# The role of omega-3 polyunsaturated fatty acids in the intensive care unit

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**Abstract**

Purpose of review: This review provides an update on the actions of omega-3 polyunsaturated fatty acids (PUFAs) and presents the most recent findings from trials in patients in the intensive care unit (ICU) setting including relevant meta-analyses. Many specialized pro-resolving mediators (SPMs) are produced from bioactive omega-3 PUFAs and may explain many of the beneficial effects of omega-3 PUFAs, although other mechanisms of action of omega-3 PUFAs are being uncovered..

Recent findings: Specialized pro-resolving mediators (SPMs) resolve inflammation, promote healing and support anti-infection activities of the immune system. Since publication of the ESPEN guidelines, numerous studies further support the use of omega 3 PUFAs. Recent meta-analyses favor the inclusion of omega-3 PUFAs in nutrition support of patients with acute respiratory distress syndrome or sepsis. Recent trials indicate that omega-3 PUFAs may protect against delirium and liver dysfunction in patients in the ICU, although effects on muscle loss are unclear and require further investigation. Critical illness may alter omega-3 PUFA turnover. There has been significant discussion about the potential for omega-3 PUFAs and SPMs in treatment of COVID-19.

Summary: Evidence for benefits of omega-3 PUFAs in the ICU setting has strengthened through new trials and meta-analyses. Nevertheless, better quality trials are still needed. SPMs may explain many of the benefits of omega-3 PUFAs.

## Introduction

Omega-3 polyunsaturated fatty acids (PUFAs) have numerous biological actions [1,2*,3*,4*] that suggest they could have an important role in clinical nutrition support. The main bioactive omega-3 PUFAs are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA); EPA and DHA are found naturally in fish oil. The most recent guidelines of the European Society for Clinical Nutrition and Metabolism for clinical nutrition in the intensive care unit (ICU) indicate that enteral nutrition enriched with omega-3 PUFAs "within nutritional doses" can be administered, but that "high dose" omega-3 PUFA enriched enteral formulas should not be given on a routine basis, and that parenteral lipid emulsions enriched with EPA and DHA (fish oil dose 0.1-0.2 g/kg body weight per/d) can be provided in patients receiving parenteral nutrition (PN) [5]. The Grade of Recommendation was O, and consensus was 85% for enteral EPA and DHA and 100% for parenteral EPA and DHA. These consensus recommendations were supported by generally low quality evidence, reflecting inconsistencies and gaps in the literature. Since these guidelines were published, new trials of both enteral and parenteral administration of omega-3 PUFAs to patients in the ICU have been conducted and many new meta-analyses have been performed. In addition, mechanistic understandings of the actions of omega-3 PUFAs have grown. There has been continued interest in a role for omega-3 PUFAs in acute respiratory distress syndrome (ARDS), sepsis and, most recently, coronavirus disease discovered in 2019 (COVID-19), and also in mitigating the effects of brain insult and in helping to overcome renal, liver and muscle dysfunction in critically ill patients. Omega-3 PUFAs have metabolic actions, for example helping to control dyslipidemia [6], that are relevant to critical illness. However, the strongest rationale for benefit from omega-3 PUFAs is based on their effects in preventing oxidative stress, reducing inflammation and promoting resolution of inflammation [7,8]. The latter effect has

gained significant attention in the last years [9,10*,11*]. Specialized pro-resolving mediators (SPMs) are endogenous lipid mediators mainly produced from the bioactive omega-3 PUFAs EPA, docosapentaenoic acid (DPA) and DHA and include resolvins, protectins and maresins. SPMs resolve inflammation, promote healing and support anti-infection activities of the immune system. Individual SPMs have been shown to have potent roles in treating lung injury, sepsis and infection in multiple animal models [12-23]. The active SPMs described in these animal studies include resolvin D1, aspirin-triggered resolvin D1, resolvin D3, aspirin-triggered resolvin D3, all produced from DHA, and resolvin E1, produced from EPA. The actions of SPMs may explain a large part of the beneficial effects of omega-3 PUFAs. In this review, we provide an update on the actions of omega-3 PUFAs and present the most recent findings from trials in patients in the ICU setting including relevant meta-analyses.

