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Role of Immunonutrients in Critically Ill Patients: A Perspective on Food, Lifestyle, and Nutrition

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Abstract

Critical illness refers to life-threatening conditions characterized by systemic inflammation, immune system dysregulation, and failure of multiple organs, often resulting from severe infections, traumatic injuries, or respiratory complications. These conditions require intensive medical care and are associated with metabolic disturbances, suppressed immunity, muscle breakdown, and impaired gastrointestinal function. Pre-existing lifestyle and nutritional factors, such as malnutrition or obesity, play a significant role in influencing outcomes during intensive care. Data from Indian healthcare settings highlight a high prevalence of infections, physical frailty, and mortality, underscoring the importance of early preventive and therapeutic interventions. Nutritional support with immune-modulating formulations has shown potential in reducing hospital stay duration, complications, and death rates when administered early through the digestive tract. However, clinical outcomes vary due to differences in patient conditions, nutritional composition, and timing of support. Economic limitations and the need for tailored treatment plans also hinder broad implementation. Despite these challenges, nutrition-based immune support presents a promising strategy for improving recovery and should be further explored in critical care settings.

Keywords: Critical illness, immunonutrition, immune response, nutritional support, sepsis, acute respiratory distress syndrome

1. Introduction

Critical illness encompasses severe, life-threatening conditions that require advanced medical care and continuous monitoring, often involving multiple organ dysfunction and carrying a high mortality risk (Singer *et al.* 2016) [46]. Conditions such as sepsis, trauma, and acute respiratory distress syndrome (ARDS) are marked by widespread inflammation, metabolic disruption, and immune system failure (Seymour *et al.* 2016) [45]. These illnesses significantly increase metabolic needs, which can lead to protein breakdown, immune suppression, and gastrointestinal complications (Calder, 2021) [5].

In critically ill patients, immune dysregulation often occurs, initiating an excessive inflammatory response that exacerbates tissue damage and contributes to organ failure (Fani *et al.* 2020) [14]. This has led to growing interest in immunonutrition, a targeted approach that uses specific nutrients to modulate immune function and reduce inflammation. Nutrients such as glutamine, arginine, and omega-3 fatty acids have been shown to improve clinical outcomes by reducing infection risk, enhancing recovery, and shortening ICU stays (Slim *et al.* 2022) [47].

Furthermore, an individual's lifestyle and dietary habits prior to illness play a significant role in critical care outcomes. Diets lacking in balance and physical inactivity weaken immune resilience and metabolic health (Calder, 2021; Wischmeyer, 2017) [5, 55]. Overconsumption of energy-dense, nutrient-poor foods contributes to chronic inflammation, insulin resistance, and microbiome imbalance (Monteiro *et al.* 2013; Frayn & Evans, 2019) [54, 52], while undernutrition results in micronutrient deficiencies that impair immunity (Bischoff *et al.* 2021; Calder, 2021) [3, 5]. Harmful habits like smoking and excessive alcohol intake further increase oxidative stress and tissue vulnerability, thereby heightening the risk of complications during acute illness or surgical interventions (Manzanares & Hardy, 2009; Kiecolt-Glaser *et al.* 2015; Wischmeyer, 2017) [22, 40, 55].

Malnutrition-whether due to overnutrition or nutrient deficiency-is now recognized as a modifiable factor that influences critical illness outcomes. Western dietary patterns, rich in processed foods, red meats, and sugary beverages, are associated with chronic inflammation and metabolic disturbances that raise ICU admission risk

(Gombart *et al.* 2020; Di Renzo *et al.* 2020; Calder, 2021; Soldati *et al.* 2018) [18, 10, 5, 48].

Evidence from a large-scale cohort study by Du *et al*. (2023) underscores the long-term consequences of unhealthy lifestyle behaviors, linking factors like poor diet, inactivity, smoking, and alcohol use to the development of chronic diseases and multiple comorbidities. This reinforces the importance of preventive lifestyle interventions to mitigate health risks and improve resilience during critical illness.

This review will examine the therapeutic potential of immunonutrition in critical care, emphasizing its biological mechanisms, clinical benefits, and integration into patient management. The goal is to highlight how nutrition-focused strategies can strengthen immune defenses, improve outcomes, and support recovery in critically ill individuals.

