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CLINICAL APPLICATION OF PROBIOTICS IN INTENSIVE CARE UNIT (ICU)

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ABSTRACT

The gut microbiome comprises a complex community of bacteria that collectively perform various essential functions in the human body. A balanced gut microbiome enhances the host's defense against infections through mechanisms such as modulation of the local and systemic immune systems, suppression of enteric pathogens, and support of intestinal epithelial barrier integrity. Conversely, an imbalance in the microbiome, known as dysbiosis, has been shown to negatively impact the host and is associated with a variety of disease conditions. This is particularly relevant in the intensive care unit (ICU) setting, where critically ill patients such as those with respiratory failure, sepsis, myocardial infarction, cardiovascular procedures, intracerebral hemorrhage, and cerebral infarction—experience ongoing disruptions of their microbiome due to both the underlying disease and iatrogenic effects of clinical interventions.

Probiotics are live, non-pathogenic microorganisms, primarily bacteria, yeasts, or fungi, that confer health benefits to the human body, especially the digestive system. Broad-spectrum antibiotic use, acute dietary changes, and disease-induced stress can all disrupt the gut microbiome's homeostasis in patients. As a result, nearly all ICU patients experience severe disruption of the gut microbiome. Case reports discussed in this article show that probiotics may reduce the incidence of ventilator-associated pneumonia (VAP), the duration of mechanical ventilation, ICU length of stay, and hospital mortality.

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1. Introduction

Probiotics are live, non-pathogenic microorganisms, primarily consisting of bacteria, yeast, or fungi, that provide health benefits to the human body, particularly the digestive system. Critically ill patients are often in a hypermetabolic state, especially in cases of trauma, burns, or systemic inflammatory response syndrome (SIRS). The gastrointestinal tract plays an immunoregulatory role influenced by the microbiota, the intestinal mucosal barrier, and the intestinal immune system. Under severe inflammatory conditions, significant changes occur in both the composition andabundance of gut microorganisms, making the body more susceptible to infections and potentially triggering SIRS or multiple organ dysfunction syndrome (MODS).[1]

Various endogenous and iatrogenic factors contribute to substantial alterations in microbiota composition among ICU patients. These include gastrointestinal motility disorders, intraluminal pH shifts, increased catecholamine production, and the use of antibiotics, proton pump inhibitors, opioids, and both enteral and parenteral nutrition. Additionally, gastrointestinal infections caused by pathogenic bacteria or viruses can also trigger microbiome disruption. In critically ill patients, the gut microbiome is continuously impaired by both the underlying disease and iatrogenic effects of medical interventions, resulting in significant gut microbiome disruption and contributing to increased patient morbidity and mortality.[2]

2. Discussion

Gut Microbiota

The normal flora of the gastrointestinal tract is a vital component of the body's natural defense system against pathogen invasion. The human microbiome includes viruses, bacteria, fungi, archaea, and unicellular eukaryotes, with an estimated more than 100 trillion bacterial cells from over 35,000 species residing within the human body. The immune function of the gut is understood through three barrier layers. The first is the ecological barrier—commensal flora that inhibits pathogen colonization by competing for space and nutrients. The second is the mechanical barrier—an intact mucosal epithelial layer that prevents microbial invasion or translocation. The third is the immunological barrier—comprising immune cells such as intraepithelial lymphocytes, macrophages, neutrophils, natural killer (NK) cells, Peyer's patches, and immunoglobulin A (IgA). If the intestinal epithelium is disrupted, pathogenic and even commensal microbes can translocate to other tissues and cause disease.[3]

Disruption of the gut barrier has been linked to numerous clinical conditions, including inflammatory bowel disease (IBD), chronic kidney disease, necrotizing pancreatitis, celiac disease, food allergies, Clostridium difficile infection (CDI), and sepsis. Dysbiosis, or imbalance of gu microbiota, commonly occurs in critically ill patients receiving antibiotics, immunosuppressants, or radiotherapy. This condition reduces microbial diversity and disrupts intestinal physiological functions. The innate and adaptive immune systems regulate microbiota colonization through mechanisms including the production of antimicrobial peptides and IgA antibodies. When dysbiosis occurs, microbial colonization may shift and impair intestinal immune function, promoting bacterial translocation and SIRS originating from the gut.[1,2]

Medical interventions during hospitalization, such as broad-spectrum antibiotics and invasive procedures, can further worsen dysbiosis and increase infection risk. Environmental factors such

as lifestyle, diet, hygiene, trauma, and critical illness also significantly influence microbiome composition.[4]