## Omega-3 PUFAs and acute respiratory distress syndrome (ARDS)

### *Clinical studies*

The administration of omega-3 PUFAs to patients with ARDS was proposed more than 20 years ago and a number of studies have been conducted mainly using enteral administration and high doses of omega-3 PUFAs, sometimes in combination with other bioactive nutrients, including antioxidants. Several systematic reviews of the literature and meta-analyses have been recently published [24,25*,26*,27]. Langlois et al. [24] identified that omega-3 PUFAs improved early (3 to 4 days) $PaO_2$ to $FiO_2$ ratio, an effect which persisted to days 7 and 8, and tended to reduce duration of mechanical ventilation and ICU length of stay (LOS) in the analysis of 12 studies (1280 patients). Only trials at higher risk of bias reported a significant reduction in

mortality and improvement in late $PaO_2/FiO_2$ ratio. A second meta-analysis included 6 studies (5 from China) and 277 patients and identified a significant improvement in $PaO_2$ and the $PaO_2$ to $FiO_2$ ratio and a shortening of ICU LOS (MD -1.29 days, 95% CI -2.14 to -0.43) and duration of ventilation (MD -1.72 days, 95% CI -2.84 to -0.60) with enteral omega-3 PUFAs [25*]. Risk of bias was high. Another meta-analysis [26*] found in 24 studies (3574 patients) a significant reduction in ventilation duration (MD -3.61 days, 95% CI -5.91 to -1.32), ICU LOS (MD -3.71 days, 95% CI -5.40 to -2.02) and 28-day mortality (RR 0.69, 95% CI 0.54 to 0.89) in patients with ARDS receiving enteral omega-3 PUFAs. However, the results for mortality were based on low-quality studies, although regarding ICU LOS, a significant reduction was observed in high-quality trials. A recent Cochrane review of 10 studies (1015 patients) of variable quality found no effect of omega-3 PUFAs on all-cause mortality in patients with ARDS, although other outcomes (oxygenation at day 4, duration of ventilator days and ICU LOS) were all significantly improved by omega-3 PUFAs [27]. From these meta-analysis, it can be concluded that omega-3 PUFAs improve oxygenation and length of ventilation in this patient group. Singer et al. [28] included additional EPA and DHA in enteral and supplemental PN in patients failing to reach the energy target enterally and compared outcomes to patients receiving control isoenergetic, iso-lipid nutrition support. This single-center, prospective, randomized (1:1 ratio), controlled, double-blind, parallel-group, phase III trial included 100 patients. Energy prescription was based on measured energy expenditure using indirect calorimetry. The primary outcome measured as $PaO_2/FiO_2$ from day 1 to day 4 was not improved by supplemental omega-3 PUFAs and no improvement in LOS, length of ventilation or mortality was noted. There was a significantly lower daily catecholamine requirement in the EPA+DHA group and this group was weaned earlier from PN. Interestingly, a significant difference in the red cell content of omega-3 PUFAs

was reached only after day 7, perhaps explaining the lack of improvement in clinical outcomes. No multivariate analysis was performed. Parikh et al. investigated the pharmacokinetics of high dose enteral omega-3 PUFAs in mechanically ventilated patients compared with healthy controls [29*]. Serum EPA and DHA were lower in the patients than controls but there were few differences between the groups in immune cell omega-3 PUFAs. However, the half-life of EPA in serum and in neutrophils was shorter in the patients than in controls suggesting higher turnover with respiratory dysfunction. This study highlights that findings in healthy participants may not always be translated to patients. Illness may alter absorption of omega-3 PUFAs or their subsequent metabolism, which may be affected by inflammation and oxidative stress.

