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REVIEW ARTICLE

Omega-3 Fatty Acid Supplementation and ICU Length of Stay: A Critical Review of Current Evidence

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ABSTRACT

Omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) derived from fish oil, have been investigated for their role in modulating inflammation and immune function in critically ill patients in the intensive care unit (ICU). An exaggerated systemic inflammatory response in critical illness often leads to multiple organ dysfunction, nosocomial infections, and prolonged hospitalization. Omega-3 supplementation has been shown to suppress proinflammatory cytokine production, increase inflammatory resolution mediators, and support cellular energy metabolism. Evidence from controlled clinical trials and meta-analyses suggests that omega-3 supplementation, particularly via parenteral administration, may reduce ICU length of stay by an average of 2–3.5 days, reduce mechanical ventilation duration, and decrease infection rates. However, results are heterogeneous and vary with dose, route of administration, and patient characteristics. Notably, several trials in unselected ICU populations have yielded neutral or negative results, particularly with high-dose enteral omega-3 formulas. This review critically synthesizes the current evidence on omega-3 supplementation and ICU outcomes, discusses both supportive and non-supportive findings, and identifies gaps requiring further investigation.

Keywords : Critical review; Fatty acids; Immunonutrition; Intensive care; Length of stay; Omega-3 fish oil.

INTRODUCTION

Omega-3 fatty acids are polyunsaturated fatty acids (PUFAs) that play a crucial role in human physiology. Their unique chemical structure, with a double bond three carbon atoms from the methyl end, gives them distinct biological properties. The three main types are alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). ALA is found abundantly in plants, while EPA and DHA are primarily derived from marine organisms such as fish and algae.

These long-chain fatty acids play a role in maintaining cell membrane fluidity, modulating signal transduction pathways, and regulating inflammation, thus attracting attention for clinical applications in critical conditions[1]. In critically ill patients, the underlying pathophysiology is often characterized by an exaggerated systemic inflammatory response, oxidative stress, and multiple organ dysfunction.

These phenomena often lead to systemic inflammatory response syndrome (SIRS) and cytokine storm, which increase the risk of organ failure and prolong ICU stay[2]. Therefore, therapeutic strategies that can suppress or modulate inflammation are highly relevant.

Administering omega-3-rich fish oil has been shown to have anti-inflammatory and immunomodulatory effects, including changes in cell membrane composition, decreased production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, and increased levels of inflammatory resolution mediators such as resolvins and protectins. Evidence from meta-analyses and randomized controlled clinical trials supports potential benefits in shortening the average ICU length of stay, decreasing ventilation duration, and reducing infectious complications. However, the evidence is not uniformly positive, and important negative trials exist[3–7].

This review aims to critically evaluate the current evidence on omega-3 fatty acid supplementation in ICU patients, with a focus on its impact on ICU length of stay. Both positive and negative/neutral findings are discussed to provide a balanced and objective synthesis for clinicians.

METHODOLOGY

This narrative review was conducted by searching the PubMed, Scopus, and Cochrane Library databases

for articles published from 2015 to 2026 using the following search terms: "omega-3 fatty acids," "fish oil," "EPA," "DHA," "critically ill," "intensive care unit," "ICU length of stay," "sepsis," "ARDS," "parenteral nutrition," and "enteral nutrition." Boolean operators (AND, OR) were used to combine search terms.

Inclusion criteria were: (1) randomized controlled trials (RCTs), systematic reviews, and meta-analyses evaluating omega-3 fatty acid supplementation in adult ICU patients; (2) studies reporting outcomes related to ICU length of stay, mechanical ventilation duration, infection rates, or mortality; (3) studies published in the English language; (4) studies published within the last 10 years, with exceptions for landmark clinical trials.

Exclusion criteria were: (1) studies conducted exclusively in pediatric or neonatal populations; (2) case reports and opinion articles; (3) studies without comparator groups. Reference lists of retrieved articles were also screened for additional relevant studies. A total of 31 references were included in this review. Given the narrative nature of this review, no formal risk-of-bias assessment or meta-analytic pooling was performed.