The Role of Probiotics in Gut Microbiota

Probiotics are live microorganisms that, when consumed in adequate amounts, provide health benefits to the host. Prebiotics are substrates that are selectively fermented to induce specific changes in the composition and/or activity of gastrointestinal microbiota, thereby benefiting the host. Synbiotics are products that contain both probiotics and prebiotics, designed to confer synergistic health benefits to the host. Probiotic species that have been widely studied include genera such as *Lactobacillus*, *Bifidobacterium*, *Streptococcus*, *Saccharomyces*, *Bacillus*, and *Enterococcus*. Most probiotics are Gram-positive bacteria, as they are part of the normal flora of the human gastrointestinal tract. The therapeutic efficacy of probiotics is influenced by various factors, including manufacturing methods and storage conditions such as humidity, temperature, acidity, oxygen levels, osmotic pressure, as well as their ability to colonize and survive in the human body (e.g., resistance to acidic pH, bile salts, and digestive enzymes).[5]

Probiotics may restore disrupted gut microbiota through two main mechanisms, inhibition or replacement of pathogenic bacteria, thereby promoting a healthier gut microbial environment and preventing pathogenic colonization and microaspiration-associated pneumonia; and systemic immunologic effects through immune modulation beyond the gastrointestinal tract. Probiotics can be used in both healthy individuals and those with health disorders, for preventive and therapeutic purposes. Their expected benefits include prevention and management of diseases by correcting metabolic imbalances, restoring microbiota disturbances, and alleviating symptoms during the early or progressive phases of illness. In healthy individuals, probiotics aim to maintain gut microbiota homeostasis and prevent the onset of disease. Mechanistically, probiotics work by selectively modulating microbial growth, inhibiting the colonization of invasive pathogens, and enhancing the body's microecological balance, particularly in the gastrointestinal tract.[1,5]

Dysbiosis refers to an imbalance in gut microbiota and is commonly observed in critically ill patients receiving antibiotics, immunosuppressants, or radiotherapy. This condition is marked by a loss of microbial diversity and alterations in intestinal physiological function. Both innate and adaptive immune systems play crucial roles in maintaining microbial colonization balance via the production of antimicrobial peptides and IgA antibodies. However, dysbiotic microbiota may disrupt this colonization environment by impairing intestinal immune function, potentially leading to bacterial translocation and the onset of systemic inflammatory response syndrome (SIRS) originating from the gut. Animal studies show that gut microbiota disruption decreases colonization resistance and impairs immune functions. In a healthy state, commensal bacteria prevent pathogen colonization by competing for nutrients, increasing IgA production, and stimulating antimicrobial peptides like regenerating islet-derived protein IIIγ (REGIIIγ). Moreover, short-chain fatty acids (SCFAs) produced by commensals serve as nutrients for enterocytes and maintain gut barrier integrity. In critical illness, reduced commensal populations lead to impaired colonization resistance and increased intestinal permeability, allowing pathogen overgrowth and systemic dissemination.[2]

Probiotics are believed to restore disrupted gut microbiota balance and confer health benefits through two main mechanisms. First, probiotics can inhibit the growth of pathogens or replace

pathogenic bacteria with non-pathogenic strains, creating a more favorable microbial environment in the gut. This process may prevent pathogenic colonization and reduce the risk of

microaspiration-related pneumonia. Furthermore, the translocation of pathogenic gut bacteria into the bloodstream and distant organs can be mitigated by the dominance of beneficial microbes. Second, gut microbiota restoration may also exert systemic immunologic effects by modulating immune responses beyond the gastrointestinal tract.[6]

Nevertheless, since the pathophysiology of microbiota disruption in critical illness is not yet fully understood, the exact mechanisms of probiotic action also remain unclear. Animal studies have demonstrated that microbiota disruption reduces colonization resistance to pathogens and causes immune dysfunction. Under healthy conditions, commensal bacteria prevent pathogen colonization through nutrient competition, enhanced immunoglobulin A (IgA) production, and stimulation of antimicrobial peptide secretion, such as regenerating islet-derived protein IIIγ (REGIII γ), by epithelial cells. Additionally, short-chain fatty acids (SCFAs) produced by commensal bacteria serve as a primary energy source for intestinal enterocytes, contributing to the maintenance of gut barrier integrity and prevention of systemic transmission of pathogenic bacteria. In critical illness, a reduction in commensal bacterial populations leads to a loss of colonization resistance and increased gut permeability, which in turn allows excessive pathogen growth and their translocation into the bloodstream and distant organs such as the lungs and brain.[2,7]