***Mechanistic studies***

The link between the single nucleotide polymorphism rs174537 in the fatty acid desaturase 1 gene and responses of patients with ARDS to a PUFA-rich enteral feed was studied in a post-hoc analysis of the OMEGA study [30], a study determining the effects of purified omega-3 fatty acids on the rate of sudden cardiac death after myocardial infarction. The authors tested for single nucleotide polymorphism-diet interactions on PUFA concentrations, inflammatory biomarkers, and patient outcomes. All patients who received the PUFA-rich formula displayed significantly higher concentrations of buffy coat EPA and DHA, and of γ-linolenic acid which was also present in the formula, but these did not differ by genotype at rs174537. However, a significant single nucleotide polymorphism-diet interaction was observed for buffy coat DHA in African Americans. Specifically, African American T-allele carriers on placebo illustrated elevated DHA concentrations. There was no significant single nucleotide polymorphism-diet interaction on pulmonary function measures, clinical outcomes, or mortality. Whilst this study does not identify an effect of the specific polymorphism investigated on how omega-3 PUFAs affect biomarkers

and outcomes in patients with ARDS, the findings do not rule out that other genetic variations might play a role in determining the effects of omega-3 PUFAs. The study does highlight that ethnicity might be an important consideration for future studies.

Exogenous administration of SPMs has been shown to be effective at improving infection clearance and promoting survival in preclinical models of lung injury including through the regulation of alveolar fluid clearance [31*]. Production of inflammatory cytokines including interleukin 6 and tumor necrosis factor is inhibited by SPMs, helping lung tissue to heal. In humans, a study of plasma from patients with ARDS revealed that lower levels of SPMs correlated with increased need for mechanical ventilation as well as longer ICU LOS [32*]. The effects of SPMs may explain the reported benefits of omega-3 PUFAs (see below) and raise the possibility that supplementing SPMs themselves may improve the outcome of ARDS, but this remains to be demonstrated clinically.

## Omega-3 PUFAs and sepsis

### *Clinical studies*

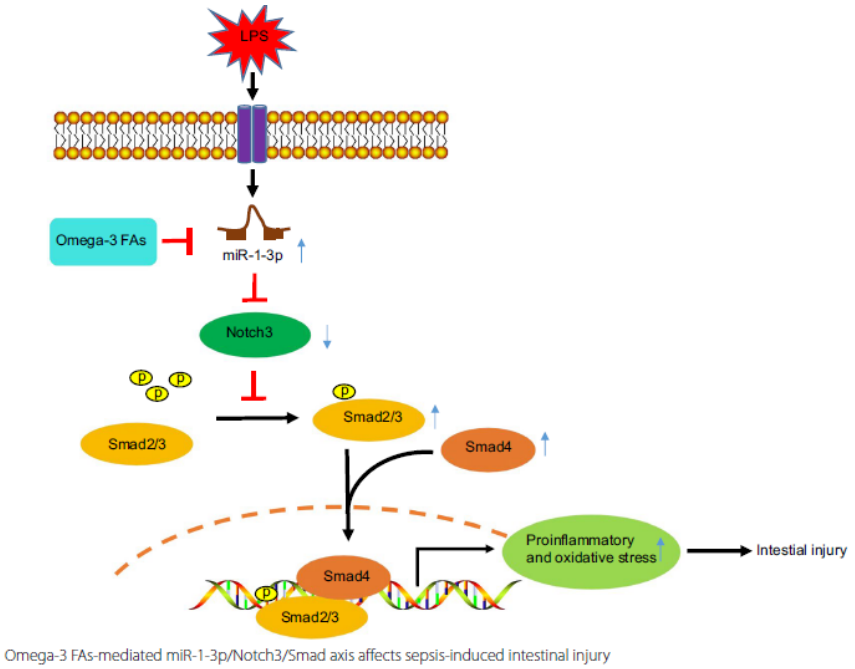
De Waele et al. [33*] suggested that since omega-3 PUFAs improve metabolic processes as well as alleviating inflammation-triggered organ dysfunction in patients with sepsis, they serve as a nutritional therapeutic against sepsis. Hereunder we review the data that might support this hypothesis. A number of meta-analyses of relevant trials of omega-3 PUFAs have been published recently [34*,35*,36,37]. Pradelli et al. [34*] reviewed 49 randomized controlled trials (RCTs) comparing omega-3 PUFA enriched PN with standard (non-omega-3 PUFA enriched) PN in adult hospitalized patients. Many of these patients were surgical patients. When data from 10 RCTs were