LITERATURE REVIEW

Omega-3 Fatty Acids: Overview and Sources

Omega-3 fatty acids are a class of PUFAs distinguished by the presence of a double bond located three carbon atoms from the methyl end of the fatty acid chain. The three primary omega-3 fatty acids are ALA (18 carbons, 3 double bonds), EPA (20 carbons, 5 double bonds), and DHA (22 carbons, 6 double bonds). ALA is found primarily in plant sources such as flaxseed and walnuts, whereas EPA and DHA are found primarily in marine organisms. EPA and DHA are incorporated into cell membrane phospholipids, where they modulate membrane fluidity, receptor function, and signal transduction pathways[1].

Fish oil supplements provide standardized doses of EPA and DHA and are available as triglycerides, ethyl esters, or re-esterified triglycerides, each differing in bioavailability. The chemical form influences absorption and therapeutic efficacy, with implications for dosing in the ICU setting where rapid clinical benefit is desired[1].

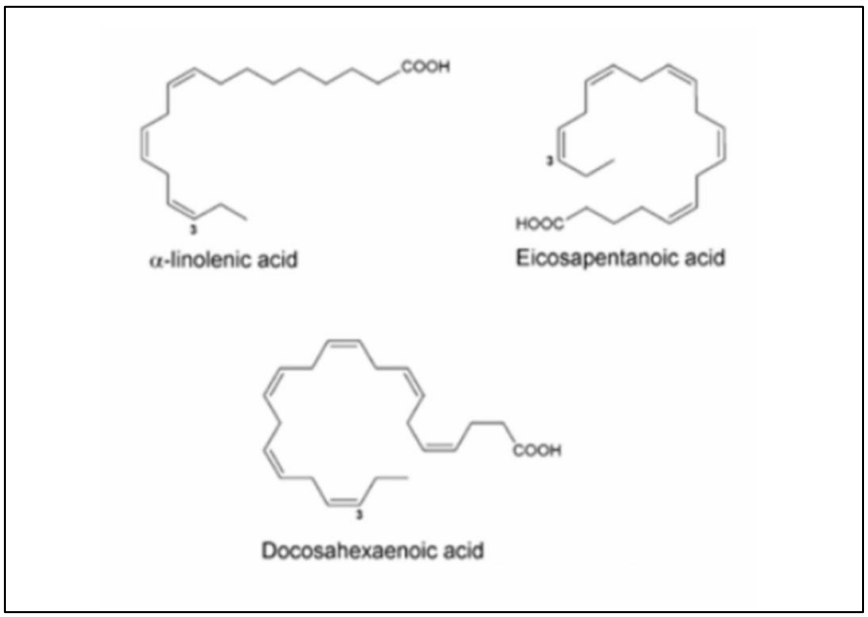

Figure 1. *Chemical structures of the three primary omega-3 fatty acids: α-linolenic acid (ALA, C18:3n-3), eicosapentaenoic acid (EPA, C20:5n-3), and docosahexaenoic acid (DHA, C22:6n-3)*

