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Impact of Immunonutrition (Arginine, Glutamine, Omega-3 Fatty Acids) in Critical Illness management

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Abstract
Immunonutrition — the targeted provision of nutrients with immune-modulating properties such as arginine, glutamine, and long-chain omega-3 polyunsaturated fatty acids (PUFAs) — has been investigated as an adjunctive therapy to modulate inflammation, preserve gut integrity, and reduce infectious and metabolic complications in critically ill patients. Evidence from perioperative and ICU trials suggests potential benefits in selected populations (reduced infections, shorter ICU stays), but results are heterogeneous and safety concerns (particularly with glutamine in certain ICU cohorts) temper routine broad application. This review summarizes mechanisms of action, key clinical trial and meta-analytic findings, dosing and safety considerations, and practical recommendations for clinicians caring for critically ill adults.

Keywords: Immunonutrition, health, foods, omega 3 fatty acids, glutamine, arginine

Introduction

Critical illness triggers profound metabolic and immune alterations including hyperinflammation, immune dysfunction, and increased gut permeability — processes that contribute to infection, organ dysfunction, and poor recovery (Wischmeyer, 2020) [16]. Immunonutrition aims to deliver substrates that can modulate these pathways: arginine, as a nitric oxide and lymphocyte-supporting amino acid, plays a crucial role in enhancing immune response and tissue repair (Calder, 2013) [3]; glutamine serves as the primary fuel for enterocytes and immune cells and functions as a precursor for glutathione, thereby maintaining redox balance and intestinal integrity (Wernerman, 2014) [15]; and omega-3 polyunsaturated fatty acids (PUFAs) — specifically eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) — modify inflammatory signaling by shifting eicosanoid production away from pro-inflammatory mediators toward pro-resolving lipid mediators (Calder, 2017) [4]. Clinical research has focused on whether supplementing these nutrients, either alone or in combination within enriched enteral or parenteral formulas, improves outcomes such as infection rates, length of stay, and mortality in surgical and critically ill populations (Singer *et al*., 2019 [14]; Preiser *et al*., 2021) [12].

Mechanisms of action — brief overview

- **Arginine:** Arginine becomes conditionally essential during physiological stress, such as trauma or sepsis, due to increased metabolic demand. It supports T-cell proliferation and immune function, promotes wound healing, and serves as a substrate for nitric oxide synthesis, which plays a key role in regulating microcirculation and host defense mechanisms (Barbul, 2008 [2]; Witte & Barbul, 2003 [17]; Preiser *et al*., 2021) [12].

- **Glutamine:** Glutamine serves as the primary fuel source for enterocytes and immune cells, aiding in the maintenance of intestinal mucosal integrity. It is also a precursor for glutathione, a vital antioxidant that protects cells from oxidative stress, thereby contributing to the preservation of gut barrier function and immune competence (Wernerman, 2014 [15]; McClave *et al*., 2016 [9]; Apostolopoulou *et al*., 2020) [1].

- **Omega-3 PUFAs (EPA/DHA):** Omega-3 polyunsaturated fatty acids, primarily eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are incorporated into cell membranes and modulate inflammatory responses. They reduce the production of pro-inflammatory eicosanoids and enhance the generation of specialized pro-resolving mediators such as resolvins and protectins, which help regulate systemic inflammation and improve respiratory and immune function (Calder, 2017 [4]; Langlois *et al*., 2019 [6]; Pradelli *et al*., 2023) [11].

Clinical evidence by nutrient

Arginine (and arginine-containing formulas)

Perioperative and surgical studies have most consistently evaluated arginine-enriched formulas, often in combination with other immune-modulating substrates such as omega-3 fatty acids and nucleotides. Meta-analyses in elective major gastrointestinal and oncologic surgery report reductions in postoperative infectious complications and, in some cases, a shorter length of hospital stay when perioperative immunonutrition is administered, especially when provided preoperatively for 5–7 days (Matsui *et al*., 2023 [8]; Wong *et al*., 2020) [18]. Evidence in medical ICU populations remains limited, and the benefits appear greatest among well-nourished surgical cohorts rather than unselected critically ill patients (Martin *et al*., 2024 [7]; Reader *et al*., 2018) [13]. The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines on clinical nutrition in surgery emphasize that data on arginine as a single intravenous supplement are sparse, with benefits more clearly demonstrated for multi-ingredient perioperative enteral formulas containing arginine, omega-3 fatty acids, and nucleotides (Preiser *et al*., 2021 [12]; Wernerman, 2014) [15].