aggregated, a reduction in ICU LOS was observed (1.95 days, 95% CI 0.42 to 3.49), and in the overall population (i.e. ICU and non-ICU patients combined) a 40% reduction in infection was observed. The Funnel plots appeared slightly asymmetrical for ICU LOS and infection rate. However, no evidence of significant bias was found. Mortality was not different between omega-3 PUFA and comparator groups. In a second meta-analysis restricted to ICU patients [35*], PN providing omega-3 PUFAs was associated with fewer infections (RR 0.62, 95% CI 0.45 to 0.86), shorter ICU LOS (-1.89 days, 95% CI -3.33 to -0.45) and shorter hospital LOS (-3.05 days, 95% CI -5.03 to -1.07). In critically ill ICU patients, omega-3 PUFAs were associated with similar reductions in infections (RR 0.65, 95% CI 0.46 to 0.94), ICU LOS (-2.14 days, 95% CI -3.89 to -0.40) and hospital LOS (-3.98 days, 95% CI -6.90 to -1.06). Data were subjected to cost effectiveness analysis for six countries and it was estimated that parenteral omega-3 PUFAs would lower overall hospital costs (compared with standard PN) in all six countries (five European and the USA). Wang et al. [36] conducted a meta-analysis of 20 RCTs that provided omega-3 PUFAs as a component of either enteral or PN to patients with sepsis. Omega-3 PUFAs were associated with lower mortality (RR 0.82, 95% CI 0.69, 0.97), shorter duration of mechanical ventilation (Weight Mean Difference -2.20 days, 95% CI -4.00, -0.40), and shorter ICU LOS (Weight Mean Difference -3.86 days, 95% CI -5.72, -2.01). Most recently, Wang et al. [37] analyzed findings of 25 RCTs of enteral or parenteral provision of omega-3 PUFAs to patients with sepsis. They found that omega-3 PUFAs reduced mortality (RR 0.74, 95% CI 0.63, 0.86), and shortened duration of mechanical ventilation (Weight Mean Difference -2.26 days, 95% CI -4.27, -0.26), ICU LOS (Weight Mean Difference -3.57 days, 95% CI -4.54, -2.59) and hospital LOS (Weight Mean Difference -9.92 days, 95% CI -15.37, -4.46). Sub-group analyses highlighted some differences according to whether omega-3 PUFAs were given enterally or parenterally.

***Preclinical studies***

Pre-clinical research has uncovered new mechanisms of action of omega-3 PUFAs that are relevant to sepsis. In rats undergoing cecal ligation and puncture, administration of omega-3 PUFAs alleviated the inflammatory response and oxidative stress injury to intestinal epithelial cells [38*]; the literature on omega-3 PUFAs and intestinal integrity was recently reviewed [39*]. Chen et al. [38*] demonstrated the mechanism of action of omega-3 PUFAs was through inactivation of the miR-1-3p/Notch3/Smad axis (see Figure 1). Recently, also in rats, Capellari et al. [40*] demonstrated that dietary omega-3 PUFAs enhance mitophagy to prevent muscle mitochondrial oxidative stress and protect from muscle catabolism.

Figure 1. Omega 3 fatty acids impair miR-1-3-dependent Notch3 activation and so decrease proinflammatory and oxidative stress. Reproduced from Ref. 38*.




Omega-3 FAs-mediated miR-1-3p/Notch3/Smad axis affects sepsis-induced intestinal injury

Omega-3 PUFAs may also have direct anti-microbial actions and may present a new approach against microbial antibiotic resistance. DHA had greater antimicrobial activity against *Acinetobacter baumannii* than the omega-6 PUFA arachidonic acid (AA) [41]. AA and DHA incorporate into the A. *baumannii* bacterial membrane and impact bacterial fitness and membrane integrity, with DHA having a more pronounced effect [41]. Another study showed that in vitro treatment with PUFAs reduces the rate at which *A. baumannii* gains resistance to erythromycin and tetracycline [42]. The importance of omega-3 PUFAs in the protection to resistant bacteria remains to be demonstrated in clinical studies.