Working Mechanisms of Omega-3 in Critical Illness

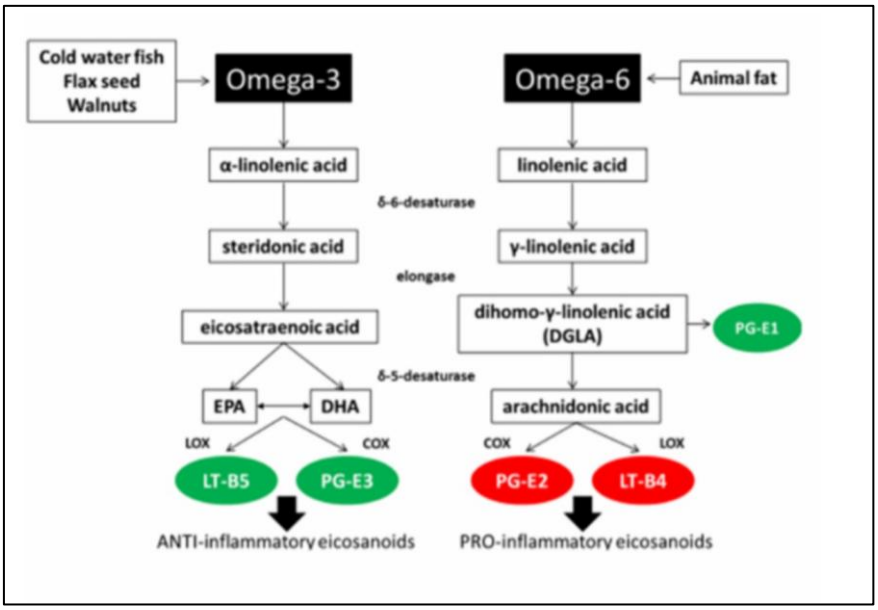

Figure 2. *Omega-3 and omega-6 fatty acid metabolic pathways showing anti-inflammatory eicosanoids (LT-B5, PG-E3) from omega-3 via LOX/COX versus pro-inflammatory eicosanoids (PG-E2, LT-B4) from omega-6.*

1. **Eicosanoid Modulation**

Eicosanoids are lipid mediators derived primarily from arachidonic acid (AA), an omega-6 PUFA, via cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 enzymes. These

molecules, including prostaglandins, thromboxanes, and leukotrienes, amplify inflammation in critically ill patients. Fish oil supplementation modulates these processes by competing with AA for incorporation into cell membrane phospholipids, thereby reducing the substrate for pro-inflammatory eicosanoid synthesis. EPA serves as an alternative substrate producing 3-series prostaglandins (e.g., PGE3) and 5-series leukotrienes (e.g., LTB5), which have weaker pro-inflammatory effects compared to AA-derived mediators[8,14].

2. **Specialized Pro-Resolving Mediators (SPMs)**

SPMs are lipid mediators derived from EPA and DHA, including resolvins, protectins, and maresins. Their production begins when these fatty acids are released from cell membrane phospholipids through phospholipase A2 during an inflammatory response. SPMs enhance efferocytosis, reduce neutrophil infiltration, and shift macrophages to a pro-resolving M2 phenotype, thereby accelerating the resolution of acute inflammation. Clinical evidence supports that fish oil supplementation increases SPM precursors such as 17-HDHA and 18-HEPE, which correlate with faster recovery[11,15–18].

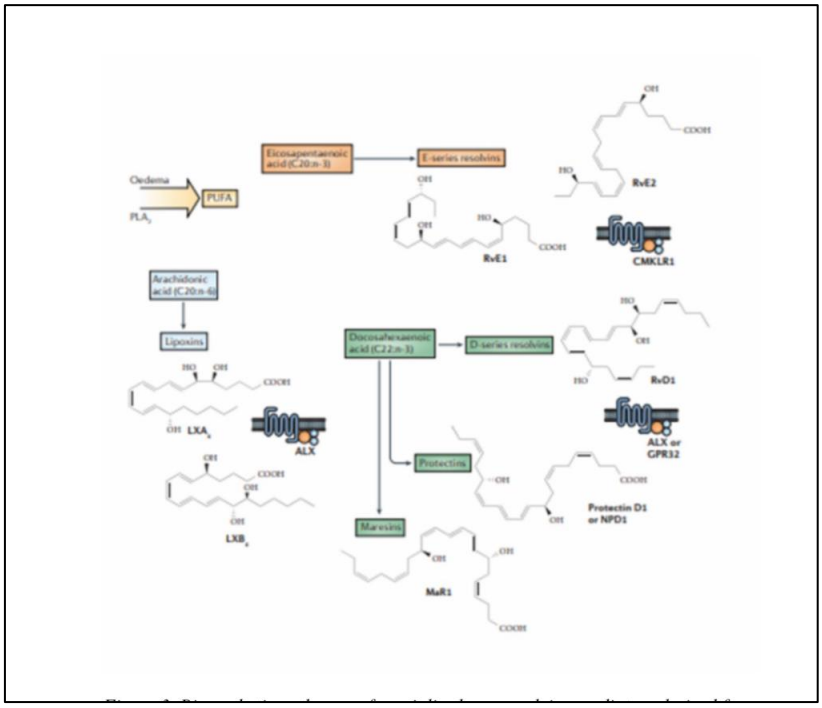

Figure 3. *Biosynthetic pathways of specialized pro-resolving mediators (SPMs). EPA produces E-series resolvins (RvE1, RvE2); DHA produces D-series resolvins (RvD1), protectins (NPD1), and maresins (MaR1); arachidonic acid produces lipoxins (LXA4, LXB4).*

