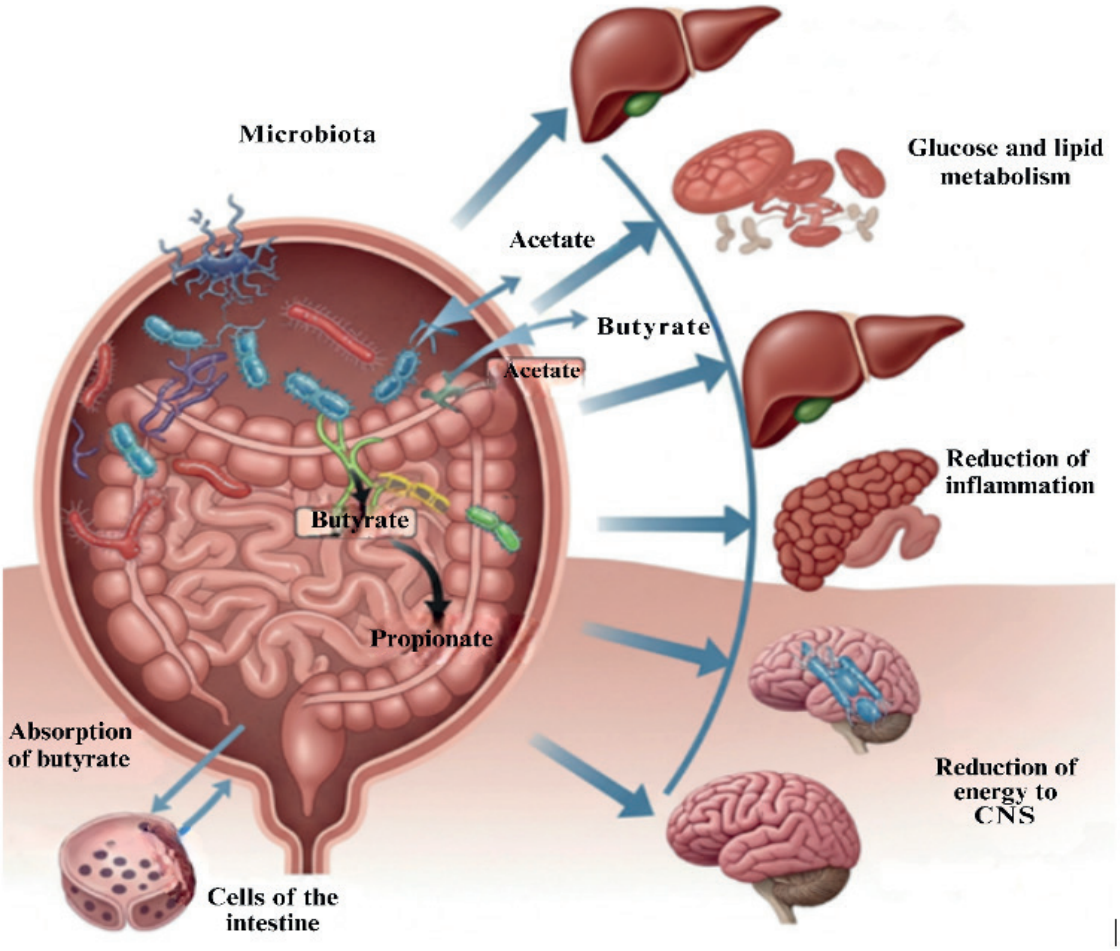
The gut microbiota plays a crucial role in host health, particularly in breaking down nutrients and producing vitamins. Deficiencies in these can lead to problems like anemia and neurological disorders. The GALT (gut-associated lymphoid tissue) functions as a unique immune system, offering protection against pathogens and toxins and promoting tolerance to foreign substances that need to be absorbed. This tissue comprises Peyer's patches, lamina propria, and intraepithelial lymphocytes, all vital for the intestine's immune defense. The relationship between nutrition and immunity underscores the importance of a balanced diet in fostering a healthy immune system. The author highlights the gut microbiota's influence on nutrient absorption and the modulation of the immune response (Chuluck *et al.*, 2023).

Beyond local effects, the gut microbiota also influences systemic immunity. It impacts distal immune responses through the expansion of extra-intestinal T cells, the production of short-chain fatty acids, the development of oral tolerance, and the control of inflammation. When new T cells are introduced into germ-free mice (those without their own T cells), they naturally multiply to maintain equilibrium. This occurs because they receive signals from special proteins (called MHC) and a substance called IL-7 (Kieper *et al.*, 2005).