The beneficial effects of restoring gut microbiota extend beyond the gastrointestinal tract via the production of immunomodulatory metabolites. Other metabolites, such as D-lactate, may travel from the intestine to the liver via the portal vein, stimulating Kupffer cells, the resident hepatic macrophages, in the clearance of pathogens. Animal studies have also demonstrated the involvement of gut microbiota in complications of critical illness, including ischemia-reperfusioninduced acute kidney injury, acute respiratory distress syndrome (ARDS), and liver injury. Therefore, probiotics are believed to prevent the detrimental consequences of gut dysbiosis and support healthy enteric and systemic immune responses.[2]

Use of Probiotics in Critically Ill Patients in the Intensive Care Unit (ICU)

The role of probiotics in the management of critically ill patients in the ICU has gained increasing attention, particularly in relation to the prevention of nosocomial infections. ICU patients often experience gut dysbiosis due to physiological stress, the use of broad-spectrum antibiotics, and invasive interventions. These conditions weaken mucosal barrier function, increase bacterial translocation, and trigger systemic inflammatory responses. Probiotics are believed to help stabilize gut microbiota, strengthen tight junctions, and reduce intestinal inflammation. Although not yet part of standard ICU protocols, many clinicians and researchers have begun to reevaluate their potential benefits. Probiotics are considered safer than many pharmacological interventions, as they are not immunosuppressive.[3]

Recent scientific narratives place probiotics as part of a supportive approach to reducing the risk of ventilator-associated pneumonia (VAP) and gastrointestinal infections. In this context, probiotics do not act directly as antimicrobial agents but rather as modulators of a balanced microbial ecosystem. Their functions support competition with pathogens, production of organic acids, and synthesis of natural antimicrobial compounds such as bacteriocins. In ventilated patients, the presence of probiotics in the oropharyngeal cavity and gastrointestinal tract may reduce pathogenic colonization that could migrate to the lungs. Furthermore, local immune responses are enhanced by increased secretory IgA production and activation of mucosal macrophages. The influence of probiotics on immune response underpins the hypothesis that probiotics have the potential to reduce infectious complications in ICU therapy.[8]

From the perspective of clinical nutrition, probiotics are categorized as non-pharmacological microbiological interventions that support gastrointestinal integrity. In critical illness, impaired gastrointestinal mucosal perfusion can lead to mucosal atrophy, cytokine hypersecretion, and increased intestinal permeability. Probiotics function by stimulating intestinal epithelial proliferation, reducing permeability, and decreasing systemic endotoxemia. This condition is significant because systemic inflammation originating from the gut is referred to as "gut-origin sepsis." It highlights that maintaining gut microbiota stability through probiotic supplementation may be a beneficial strategy to preserve epithelial barrier function and mucosal immunity. Moreover, probiotics are also believed to play a role in bile acid metabolism and vitamin synthesis, which are advantageous during the catabolic phase in ICU patients.[5]

From an immunological standpoint, probiotics can influence systemic immune responses through interactions between commensal microbes and mucosal immune cells. Probiotics have been shown to stimulate Toll-like receptor pathways, increase anti-inflammatory expression such as interleukin-10 (IL-10), and suppress proinflammatory mediators like tumor necrosis factor-alpha (TNF-α). These mechanisms are essential for controlling the excessive systemic inflammation commonly observed in patients with sepsis or other critical conditions. In this immunomodulatory context, probiotics do not suppress immunity but rather balance inflammatory responses to remain adaptive and non-destructive to tissues. This supports the assumption that probiotics can be used as supportive therapy to regulate immune dysfunction in critical illness.[3,5]

Infections such as ventilator-associated pneumonia (VAP), sepsis, and urinary tract infections (UTIs) are leading causes of clinical deterioration and mortality in critically ill patients. These patients frequently undergo significant changes in gut microbiota composition, where pathogenic bacteria outnumber beneficial ones. One study evaluating gut microbiota in patients with severe systemic inflammatory response syndrome (SIRS) found a significant decrease in beneficial bacteria and a marked increase in *Pseudomonas* species. This study was the first to demonstrate gut microbiota alterations in critically ill patients.[9] Subsequent studies in SIRS patients showed that such microbiota changes contributed to gastrointestinal motility disorders, which in turn increased complications and mortality. In critically ill individuals, commensal bacteria from the *Firmicutes* and *Bacteroidetes* phyla are often replaced by pathogens from the *Proteobacteria* phylum. This shift is primarily attributed to the use of broad-spectrum antibiotics, which eliminate protective gut bacteria. Therefore, adequate enteral nutrition is important for maintaining gut health in ICU patients. Strategies being considered include the administration of probiotics, prebiotics, synbiotics, and even fecal microbiota transplantation.[1,3]