3. NF-κB Pathway Inhibition

EPA and DHA inhibit the NF-κB pathway, a central regulator of inflammation that drives cytokine production. The primary mechanism involves preventing nuclear translocation of NF-κB, thereby suppressing transcription of proinflammatory genes such as those encoding TNF-α, IL-1, and IL-6. These fatty acids activate PPARs (α and γ), which physically interact with NF-κB subunits to block their DNA-binding activity, reducing endothelial activation and leukocyte infiltration[6,19–20].

4. Leukocyte Function Modulation

Omega-3 fatty acids modulate leukocyte function by altering cell membrane composition and eicosanoid production. Following administration, EPA and DHA rapidly incorporate into phospholipid membranes of monocytes and neutrophils, displacing arachidonic acid. These modifications reduce proinflammatory cytokine production, suppress NF-κB activation, and attenuate the oxidative burst and chemotaxis of neutrophils. Parenteral fish oil achieves peak membrane incorporation within 2–3 days and correlates with decreased ventilation duration and reduced infection rates[8].

Pathophysiology of Critical Illness and Rationale for Omega-3 Supplementation

Critical illness triggers a systemic inflammatory cascade known as SIRS, initiated by the release of proinflammatory cytokines such as TNF-α and IL-1, which rapidly activate NF-κB, driving the expression of additional proinflammatory mediators. This robust response can lead to widespread tissue damage, organ dysfunction, and prolonged ICU stay[2]. Omega-3 supplementation addresses this by altering the phospholipid composition of cell membranes and producing anti-inflammatory eicosanoids, resolvins, and protectins. In addition, omega-3s support cellular energy metabolism and membrane integrity, improve mitochondrial function, and reduce oxidative stress, potentially suppressing complications such as acute lung injury, kidney injury, and cardiovascular dysfunction[4–5,25].

Routes of Administration: Enteral vs. Parenteral

Enteral omega-3 supplementation involves introducing fish oil-enriched formulations via the gastrointestinal tract, supporting gut integrity and modulating inflammation.

However, the enteral route may be limited in critically ill patients with impaired bowel function or feeding intolerance. Parenteral administration delivers omega-3 directly into the bloodstream, bypassing the gastrointestinal tract, and is particularly relevant for patients who cannot tolerate enteral feeding[4,7].

Importantly, the evidence base differs by route. Meta-analyses have shown that parenteral omega-3 administration is more consistently associated with reductions in ICU length of stay and mortality, whereas enteral omega-3 supplementation has yielded more variable results, with several trials showing no significant benefit in unselected ICU populations. Wang et al. (2022) found that parenteral fish oil significantly reduced mortality, while enteral supplementation did not reach statistical significance for this outcome[4,5].

Clinical Evidence: Supportive Findings

Several meta-analyses and RCTs have demonstrated positive outcomes with omega-3 supplementation in ICU patients. Wang et al. (2022) pooled data from 25 clinical trials in septic patients and found a significant reduction in ICU length of stay of approximately 3.57 days (95% CI −4.54 to −2.59), as well as reduced hospital length of stay, mechanical ventilation duration, and mortality. Parenteral administration was associated with greater benefit[4].

Pradelli et al. (2020) performed a systematic review with meta-analysis and cost-effectiveness analysis of omega-3 fatty acid-containing parenteral nutrition in ICU patients. Their results showed significant reductions in ICU and hospital length of stay and infection rates, along with a favorable cost-effectiveness profile[3].

Lu et al. (2017) conducted a meta-analysis of 17 RCTs in septic patients and found that omega-3 supplementation was associated with a reduction in ICU length of stay of about 3.8 days and mechanical ventilation duration of about 2.3 days, although no significant mortality reduction was found[6].