1.1 Pathophysiology of Critical Illness

Pathophysiology refers to the disruption of normal physiological processes due to illness or injury, focusing on the mechanisms underlying symptoms and disease progression. In critical illness, profound physiological disturbances demand an understanding of immune responses, muscle metabolism, and gastrointestinal integrity to guide therapeutic strategies. One crucial intervention is immunonutrition, which addresses the elevated metabolic demands and compromised immune function seen in these patients.

1.1.1 Immune Response in Critical Illness

Severe infections, trauma, and sepsis trigger a surge in pro-inflammatory mediators like IL-1β, IL-6, TNF-α, and IFN-γ (Fani *et al.* 2020) [14]. This hyperinflammatory state can cause endothelial damage, hypotension, and multi-organ failure (Cecconi *et al.* 2020; Singer *et al.* 2016) [8, 46]. The body attempts to counterbalance this through the compensatory anti-inflammatory response syndrome (CARS), but this often results in immunosuppression and increased risk of secondary infections (Liu *et al.* 2021) [26]. Consequently, patients may experience leukocyte dysfunction and weakened immunity (Barazzoni *et al.* 2021; Dushianthan *et al.* 2019) [3, 12].

1.1.2 Muscle Catabolism and Nitrogen Imbalance

Critical illness accelerates muscle protein breakdown, leading to severe muscle loss and a negative nitrogen balance (Casaer & Van den Berghe, 2020). Stress hormones such as cortisol and glucagon drive gluconeogenesis and amino acid utilization for immune function (Wischmeyer *et al.* 2021; Jafari *et al.* 2015) [55, 23]. Intensive care unit (ICU) patients may lose up to 1% of their skeletal muscle mass daily (Weijs *et al.* 2014) [53]. This catabolism, compounded by oxidative stress and immobilization, contributes to ICU-acquired weakness (Heyland *et al.* 2021; D'Ignazio *et al.* 2020) [21, 11].

1.1.3 Gut Dysfunction and Nutrient Malabsorption

The gastrointestinal tract is particularly vulnerable in critical illness. A compromised gut barrier allows translocation of bacteria and endotoxins into the bloodstream, triggering systemic inflammation (Reintam Blaser *et al.* 2021) [41]. This impairs nutrient absorption and disrupts the balance of gut microbiota, favoring pathogenic over beneficial species (Clark *et al.* 2020; Niu *et al.* 2021) [9, 38]. These alterations elevate the need for nutrients such as protein (1.3–2.0 g/kg/day), glutamine, arginine, antioxidants, vitamin D, and zinc to promote tissue repair, immune regulation, and oxidative balance (ESPEN, 2019; Martindale *et al.* 2020; Rondanelli *et al.* 2021) [13, 31, 42].

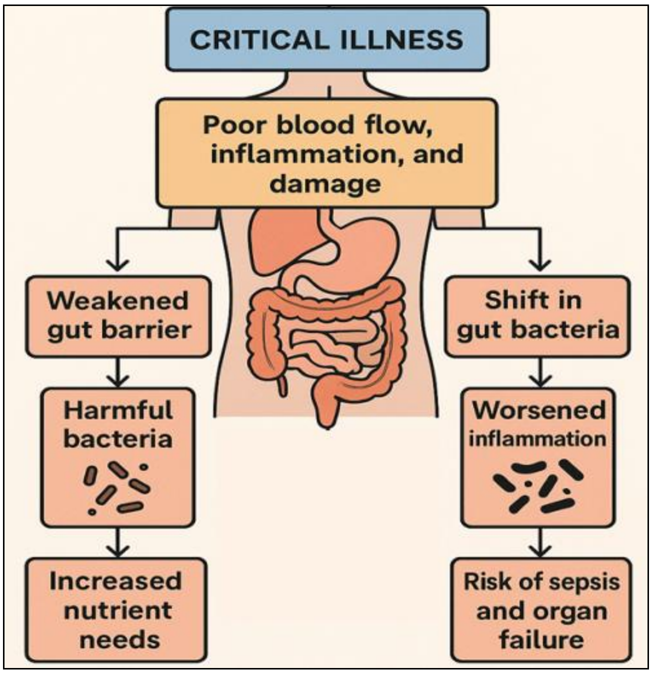

Fig 1: Representing Impact of Critical Illness on Gut Dysfunction and Nutrient Imbalance

1.2 Prevalence of Critical Illness in India

A study in Indian ICUs revealed that 20% of patients were classified as frail, highlighting the vulnerability of this population (Tirupakuzhi *et al.* 2023) [50]. Sepsis, driven by both gram-positive and gram-negative infections, remains a leading cause of ICU admission. Alarmingly, the mortality rate in Indian ICUs is estimated at around 25% (Mani, 2021) [30]. These outcomes are further influenced by systemic challenges including limited ICU beds, inadequate trained staff, and resource constraints. Additionally, delirium affects approximately 22–29% of ICU patients in India, reflecting significant neurological morbidity (Khurana *et al.* 2011) [24].