Furthermore, in situations where the immune system is compromised, some of these new T cells multiply very rapidly. This is particularly evident in animals with more fragile immune systems and happens even without the presence of IL-7 or sufficient other T cells to send signals. This rapid T cell multiplication in specific conditions isn't solely dependent on normal equilibrium signals but is driven by factors present in animals with weakened immune systems. In this context, short-chain fatty acids (SCFAs) play a crucial role in producing regulatory T cells (Meijer *et al.*, 2010). Studies indicate that fiber-rich diets reduce plasma concentrations of inflammatory markers, with increased SCFA production from fermentation contributing to these beneficial effects. The intricate communication between the gut microbiota and the immune system involves various interaction mechanisms. While the biochemical process of converting carbohydrates into SCFAs by gut bacteria is well understood, data on the overall production rates of these compounds by the intestinal microbial community remain scarce. This gap is largely due to the difficulty of collecting samples from the human large intestine and underscores the undeniable benefits of SCFAs for mammals (den Besten *et al.*, 2013). However, most investigations into their metabolic synthesis have been conducted in rodents, making it challenging to translate these findings to humans given the limited studies focused on human individuals. Despite some controversies in the literature, SCFAs influence innate immunity, impairing the development of dendritic cells (DCs) and, consequently, their ability to stimulate T lymphocytes, impacting the effector response of adaptive immunity (Corrêa-Oliveira *et al.*, 2016).

The production of short-chain fatty acids (SCFAs) by the gut microbiota stimulates the production of regulatory T cells, which help prevent excessive inflammatory responses. Intestinal microorganisms metabolize indigestible carbohydrates into SCFAs, such as acetate, butyrate, and propionate. These compounds, which are chemically well-characterized, significantly impact health by regulating various metabolic pathways in the gut and distant organs like the liver, adipose tissue, muscles, and brain. Currently, SCFAs are recognized for their diverse physiological effects, which include modulating energy homeostasis, glucose and lipid metabolism, inflammation, immunity, and even cancer (de Vos *et al.*, 2022; Rastelli *et al.*, 2019). Under healthy conditions, colonocytes utilize butyrate as an energy source through mitochondrial beta-oxidation, maintaining an anaerobic environment in the intestinal lumen. Furthermore, butyrate activates the PPARγ receptor, which inhibits iNOS synthesis, resulting in reduced nitric oxide and nitrate production (Vos *et al.*, 2022).

Figure 2 - SCFAs: the impact of gut microbiota on overall health.



Source: (Adapted). Author, 2025

2.4 Role of gut microbiota in modulating the immune response

The gut microbiota plays a crucial role in the development and functionality of the immune system, influencing the body's immune response. The generation and development of myeloid cells depend on the microbiota, which acts through the systemic gain of products and metabolites. The presence of beneficial microorganisms enhances the inflammatory response and regulates the production of antibodies and cytokines, promoting anti-inflammatory cytokines and activating regulatory cells that inhibit exacerbated immune responses (Belkaid *et al.*, 2017).

Furthermore, the gut microbiota affects systemic immune responses through the expansion of extraintestinal T cells, the production of short-chain fatty acids, and the development of oral tolerance, maintaining mucosal immunity through the proliferation of CD4+ T cells and Th1, Th2, and Th17 responses (Samuelson *et al.*, 2015). Alterations in the microbiota not only favor opportunistic pathogens but also have a significant impact on host health, potentially contributing to autoimmune and allergic diseases in sites distant from the intestinal mucosa. Recent studies in animal models highlight that commensal microbiota is linked to these pathological processes, but variability in microbiota composition across different mouse strains

and among commercial breeders can lead to contradictory data on autoimmune diseases (Hooper *et al.*, 2012).

The immune system is influenced not only by its symbiotic relationship with the microbiota but also by the host's nutritional status. There is a multidirectional interaction among diet, the immune system, and commensal microflora, with dietary changes affecting both. Dietary control of immune cells is mediated by metabolic needs and the detection of food metabolites. The gut microbiota influences the activation and differentiation of immune cells, such as T lymphocytes, NK cells, and dendritic cells, in addition to modulating the immune response through the production of metabolites like short-chain fatty acids and vitamins (Belkaid *et al.*, 2014).