In specific subpopulations, Chen et al. (2017) demonstrated that fish oil supplementation in patients with severe sepsis complicated by acute gastrointestinal injury improved 60-day survival and modulated T lymphocyte

subsets[25]. In cardiac surgery patients, Ouagueni et al. (2024) found that perioperative omega-3 supplementation reduced hospital stay by 0.6 days[10].

Clinical Evidence: Negative and Neutral Findings

Despite the supportive evidence, several important trials have yielded neutral or negative results. The OMEGA trial (Rice et al., 2011), a large multicenter RCT, randomized ARDS patients to receive enteral supplementation with omega-3 fatty acids, gamma-linolenic acid, and antioxidants versus an isocaloric control. The trial was stopped early for futility, finding no improvement in ventilator-free days, ICU-free days, or mortality in the omega-3 group[30].

Hall et al. (2015) conducted a pilot RCT of parenteral fish oil in critically ill patients with sepsis. While they observed trends toward improvement in organ dysfunction scores, the trial did not find statistically significant reductions in ICU length of stay in the overall study population[27].

Koekkoek et al. (2019), in their systematic review and meta-analysis of enteral omega-3 fatty acids in the critically ill, concluded that enteral omega-3 supplementation alone did not significantly reduce ICU length of stay or mortality. The overall quality of evidence was rated low to very low[5].

Singer et al. (2021) randomized critically ill patients to enteral and supplemental parenteral nutrition enriched with omega-3 PUFAs versus standard nutrition, finding no significant differences in infectious complications, organ dysfunction, or ICU length of stay[7].

These findings highlight that the benefit of omega-3 supplementation is not universal and may depend on the route of administration (parenteral > enteral), patient population, timing, and dosing.

Omega-3 Fish Oil and Sepsis

Sepsis is characterized by a dysregulated immune response to infection, involving excessive production of proinflammatory cytokines, oxidative stress, endothelial dysfunction, and mitochondrial damage. Omega-3 fatty acids influence the inflammatory process by competitively inhibiting arachidonic acid metabolism, reducing pro-inflammatory eicosanoid synthesis, and serving as precursors for

SPMs that promote inflammatory resolution and tissue repair[4,25].

Clinical trial outcomes of omega-3 in sepsis have been somewhat variable. Wang et al. (2022) found that the route of administration was a significant modifier: parenteral fish oil significantly reduced mortality, while enteral supplementation did not[4,6,25].

Immunomodulatory Effects in Critical Care

Critical illness often leads to impaired immune function, manifested as immunoparalysis, which increases susceptibility to secondary infections. Omega-3 PUFAs modulate the production of pro-inflammatory and anti-inflammatory cytokines, recalibrating the immune response. They enhance neutrophil function, facilitate neutrophil migration, and increase SPM production[5,21–24].

Clinical studies have shown that omega-3 supplementation is associated with reduced incidence of ventilator-associated pneumonia and bloodstream infections in ICU patients. However, the magnitude of benefit varies across studies[5,23,24].

Safety and Side Effects

Omega-3 fish oil formulations have generally been shown to be safe in critically ill patients. Clinical trials have reported no serious adverse events directly attributable to omega-3 supplementation, including no increased incidence of bleeding or infectious complications. Doses exceeding 0.05 g/kg/day have been associated with clinical benefits without increased risk. Monitoring protocols should be implemented to observe coagulation, immune function, and inflammatory status during administration[8].

Clinical Guideline Recommendations

The European Society for Clinical Nutrition and Metabolism (ESPEN) recommends the integration of omega-3 fatty acids as part of immune nutrition in critically ill patients, particularly via parenteral administration. The Canadian Critical Care Nutrition Group guidelines also reference the potential benefits of omega-3-enriched formulas, although they note the heterogeneity of evidence[4,7]

SUMMARY TABLE OF KEY CLINICAL STUDIES

Table 1. *Summary of key clinical studies on omega-3 fatty acid supplementation in ICU patients.*