2. Role of Immunonutrients in Critical Illness

Immunonutrients are specific dietary components that modulate immune function, reduce inflammation, and support recovery in critically ill patients (Gianotti *et al.* 2022) [16]. They are especially beneficial in ICU settings where oxidative stress, immune dysfunction, and metabolic disruptions are prominent. Evidence suggests that incorporating immunonutrients into nutritional strategies lowers infection risk, shortens ICU stays, and improves survival (Slim *et al.* 2022) [47]. Important immunonutrients include glutamate, arginine, omega-3 fatty acids, nucleotides, antioxidants, vitamin D, and β-hydroxy β-methylbutyrate (HMB) (Soldati *et al.* 2018) [48].

2.1 Glutamine

Glutamine becomes a conditionally essential amino acid during periods of critical illness due to the body's increased metabolic demands. It plays a crucial role in supporting immune cells such as lymphocytes and macrophages, and helps maintain the structural and functional integrity of the intestinal lining (Sun *et al.* 2021) [49]. As a precursor to glutathione-one of the body's most important antioxidants-glutamine helps reduce oxidative stress, strengthens mucosal barriers, and defends against free radical damage. It also promotes the proliferation of lymphocytes and the health of enterocytes (intestinal cells), preventing microbial translocation from the gut into the bloodstream-a common cause of infections in critically ill patients (Molfino *et al.* 2023) [34]. Clinical evidence has shown that glutamine supplementation reduces the risk of infections, enhances immune recovery, and improves survival, especially in patients with severe burns, trauma, or post-surgical stress. Furthermore, it aids in nitrogen transport and acid-base balance, supporting overall metabolic stability during illness.

2.2 Arginine

Arginine is essential for immune function, particularly in the activation and proliferation of T-cells. It also plays a key role in wound healing by promoting collagen synthesis and tissue repair. Additionally, arginine serves as a precursor for nitric oxide (NO), a molecule that supports vasodilation and improves tissue perfusion, ensuring better oxygen and nutrient delivery to injured tissues (Beier-Holgersen & Boesby, 2021) [2]. However, in septic patients, the increased production of NO can exacerbate vasodilation and hypotension, potentially worsening cardiovascular instability. Therefore, while arginine supplementation can boost immune defenses and recovery in trauma and surgical cases, it must be used with caution in hemodynamically unstable patients or those with septic shock.

2.3 Omega-3 Fatty Acids

Omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have well-established anti-inflammatory properties. They reduce the production of pro-inflammatory cytokines such as IL-6 and TNF-α, and modulate immune cell activity by altering the composition of cell membranes (Singer *et al.* 2016) [46]. These fatty acids also give rise to specialized pro-resolving mediators (SPMs), which help resolve inflammation without compromising immune defense. In patients with Acute Respiratory Distress Syndrome (ARDS) and sepsis, omega-3 supplementation has been shown to improve oxygen exchange, reduce ventilator dependency, and shorten ICU stays. Additionally, they help in maintaining endothelial function and may offer cardiovascular protection during systemic inflammation.

2.4 Nucleotides

Nucleotides are the building blocks of DNA and RNA, making them essential for cell replication, DNA repair, and immune responses. During critical illness, the body's demand for nucleotides increases significantly due to rapid immune cell turnover and tissue repair needs. Supplementing nucleotides has been shown to support the growth and function of lymphocytes and enhance the activity of gut-associated lymphoid tissue (GALT), which is vital for intestinal immune defense (Li *et al.* 2022) [25]. In patients with compromised nutritional intake or gut dysfunction, exogenous nucleotides can improve recovery, reduce infection risk, and support mucosal healing.