Table 1 - Effects of gut microbiota on immune response.

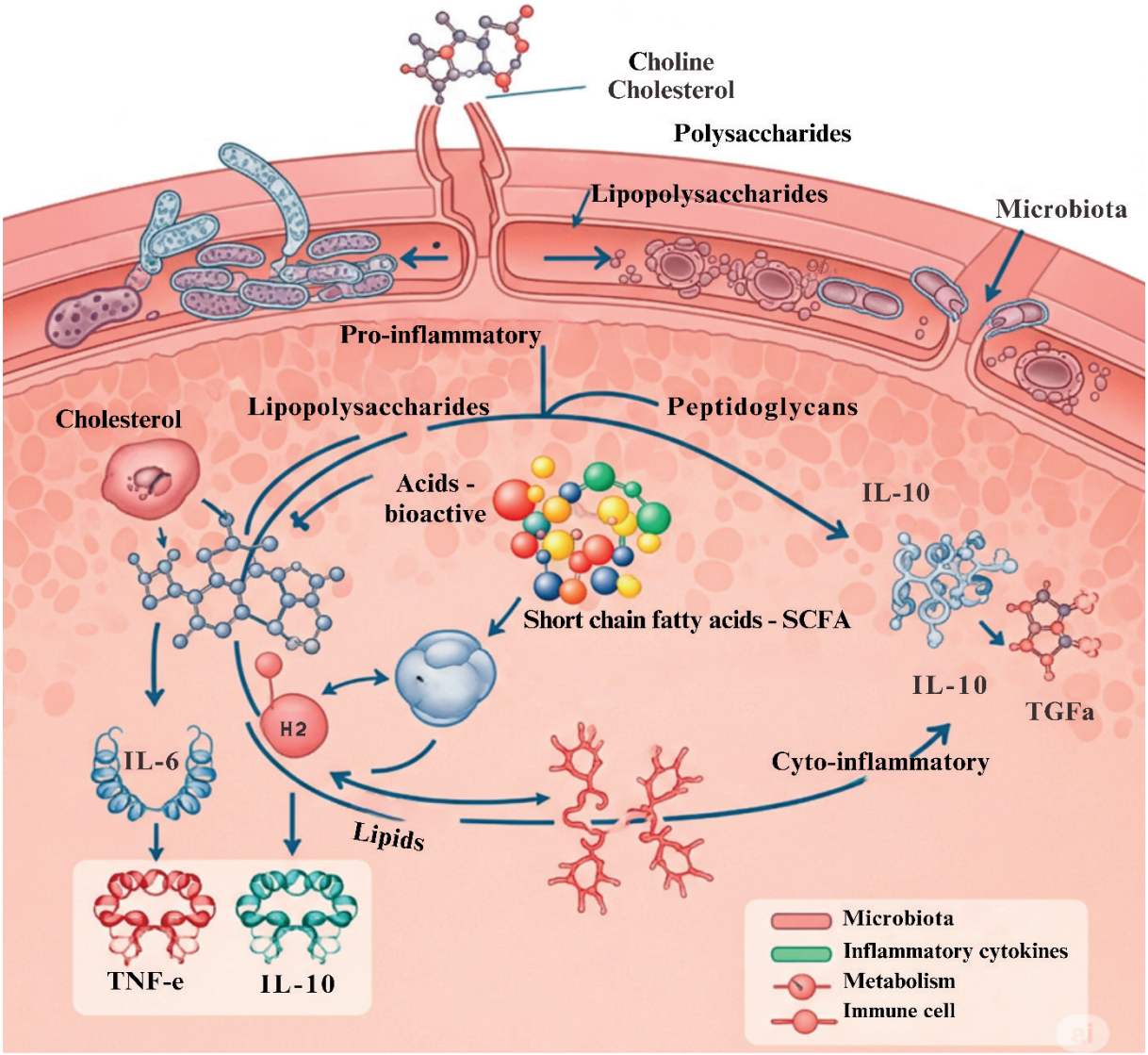
Dietary Component	Independent Effect	Receptor/Pathway	Associated Disease/Effect
Lipopolysaccharide	Activates an immune response	CD14/[1]TLR4	Insulin resistance
Peptidoglycan	Activates an immune response	[2]NOD1	Insulin resistance
Choline	Converted into TMAO by gut bacteria	[3]FMO (Flavin monooxygenase)	Cardiovascular disease
Cholesterol	Converted into primary bile acids		Increases triglyceride (TGR) levels, promotes energy expenditure, increases [4]GLP-1 secretion, and protects against atherosclerosis
Polysaccharides	Fermented by gut bacteria into short-chain fatty acids	[5]GPR41 e [6]GPR43	Energy source, regulation of hormones like 7PYY and GLP-1, inflammation modulation.