Effectiveness of Probiotic Use in Critically Ill Patients in the Intensive Care Unit (ICU)

A recent meta-analysis by Konsta et al. (2025), which included 33 clinical trials with a total of 5,106 critically ill patients, demonstrated that probiotics or synbiotics significantly reduced the incidence of nosocomial infections, including ventilator-associated pneumonia (VAP), and shortened the duration of mechanical ventilation, ICU stay, and hospital length of stay, without a significant impact on mortality.[10] Additional analysis from the SCOVID 2023 meta-analysis also confirmed a ~20% reduction in VAP risk. These findings suggest that probiotics hold strong potential for infection prevention. A meta-analysis focusing specifically on ventilated patients (15 studies, n = 4,693) reported an odds ratio for VAP of 0.58 (95% CI: 0.41–0.81), as well as reductions in bacterial colonization, duration of ventilation (-1.57 days), and ICU length of stay (- 1.87 days).[11] The most recent VAP prevention meta-analysis also concluded that probiotics significantly reduced VAP

incidence, decreased oropharyngeal and gastric pathogen colonization, and shortened ICU stays. Physiologically, probiotics are known to play a key role in maintaining the integrity of the intestinal mucosal barrier and regulating immune responses to pathogen colonization. In the context of VAP, their mechanisms include competing with pathogenic microorganisms in the gut and oropharynx, inhibiting pathogen adhesion to mucosa, and modulating mucosal immune responses to reduce systemic inflammation. One extensively studied strain, *Lactobacillus rhamnosus* GG (LGG), has proven to be safe and clinically effective in reducing VAP incidence by lowering pathogenic colonization in the lower respiratory tract.[11]

Several clinical trials have evaluated the role of probiotics and synbiotics in preventing VAP in ICU patients, although the specific formulations and strains used were varied and not always analyzed separately. Most studies involved adult populations, with the majority of patients receiving enteral nutrition through various routes. Some studies reported a significant reduction in VAP incidence in the probiotic group compared to placebo, along with shortened ICU stays and total hospitalization duration. However, other studies found no meaningful differences in length of stay or mortality. Microbiological data suggest that colonization by potentially pathogenic microorganisms such as *Enterobacteriaceae*, *Staphylococcus aureus*, and *Candida spp.* Was significantly lower in probiotic groups, although eradication rates did not differ. Probiotics also significantly increased the population of beneficial bacteria in feces, although effects on diarrhea and colonization by multidrug-resistant organisms have not reached statistical significance. Nevertheless, one study found that probiotic therapy reduced the incidence and duration of *Clostridioides difficile*-associated diarrhea. Overall, these findings suggest that probiotics may offer benefits in ICU settings, although their effectiveness remains variable and is influenced by multiple factors, including probiotic type, strain, and patient characteristics.[12]

A systematic review comparing the effects of probiotics and synbiotics in the ICU showed that single-strain probiotic interventions at high doses ($\geqslant 5 \times 10^9$ CFU/day) and with a duration of $\geqslant$14 days yielded more consistent clinical outcomes than combined synbiotic therapies. In critically ill patients, probiotic interventions without prebiotics appear to be more effective in reducing ICU related infections, despite the widespread use of synbiotics.[10]

In critically ill patients, profound alterations in the composition and function of gut microbiota—referred to as dysbiosis—are triggered by physiological stress, the administration of broadspectrum antibiotics, and limited enteral nutrition. This dysbiosis leads to a reduction in beneficial commensal bacteria such as *Lactobacillus* and *Bifidobacterium*, and an overgrowth of opportunistic pathogens that compromise the integrity of the intestinal mucosa. As a result, gut permeability increases, allowing bacterial translocation or microbial toxins to enter systemic circulation. This process triggers systemic inflammatory responses that can ultimately lead to sepsis.[13] Additionally, abnormal interactions between disrupted microbiota and the mucosal immune system can result in excessive immune cell activation and the release of proinflammatory cytokines. Such an environment disrupts the balance between protective immune responses and harmful inflammation. Thus, dysbiosis in critically ill patients greatly contributes to susceptibility to systemic infections and secondary immunosuppressive complications.[2]