2.5 Antioxidants

Antioxidants play a pivotal role in protecting cells from oxidative damage caused by free radicals, which are often elevated during systemic inflammation and critical illness. Key antioxidants such as vitamins C and E, zinc, and selenium not only neutralize reactive oxygen species (ROS) but also support immune cell function and wound healing (Hemilä & Chalker, 2021) [20]. High-dose vitamin C has shown promise in improving organ function, reducing ICU length of stay, and lowering mortality in patients with sepsis. Zinc is involved in the development and activation of immune cells and supports barrier integrity, while selenium is crucial for antioxidant enzyme function like glutathione peroxidase. Together, these nutrients help maintain immune homeostasis and enhance resilience against secondary infections during critical care.

2.6 Vitamin D

Vitamin D plays a vital role in supporting both the innate and adaptive immune systems. It helps balance the production of cytokines-chemical messengers that regulate inflammation-and maintains the integrity of mucosal barriers, such as those in the lungs and gut, which act as the body's first line of defense against pathogens. By enhancing the activity of immune cells like macrophages and dendritic cells, vitamin D improves the body's ability to recognize and destroy invading microorganisms.

Deficiency of vitamin D is commonly observed in critically ill patients due to limited sunlight exposure, poor nutritional intake, and increased metabolic demands during illness. Low levels have been strongly linked to a higher risk of infections, prolonged ICU stays, and worse respiratory outcomes, especially in patients suffering from viral infections like COVID-19. In COVID-19, studies have shown that vitamin D deficiency may contribute to severe lung damage, exaggerated inflammatory responses (cytokine storms), and increased mortality. Emerging research suggests that timely correction of vitamin D levels in deficient individuals may improve immune function, reduce inflammation, and potentially lead to better clinical outcomes in critical care settings.

2.7 β-Hydroxy β-Methylbutyrate (HMB)

HMB, a naturally occurring compound derived from the essential amino acid leucine, plays a significant role in maintaining muscle health during critical illness. In catabolic conditions such as trauma, burns, sepsis, or prolonged immobility, muscle protein breakdown often exceeds synthesis, leading to severe muscle wasting. This muscle loss contributes to delayed recovery, increased ventilator dependence, and longer ICU stays.

HMB helps mitigate these effects by stimulating protein synthesis and reducing muscle degradation, mainly through activation of the mTOR (mechanistic target of rapamycin) pathway**,** which is essential for muscle growth and repair. It also decreases the activity of the ubiquitin–proteasome pathway, a key mechanism in muscle protein breakdown.

Furthermore, HMB has been shown to enhance immune function, reduce systemic inflammation, and support the maintenance of lean body mass in critically ill patients, particularly those suffering from sepsis, cancer cachexia, and post-operative stress. It also aids in preserving diaphragm muscle strength, which is crucial for respiratory function in ventilated patients.

Several studies have reported that supplementation with HMB, especially when combined with arginine and glutamine, improves outcomes such as muscle mass retention, wound healing, and hospital discharge rates in elderly or ICU patients. This makes HMB a promising adjunct in nutritional therapy aimed at reducing ICU-acquired weakness and improving recovery trajectories in critically ill populations.

3. Mechanism of Action of Immunonutrients

Immunonutrients exert their effects by enhancing immune function and reducing inflammation through multiple biological pathways. Omega-3 fatty acids and glutamine help reduce the production of harmful inflammatory substances like TNF-α and IL-1β, which helps control the body's inflammatory response. Glutamine also supports the production of glutathione, a powerful antioxidant inside cells that protects them from damage caused by oxidative stress. For glutathione to work effectively, the enzyme glutathione peroxidase is essential-and this enzyme depends on selenium to function well.

Arginine plays a key role in the immune system by boosting T-cell activity and helping produce nitric oxide, a compound that helps fight infections and regulate immune responses. Nucleotides also support the quick repair and growth of immune cells, which is especially important during critical illness when the immune system is under heavy strain. Together, these nutrients help the body fight off infections more effectively and improve overall immune strength.