Legend for Table 1 - Here is the translated legend for your table: **[1]TLR4:** (TLR4: Toll-like receptor 4, an immune receptor that recognizes pathogen-associated molecular patterns). **[2]NOD1:** (Nucleotide-binding oligomerization domain 1, an intracellular receptor that recognizes peptidoglycans). **[3]FMO:** (Flavin monooxygenase, an enzyme that oxidizes nitrogenous compounds). **[7]PYY** and **[4]GLP-1:** (Intestinal hormones that regulate appetite and insulin secretion). **[5]GPR41** and **[6]GPR43:** (G protein-coupled receptors that detect short-chain fatty acids).

Source: (Belkaid *et al.*, 2014).

The gut microbiota significantly impacts host metabolism, both independently and dependently on diet. As illustrated, the microbiota produces pro-inflammatory molecules like lipopolysaccharides and peptidoglycans, which can influence metabolism via immune response-mediating proteins. Dietary nutrients such as choline, cholesterol, and polysaccharides are metabolized by the microbiota, leading to the generation of bioactive compounds. For example, choline may be associated with cardiovascular diseases. The activation of the TGR5 receptor by cholesterol can increase energy expenditure and GLP-1 secretion, offering protection against heart disease. Polysaccharides can be converted into short-chain fatty acids (SCFAs), which regulate hormones and modulate inflammation through GPR41 and GPR43 receptors. The microbiota's regulation of the inflammatory response is crucial for immune modulation. The microbiota can inhibit pro-inflammatory cytokines like TNF-α and IL-6 while promoting the production of anti-inflammatory cytokines such as IL-10 and TGF-β. This balance is critical, as an exacerbated inflammatory response can trigger autoimmune and chronic inflammatory diseases (Belkaid *et al.*, 2014).

Figure 3 - Intestinal microbiota: impact on metabolism and inflammatory response



Source: (Adapted). Author, 2025

Beyond its action against invading microbes, the microbiota controls infections and calibrates both innate and adaptive immunity. This interaction is bidirectional: while the microbiota modulates the immune response, the immune response, in turn, can affect the microbiota's composition. For example, an excessive inflammatory response can lead to intestinal dysbiosis, an imbalance in the microbiota (Molloy *et al.*, 2012).

A pilot study in critically ill patients revealed variations in gut microbiota dysregulation. In this observational cohort, the fecal microbiota of 34 patients admitted to intensive care units was analyzed, with 15 healthy individuals serving as controls. The microbiota was phylogenetically characterized through 16S rRNA gene sequencing, establishing associations with clinical outcomes. Fecal sample collection is crucial for understanding patients' gastrointestinal health

and immunity, guiding interventions that aim to optimize health and immune response in both groups (Lankelma *et al.*, 2016).

A common characteristic observed was the absence of genera like *Faecalibacterium*, *Blautia*, *Ruminococcus*, *Subdoligranulum*, and *Pseudobutyrivibrio*. These bacteria are important in degrading complex plant polysaccharides that humans cannot break down, converting them into acetate and butyrate, essential energy sources for colon epithelial cells (Rajilic-Stojanovic, 2014). Therefore, microbiota disturbances in ICU patients can indirectly reduce energy resources, with significantly lower levels of acetate and butyrate in critically ill patients compared to healthy controls (O'Keefe, 2018). The disappearance of *Faecalibacterium prausnitzii*, which has known anti-inflammatory properties, could potentially promote an unfavorable inflammatory state in the gut (Vos *et al.*, 2012).

Intestinal dysbiosis has been associated with clinical complications in critically ill patients, revealing decreased bacterial diversity and increased colonization by pathogens. This condition can result in bacterial translocation, where bacteria and toxins cross the intestinal barrier, leading to a systemic inflammatory response. Studies show that critical illness is characterized by the loss of commensal flora and overgrowth of potentially pathogenic bacteria, which increases susceptibility to nosocomial infections (Latorre, 2015).