Study	Design	Population	Route	Dose	Main Outcomes	Result
Pradelli et al. (2020)	SR + MA	ICU (mixed)	Parenteral	Variable	Reduced ICU & hospital LOS; reduced infections; cost-effective	**Positive**
Wang et al. (2022)	SR + MA (25 trials)	Adult sepsis	EN & PN	Variable	ICU LOS reduced ~3.57 days; reduced mortality (PN); reduced MV	**Positive (pn>en)**
Lu et al. (2017)	SR + MA (17 RCTs)	Adult sepsis	Mixed	Variable	ICU LOS reduced ~3.8d; MV reduced ~2.3d; no mortality benefit	**Positive (los)/neutral (mort.)**
Rice et al. (2011) OMEGA Trial	Multicenter RCT	ALI / ARDS	Enteral	High-dose EPA+DHA+GLA	No improvement; stopped for futility	**Negative**
Hall et al. (2015)	Pilot RCT	Sepsis	Parenteral	Fish oil emulsion	Trend improved SOFA; no significant LOS reduction	**Neutral**
Koekkoek et al. (2019)	SR + MA	Critically ill	Enteral	Variable	No significant reduction in LOS or mortality	**Neutral**
Singer et al. (2021)	RCT (double-blind)	Critically ill	EN + PN	Omega-3 enriched	Improved FA profiles; no difference in infections/LOS	**Neutral**
Chen et al. (2017)	RCT	Severe sepsis + GI injury	Parenteral	Fish oil	Improved 60-day survival; modulated T-cell subsets	**Positive**
Ouagueni et al. (2024)	SR + MA	CABG	Oral	Variable	Hospital LOS reduced by 0.6 days	**Positive (modest)**
Notz et al. (2022)	SR + MA	Critically ill	Parenteral	Omega-6 sparing ILEs	Limited positive results; significance only in pooled analyses	**Neutral**
Langlois et al. (2019)	SR + MA	ARDS	Mixed	Variable	Trend decreased MV; mixed LOS results	**Mixed**

Abbreviations:

SR= systematic review; MA= meta-analysis; RCT= randomized controlled trial; LOS= length of stay; MV= mechanical ventilation; EN= enteral nutrition; PN= parenteral nutrition;

ARDS= acute respiratory distress syndrome; CABG= coronary artery bypass graft; GLA= gamma-linolenic acid.

Color coding:

POSITIVE= significant benefit; NEUTRAL= no significant benefit; NEGATIVE= stopped for futility; MIXED= inconsistent results.

DISCUSSION

The current body of evidence on omega-3 fatty acid supplementation in ICU patients presents a nuanced picture.

While several meta-analyses and RCTs support a beneficial effect—particularly for fish oil-containing parenteral nutrition in septic patients—other well-designed trials, most notably the OMEGA trial, have shown no benefit for enteral omega-3 supplementation in unselected ARDS patients. The recent meta-analysis by Notz et al. (2022) further highlighted that even with omega-6 sparing parenteral formulations, the evidence for consistent clinical benefit remains limited[31].

The mechanistic rationale is strong, with well-established pathways including eicosanoid modulation, SPM production, NF-κB inhibition, and leukocyte function modulation. However, translating these mechanisms into consistent clinical outcomes has proven challenging due to heterogeneity among trials.

Parenteral omega-3 appears to offer the most consistent benefits, potentially because it bypasses gastrointestinal limitations and achieves more rapid membrane incorporation. The benefit appears most pronounced in sepsis subgroups.

The overall quality of evidence ranges from low to moderate. Future research should focus on large, multicenter, adequately powered RCTs with standardized dosing protocols and clearly defined patient populations.

CONCLUSION

Omega-3 fatty acids, particularly EPA and DHA from fish oil, have a strong mechanistic rationale for modulating inflammation, enhancing immune function, and supporting energy metabolism in ICU patients. Evidence suggests that omega-3 supplementation—particularly via parenteral administration—may shorten ICU stays by several days, reduce mechanical ventilation duration, and decrease nosocomial infection rates. However, the evidence is not uniformly positive. Important negative and neutral trials have failed to demonstrate consistent clinical benefit, especially with enteral omega-3 in unselected ICU populations. The benefits appear most consistent for parenteral fish oil in sepsis subgroups.

Therefore, while integrating fish oil into critical care nutrition strategies has potential to improve patient outcomes, clinicians should exercise judgment in selecting appropriate patients and administration routes. Further high-quality, large-scale trials are needed.

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