Glutamine

Glutamine showed biological plausibility and positive signals in early small trials, supporting immune function, gut integrity, and antioxidant capacity (Wernerman, 2014 [15]; Mundi *et al*., 2016) [10]. However, large modern randomized data altered practice. The REDOXS trial, a multicenter RCT, found no benefit and signalled potential harm, including increased mortality, when high-dose glutamine (combined enteral and intravenous) was administered to a heterogeneous, severely ill ICU population (Heyland *et al*., 2013) [5]. Subsequent meta-analyses have highlighted dose-dependent effects and potential risks, particularly in patients with multi-organ failure or renal/hepatic dysfunction (Martin *et al*., 2024 [7]; Apostolopoulou *et al*., 2020) [1]. Current consensus is cautious: routine high-dose glutamine supplementation is not recommended for all critically ill patients; selective use (lower doses, certain surgical or trauma subgroups, or enteral-only administration) may be reasonable within protocols and with attention to contraindications (Wernerman, 2014 [15]; Mundi *et al*., 2016) [10].

Omega-3 fatty acids (EPA/DHA)

Omega-3 PUFAs, delivered enterally (in immunomodulatory diets) or parenterally as fish-oil containing lipid emulsions, have been studied extensively in ARDS, sepsis, and postsurgical settings. Some trials and meta-analyses show improved oxygenation (PaO_2/FiO_2), trends toward shorter ventilator duration, and reduced ICU stay in ARDS when fish-oil enriched enteral diets are used; however, heterogeneity in timing, dose, and concomitant nutrients complicates interpretation (Langlois *et al*., 2019 [6]; Pradelli *et al*., 2023) [11]. Parenteral lipid emulsions containing fish oil show favorable effects on infectious complications in some network meta-analyses compared with traditional soybean-based emulsions (Pradelli *et al*., 2023 [11]; Reader *et al*., 2018) [13]. Overall, omega-3 supplementation appears biologically plausible and potentially beneficial in ARDS and other severe inflammatory states, but more targeted, confirmatory trials are desirable (Langlois *et al*., 2019 [6]; Wernerman, 2014) [15].

Combined immunonutrition (multi-ingredient formulas)

Many clinical studies have evaluated combined formulas (arginine + omega-3s + nucleotides ± glutamine). Perioperative immunonutrition with combined formulas consistently reduces postoperative infections in gastrointestinal and oncologic surgery and may shorten hospital stay; evidence for improved mortality is inconsistent (Wong *et al*., 2020 [18]; Matsui *et al*., 2023) [8]. In general ICU populations, trials are mixed: improvements in surrogate outcomes (infections, LOS) are reported in several meta-analyses, but heterogeneity in enrolment criteria, formula composition and timing complicates definitive conclusions (Martin *et al*., 2024 [7]; Langlois *et al*., 2019) [6]. Thus, combined immunonutrition has the strongest evidence base in elective surgical settings and a more equivocal role in the medical ICU (Preiser *et al*., 2021 [12]; Reader *et al*., 2018) [13].

Safety, dosing and practical considerations

- **Glutamine:** avoid routine high-dose glutamine in unselected critically ill patients (REDOXS signals harm); exercise extreme caution in multiorgan failure and in renal/hepatic impairment. If used, follow dosing ranges evaluated in safer, smaller trials (lower doses) and institutional protocols (Wernerman, 2014 [15]; Mundi *et al*., 2016) [10].
- **Arginine:** beneficial in perioperative enteral regimens; isolated intravenous arginine supplementation lacks robust ICU data—prefer enteral perioperative protocols where evidence is strongest (Wong *et al*., 2020; Matsui *et al*., 2023) [8].
- **Omega-3 PUFAs:** dosing and route vary; enteral immunomodulatory diets with EPA/DHA have been used in ARDS; parenteral fish-oil emulsions are an alternative where enteral delivery is not possible. Monitor for bleeding risk when combined with anticoagulants and follow product-specific dosing (Langlois *et al*., 2019; Pradelli *et al*., 2023) [11].