Furthermore, sepsis remains one of the leading causes of death worldwide. According to the World Health Organization, probiotics are non-pathogenic live microorganisms that have well-documented beneficial effects when administered in adequate amounts. They work by modifying the intestinal flora, inducing the production of antimicrobial peptides, releasing antimicrobial factors, and stimulating mucus and IgA production, among other mechanisms. Modulating the gut microbiota through probiotics, prebiotics, and synbiotics has been explored as a therapeutic approach to reduce complications in critically ill patients. Alternatives such as selective antibiotic therapy and fecal microbiota transplantation are also under study. However, it's crucial to consider each patient's individual characteristics, such as their clinical condition and comorbidities, and to evaluate the risks and benefits of these therapeutic approaches (Watson *et al.*, 2003; Luyer *et al.*, 2005).

2.5 Impact of intestinal dysbiosis in critically ill patients

While antibiotics are one of the greatest inventions of the 20th century, their potential side effects are increasingly recognized. It's been suggested that antibiotic-induced alterations in gut flora could have serious and long-lasting consequences for human physiology. A decrease in intestinal microbial diversity may be particularly relevant for critically ill patients, as the vast majority of patients in an intensive care unit (ICU) are treated with antibiotics (Lankelma, 2016; Pamer, 2016).

The U.S. Centers for Disease Control reveal that 55% of all hospitalized patients receive an antibiotic during their stay, and in the ICU, this number rises to 70% of patients. Intestinal

dysbiosis is characterized by an imbalance in the composition of the gut microbiota, which can lead to clinical complications in critically ill patients. This imbalance can be caused by various factors, such as excessive antibiotic use, inadequate diet, and stress. Dysbiosis has been associated with a range of diseases, including inflammatory bowel diseases, allergies, and autoimmune conditions. These concerns surrounding antibiotics are exacerbated by the fact that currently used antibiotics, intended to treat infection, not only kill pathogens but also "health-promoting" microbes. These adverse effects include the hypothetical loss of commensal gastrointestinal microbiota, which allows for the overgrowth of undesirable organisms (dysbiosis) (Wischmeyer *et al.*, 2016).

Thus, the resulting dysbiosis (alteration of microbial composition) can be unfavorable and associated with the development of various diseases. Comparing the diversity of the microbial population and the microbiota among different individuals has led to identifying its association with different pathological conditions. The gut is composed of an epithelium, an adaptive immune system, and a microbiome. Each plays a crucial role in maintaining health and in the pathophysiology of critical illness. Alterations in gut microbiota and intestinal barrier homeostasis can be transmitted and propagated by downstream organs, such as the spleen and lungs, where large populations of immune cells are housed (Goma, 2020).

According to Wischmeyer *et al.* (2016), changes in intestinal homeostasis and gut microbiota in critical illness have been associated with increased production of inflammatory cytokines, intestinal barrier dysfunction, and increased cellular apoptosis, all of which can contribute to multiple organ failure.

The effects of the microbiota on systemic immunity, particularly the influence of commensal bacteria on the balance of T-cell subsets, are now known to extend far beyond the intestinal lamina propria. Homeostatic cell proliferation is driven by the microbiota or its penetrating molecules (Hooper *et al.*, 2012).

The relationship between intestinal dysbiosis and clinical complications is complex and multifaceted. While bacterial translocation clearly occurs in some preclinical models of critical illness, data regarding humans have generally remained inconclusive or do not support this as a common phenomenon observed in critically ill patients, although it's likely to occur under specific pathophysiological conditions (Earley, 2015).

Dysbiosis can lead to a state of chronic inflammation, which in turn can increase susceptibility to infections and worsen clinical outcomes in critically ill patients. Furthermore, dysbiosis can affect nutrient absorption and the gut barrier function, potentially leading to increased intestinal permeability and the entry of toxins into the body. While biomarkers of intestinal insufficiency are not frequently used, they have shown great promise in diagnosis. Plasma citrulline concentration is a marker of the functional metabolic mass of enterocytes, so a decrease in serum citrulline is a potential marker of intestinal injury. Additionally, intestinal fatty acid-binding protein is located in enterocytes and is released after enterocyte injury, so an increase in this protein is also a potential marker of intestinal injury (Klingensmith and Coopersmith, 2016).