## Omega-3 PUFAs and COVID-19

### *Preclinical studies*

The realization that severe COVID-19 is linked with hyperinflammation ("cytokine storm") and immunosuppression led to suggestions that omega-3 PUFAs have a role in both prevention and treatment of COVID-19 [43-45]. As well as effects on chemokines and cytokines, infection with SARS-CoV-2 is associated with alterations in circulating lipid mediators [46] including SPMs [47*,48*] and this has further emphasized the potential benefits of omega-3 PUFAs in this setting [49*] (Figure 2). Furthermore, the application of SPMs in COVID-19 has been widely discussed [50-52]. Many of the distressing aspects of COVID-19, including the pneumonia-like presentation, ARDS, and excessive inflammation (manifested as high circulating concentrations of cytokines and high blood leukocyte numbers) have been shown to be improved in preclinical studies with SPMs [31*].

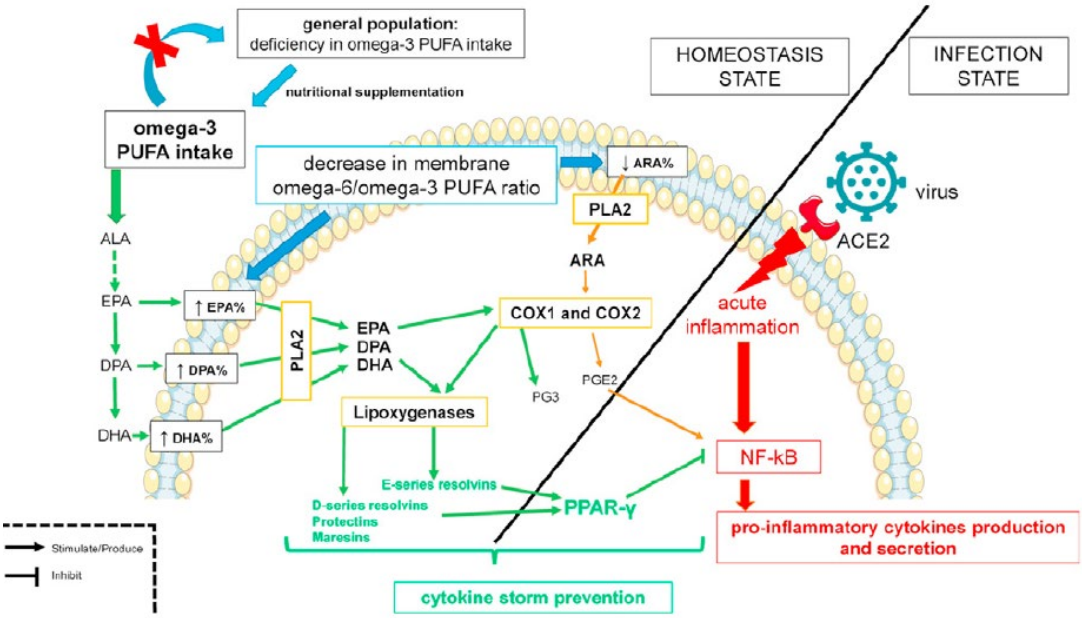
### *Clinical studies*

A modest sized single center double-blind, randomized trial of low dose omega-3 PUFAs daily for 14 days in patients with COVID-19 in the ICU included 128 patients (42 patients in the study group and 86 in the control group) and reported improved markers of kidney function and some markers of respiratory function, increased blood lymphocyte numbers and improved survival at one month compared with a control group, although many other outcomes were not different between the two groups [53]. It should be noted that the data only presented for per-protocol analysis with numerically more deaths in the intervention group excluded (i.e., 7 of 42 died (17%) as compared to control 7 of 86 (8%))

***Mechanistic aspects***

In addition to their roles in modulating inflammation and supporting the immune response, omega-3 PUFAs may have other effects of relevance to SARS-CoV-2 infection and COVID-19. For example, omega-3 PUFAs may modulate membrane rafts where angiotensin-converting enzyme 2 and transmembrane protease serine 2 are mainly expressed preventing viral entry into host cells [54*]. Furthermore SARS-CoV-2 activates sterol receptor element binding proteins [55] and omega-3 PUFAs may counteract this. Omega-3 PUFAs have been also hypothesized to improve neurological symptoms of COVID-19 such as headache, nausea, vomiting and other neurological disorders, again with SPMs being implicated in the proposed benefits [56].