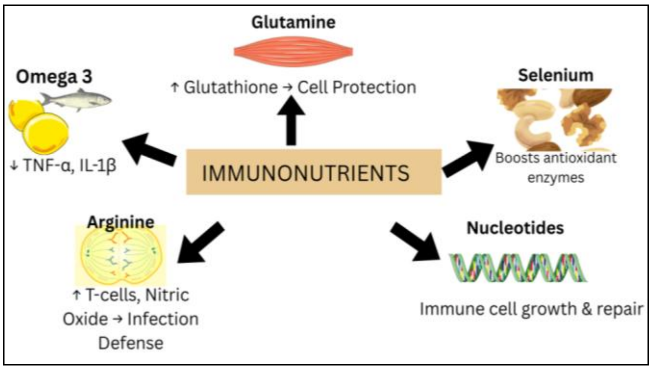

Fig 2: Representing Immunonutrients and their mechanism of action

4. Clinical Applications of Immunonutrition

Immunonutrition has shown helpful results in various clinical situations, especially for patients who are critically ill and experiencing high levels of inflammation, oxidative stress, or weakened immunity. Nutrients like glutamine, omega-3 fatty acids, and antioxidants have been found to help manage the body's excessive inflammatory response, especially during conditions like sepsis. Although not all clinical trials agree, many research reviews have suggested that giving these nutrients early and in the right amount can lower the risk of death and reduce the number of days patients spend in the ICU. However, not all nutrients are suitable for everyone. For instance, arginine may not be safe in sepsis as it could lead to unstable blood pressure.

In surgical patients-particularly those undergoing gastrointestinal surgeries-these nutrients have been associated with fewer infections, better healing, and shorter hospital stays. Giving immunonutrients before and after surgery seems especially helpful. In people with serious lung conditions like Acute Respiratory Distress Syndrome (ARDS), formulas rich in omega-3 fatty acids and antioxidants (like vitamin E and selenium) have helped improve breathing and reduce inflammation in the lungs. Studies have shown that such nutrition can lower the need for ventilators and speed up recovery.

Organizations like ESPEN and ASPEN recommend starting immunonutrition early-within 24 to 48 hours after ICU admission-and advise giving it through the digestive system when possible. This helps maintain gut function and lowers the risk of complications.

5. Current Research

Recent studies and reviews have shown both positive and mixed results about the effectiveness of immunonutrition. On the positive side, nutrients like glutamine and omega-3s seem to reduce inflammation, improve healing, and lead to better recovery in surgical and critically ill patients. However, the outcomes aren't always consistent. Differences in patient types, the specific nutrients used, their doses, and when they are given all affect the results. For example, glutamine may help surgical patients but might worsen outcomes in patients with severe sepsis or multiple organ failure. Arginine is also debated—it helps the immune system but might lower blood pressure dangerously in septic patients.

So, while there is strong biological support for using immunonutrition, doctors still need to carefully consider each individual case. More large-scale, high-quality studies are needed to clarify when and how to use these nutrients best.

6. Challenges and Considerations

Despite its potential benefits, there are several challenges that limit the use of immunonutrition in daily hospital practice. One major issue is the high cost of specialized formulas like Impact® or Oxepa®, making them hard to afford in hospitals with limited resources. Also, every patient is different, so their nutrient needs must be personalized based on their health, type of illness, and other medical conditions. Giving too much or too little can cause problems like overfeeding or imbalanced nutrition.

Another challenge is how these nutrients may affect medications. For example, omega-3 fatty acids can interact with blood thinners, and selenium can affect cancer treatments. Some hospitals may not stock these special nutritional formulas, and proper preparation often needs trained staff. Ethical questions can also arise, especially when deciding whether to start immunonutrition in patients with unclear chances of survival or those nearing end-of-life care.

7. Future Perspectives

The future of immunonutrition looks promising and exciting. Researchers are now studying natural compounds like curcumin and quercetin, as well as probiotics and postbiotics, which may help balance the gut and reduce inflammation. Advances in nutrigenomics and metabolomics offer hope for personalized nutrition based on a person's genes, gut bacteria, and metabolism, making treatments more accurate and effective.

New approaches may also combine immunonutrition with medications, rehabilitation, and microbiome therapies to offer a more complete care strategy. Artificial intelligence and machine learning may soon help doctors predict which nutrients a patient needs and how they might respond, making care even more personalized and precise.

8. Conclusion

Immunonutrition is emerging as a valuable supportive therapy for critically ill patients, especially those recovering from surgery, trauma, or serious lung issues like ARDS. Nutrients like glutamine, arginine, omega-3 fatty acids, antioxidants, nucleotides, and vitamin D have shown potential in improving immune function, reducing inflammation, and speeding up recovery. When used correctly and at the right time, these nutrients can help shorten ICU stays and lower infection risks. However, results may vary from patient to patient, and more research is still needed to figure out the best nutrient combinations and doses. Leading medical groups recommend early use of enteral immunonutrition when appropriate, but always with individual assessment. Overall, immunonutrition should be viewed as one part of a larger critical care plan that includes medical treatments, nutrition, and rehabilitation-not as a standalone solution.

9. Acknowledgement

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