Probiotics function through multiple mechanisms to address dysbiosis in critically ill patients. These microorganisms help restore gut microbial balance by competing with pathogens, producing organic acids, and increasing protective mucus production by intestinal epithelial cells. Probiotics also strengthen the intestinal epithelial barrier by enhancing the expression of tight

junction proteins that maintain the cohesion of epithelial cells. This action reduces the risk of bacterial translocation from the intestinal lumen into systemic circulation—one of the main pathogenic pathways leading to sepsis. Additionally, probiotics interact with mucosal immune cells such as dendritic cells and lymphocytes to promote balanced immune regulation. They have been shown to increase the production of immunoglobulin A (IgA) and reduce excessive release of proinflammatory cytokines like IL-6 and TNF-α. Therefore, probiotics hold potential as immunomodulatory agents that support immune homeostasis in critically ill patients.[10,13]

In patients with sepsis, excessive immune responses are a major driver of organ damage. Probiotics may exert protective effects by modulating both innate and adaptive immune activation pathways, and by enhancing immune tolerance signaling toward luminal antigens. Interactions between probiotics and receptors such as Toll-like receptors (TLRs) in the intestinal mucosa can stimulate protective immune responses without inducing excessive inflammation. In this context, the healthy microbiota shaped by probiotics helps rebalance the ratio of proinflammatory Th17 cells to antiinflammatory regulatory T cells. This imbalance, common in sepsis, may be partially corrected by probiotics through the upregulation of regulatory cytokines such as IL-10 and TGF-β. Probiotics can also reduce the production of lipopolysaccharides (LPS) from Gram-negative bacteria in the gut—key triggers of systemic inflammatory responses. By lowering the antigenic and endotoxin burden, probiotics help prevent the progression of localized infections into systemic sepsis. Hence, probiotics have a vital physiological role in maintaining immune balance and preventing further systemic injury in sepsis.[13]

One of the main challenges in evaluating the effectiveness of probiotics in critically ill patients lies in the lack of consistent laboratory indicators, such as fecal bacterial cultures, short-chain fatty acid (SCFA) levels, or fecal pH. This inconsistency hampers comparison across studies and the objective measurement of intervention outcomes. Research has shown that patients with SIRS often exhibit gut microbiota alterations characterized by decreased SCFA and increased fecal pH prior to probiotic intervention.11 However, probiotic supplementation has been associated with increased beneficial bacteria, decreased fecal pH, and reduced infection rates, although data remains limited. Clinically, these trends are promising, but validation through standardized biomarkers is still needed. Additionally, careful monitoring for adverse effects such as bacteremia or fungemia—especially in immunocompromised patients—is essential when determining the safety and efficacy of probiotic use in critical care settings.[8]

The use of probiotics in critically ill and septic patients still presents several limitations that warrant careful consideration. One of the main concerns is the risk of infection resulting from probiotic bacterial translocation into the bloodstream, potentially leading to bacteremia, particularly in patients with compromised immunity or disrupted gut mucosa. Variability in probiotic strains, doses, and treatment durations across studies also contributes to inconsistent outcomes and challenges in drawing strong clinical conclusions. Some patients may experience gastrointestinal side effects, such as bloating or diarrhea, which can interfere with nutritional management in ICU settings.11 Another limitation is the unclear consistency in probiotic mechanisms for modulating immune and systemic inflammatory responses. While probiotics theoretically stabilize gut barriers and reduce pathogenic bacterial colonization, such benefits are often not consistently observed in clinical practice. Differences in patient factors—such as age, nutritional status, and comorbidities, also influence individual responses to probiotic interventions.[8,10]

3. Conclusion

Critically ill patients in the ICU experience significant gut microbiome disruption known as dysbiosis. Dysbiosis has been associated with poor clinical outcomes, increased reinfection risk, and higher readmission rates. Probiotic administration has been shown to improve outcomes in severe infections; however, the underlying biological mechanisms remain incompletely understood. Moreover, inconsistent findings across studies, safety concerns, and negative outcomes from some large clinical trials challenge the definitive conclusion regarding probiotic efficacy in ICU settings. Further experimental and clinical research is needed, particularly focusing on mechanistic insights, to optimize the microbiome's role as a diagnostic and therapeutic tool. While the approach of microbiome modulation in ICU care may require re-evaluation, it still holds considerable potential to improve long-term outcomes in critically ill patients.

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