Intestinal dysbiosis can impact the immune response by altering neurotransmitter production in the gut. Studies indicate that the gut microbiota influences the synthesis of neurotransmitters, including serotonin, which regulates mood and immune response. Dysbiosis can result in decreased production of these neurotransmitters, exacerbating clinical complications in critically ill patients (O'Mahony *et al.*, 2015).

The enteric nervous system (ENS), often called the "second brain," is a complex network of cells throughout the digestive tract (Knauf, 2020). Neurons located in the myenteric and submucosal plexuses form microcircuits that include intrinsic primary afferent neurons, interneurons, and excitatory/inhibitory motor neurons that innervate muscles. Research shows that certain bacterial strains can directly influence the synthesis and release of neurotransmitters, such as serotonin and gamma-aminobutyric acid (GABA), which play crucial roles in mood regulation and immune response modulation (Furness, 2012).

2.6 Microbial imbalance and immunosuppression

A decrease in microbial diversity and an imbalance in the gut microbiota have been associated with immunosuppression in critically ill patients, making them more vulnerable to infections and complicating treatment (Hooper, 2012). The gut microbiota plays a fundamental role in immune system homeostasis, and a balanced composition is crucial for the development and regulation of immune responses (Wischmeyer, 2016). Critically ill patients frequently exhibit immune compromise due to underlying clinical conditions and invasive medical interventions, resulting in increased susceptibility to opportunistic infections.

Studies indicate that therapeutic interventions focused on the gut microbiota, such as fecal transplantation and the use of specific probiotics, can be promising strategies to improve the immune response in these patients. Silva *et al.* (2019) showed that probiotic administration can enhance immune function and reduce infections, while the observed recovery in patients who received fecal transplant therapy suggests that restoring the gut microbiota can optimize immunity and clinical outcomes.

Lankelma (2016) concluded that the severity of the condition and the use of broad-spectrum antibiotics can alter the composition of the gut microbiota, leading to dysbiosis, which contributes to the loss of microbial diversity and the predominance of opportunistic pathogens. Dysbiosis can trigger inflammatory responses that worsen patient health and prolong recovery time.

The relationship between gut microbiota and immunity is complex and has been studied in animal models, such as mice. In both mice and humans, the gut microbiota is associated with metabolic conditions like obesity and insulin resistance (Hooper *et al.*, 2012). However, the composition of the gut microbiota varies significantly between these species; mice exhibit a more homogeneous microbiota, while humans show greater interindividual variation. This is due to the more diversified human diet, which more significantly impacts microbiota

composition. Additionally, environmental factors, such as antibiotic exposure, have distinct effects on the two groups.

Samuelson (2015) emphasizes that understanding the differences between mice and humans is vital for personalizing microbiota-related therapeutic interventions. While mouse studies provide valuable insights, their results need to be validated in humans to ensure clinical relevance. The comparison between gut microbiota in mice and humans underscores the complexity of this interaction. Both models are essential for deepening our understanding, but the translation of findings into clinical practice must carefully consider the biological and environmental differences between species.

CONCLUSION

The analyzed studies reveal the complex relationship between the gut microbiota and immunity in critically ill patients, highlighting the need for a multidisciplinary approach in both research and clinical practice. The hospital environment can influence microbiota composition, making it difficult to distinguish between the effects of the underlying disease and those of the environment. Various factors, such as age, sex, medical history, and exposure to treatments, cause fluctuations in the microbiota and immune response, complicating accurate diagnoses. Collecting microbiological samples from hospitalized patients can be invasive and logistically challenging, resulting in limited datasets and hindering the generalization of results. Additionally, the use of antibiotics and other intensive therapies can significantly impact microbiota composition. Studies in animal models may limit the translation of results to humans, emphasizing the need for more clinical research. Determining the causal relationship between microbiota changes and immune response is complex and requires longitudinal studies.

The results indicate that the microbiota, a diverse community of microorganisms in the gastrointestinal tract, plays a crucial role in maintaining the immune system. Understanding this interaction can optimize treatment and improve clinical outcomes. Therapeutic interventions, such as probiotics, prebiotics, and fecal microbiota transplantation, have shown potential in modulating the immune response. Thus, research in this area not only enriches the understanding of human physiology but also offers valuable perspectives for treating critically ill patients.

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