Clinicians should individualize decisions based on patient phenotype (surgical vs medical, degree of organ failure), timing (perioperative vs established multiorgan failure), enteral access and institutional formulary. High-quality catheter care and metabolic monitoring remain essential when parenteral components are used (Reader *et al*., 2018 [13]; Preiser *et al*., 2021) [12].

Gaps and future directions

Heterogeneity of trial populations, inconsistent formula compositions, variable dosing and timing, and differences between perioperative and general ICU populations limit broad generalization. Key research needs include: well-powered ICU RCTs stratified by phenotype (e.g., ARDS, sepsis, trauma), head-to-head comparisons of enteral immunonutrition vs standard care with standardized nutrient doses, and mechanistic studies to identify responders (biomarkers of inflammation, nutrient status, microbiome signatures). Recent systematic reviews highlight the promise of immunonutrition while underscoring the need for precision approaches.

Table 1: Impact of Immunonutrition (Arginine, Glutamine, Omega-3 Fatty Acids) on Clinical Outcomes in Critically Ill Patients

Nutrient / Formula	Patient Population	Key Outcomes	Observed Benefits	Key Safety/Considerations	References
Arginine (alone or in perioperative enteral formulas)	Elective gastrointestinal and oncologic surgery	Postoperative infections, hospital length of stay, immune function	Reduced postoperative infections, shorter hospital stay in perioperative setting; improved T-cell function	IV arginine alone lacks robust ICU evidence; avoid high doses in unstable critically ill	Wong *et al*., 2020; Matsui *et al*., 2023 [8]
Glutamine (enteral or parenteral)	Critically ill ICU patients, trauma, surgical	Mortality, infections, length of stay, gut barrier function	Early small trials showed improved nitrogen balance, reduced infections; REDOXS	Avoid routine high-dose in multiorgan failure; monitor renal/hepatic function; dose	Wernerman, 2014 [15]; Mundi *et al*., 2016 [10];

			trial reported no mortality benefit and possible harm in high-dose/unstable patients	carefully if used	Apostolopoulou *et al*., 2020 [1]
Omega-3 PUFAs (EPA/DHA, enteral or parenteral)	ARDS, sepsis, surgical ICU	Oxygenation, inflammatory markers, ICU length of stay, infections	Improved PaO_2/FiO_2 ratio in ARDS; reduced inflammatory markers; trend toward shorter ICU stay and fewer infections	Monitor for bleeding risk with anticoagulants; dosing and route vary; combination with other nutrients common in formulas	Langlois *et al*., 2019 [6]; Pradelli *et al*., 2023 [11]
Combined immunonutrition (arginine + omega-3s + nucleotides ± glutamine)	Perioperative gastrointestinal/oncologic surgery, general ICU	Postoperative infections, hospital/ICU LOS, mortality	Reduces postoperative infections; may shorten hospital/ICU stay; inconsistent mortality benefit; mixed results in general ICU	Individualize based on patient phenotype, timing, organ failure; monitor metabolic and catheter-related complications	Martin *et al*., 2024 [7]; Reader *et al*., 2018 [13]; Preiser *et al*., 2021 [12]

Conclusion

Immunonutrition with arginine, glutamine and omega-3 fatty acids offers biological plausibility and clinically meaningful benefits in selected settings—most convincingly in perioperative care for major surgical patients and in some inflammatory lung disorders. However, heterogeneity of evidence and important safety signals (notably with glutamine in unselected, severely ill ICU cohorts) require careful, individualized application. Future precision trials to define which patients are most likely to benefit, optimal dosing regimens, and timing will help integrate immunonutrition more confidently into critical care practice. Until then, clinicians should apply current evidence judiciously: use perioperative combined immunonutrition where indicated, avoid routine high-dose glutamine in unstable ICU patients, and consider omega-3 strategies in ARDS within local protocols.

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