Figure 2. Omega-3 PUFAs may have a favorable effect on critical illness by inhibiting NF-kB activation and decreasing the cytokine storm. Reproduced with permission from Ref.49*.




**Omega-3 PUFAs, brain injury and neurological function**

There has been interest in omega-3 PUFAs as a treatment for acute brain injury for several years, with encouraging supporting data from pre-clinical studies [57]. Brain damage can be observed after cardiac arrest. An association between grey to white ratio and plasma lysophosphatidylcholine DHA (LPC-DHA) levels was observed in patients following cardiac arrest [58*]. Human plasma samples were collected prospectively within 1 hour after recovering spontaneous respiration rate after cardiac arrest in a cohort study including 45 patients. A CT scan was performed within 8 hours after the event and the grey to white ratio was evaluated blinded in 16 of these patients. A cutoff point of 1.15 for the grey to white ratio was used for dichotomising. Plasma LPC-DHA levels were significantly higher in the patients with grey to white ratio > 1.15 than in those with grey to white ratio $\leq 1.15$ (0.51 μmol/l vs 0.20 μmol/l). It is proposed that low availability of LPC-DHA may play a causative role for brain injury after cardiac arrest [58*]. In

rats, supplementing with LPC-DHA normalized brain levels of LPC-DHA and alleviated neuronal cell death, activation of astrocytes, and expression of various inflammatory and mitochondrial dynamics genes [59]. Another study observed that acute brain injury (intracerebral hemorrhage) triggers the synthesis of neuroprotectin D1, a DHA-derived SPM: neuroprotectin D1 levels were higher in patients with better 90-day outcome [60]. Neuroprotectin D1 is synthesized from DHA via 15-lipoxygenase and the gene encoding this enzyme was almost undetectable in patients with modified Rankin score 4-6 and worse outcome. The authors suggest that early synthesis and abundance of neuroprotectin D1 is likely an important protective factor [60].

Kagan et al. [61] prospectively included initially 150 multiple trauma patients who received high dose or no omega-3 PUFAs. Fifty one were followed and interviewed after 6 months. None of the tests evaluating anxiety, depression, or post-traumatic stress disorder at 6 months were different between the study group and the control group. Administration of fish oil in this population does not seem to prevent post-traumatic stress disorder in multiple-trauma patients.

Naghibi et al. [62*] conducted a RCT of daily omega-3 PUFAs in 162 mechanically ventilated patients and assessed delirium twice daily for 10 days after admission. In the omega-3 PUFA group there was a 40% reduction in patient days with delirium, a 25% reduction in days of mechanical ventilation and ICU stay and a 50% non-significant reduction in mortality. These findings should be interpreted carefully since it is a single center study with optimistic results.

**Omega-3 PUFAs and kidney, liver and muscle damage**

A systematic review from 49 RCTs evaluated the efficacy and safety of omega-3 PUFAs in patients undergoing dialysis [63]. Compared with the control group, the group receiving omega-3

PUFAs exhibited lower serum triglyceride, C-reactive protein, tumor necrosis factor and phosphorus levels, and higher blood hemoglobin and serum parathyroid hormone levels. No differences were observed in total cholesterol, low density lipoprotein cholesterol or albumin levels. These results support administration of supplemental omega-3 PUFAs to patients undergoing chronic dialysis.

Liver function markers are less disturbed in critically ill patients receiving omega-3 PUFAs compared with controls according to a meta-analysis [64]. A recent study evaluated lipid-free PN and PN including one of three different lipid blends on liver function in post-surgical critically ill patients [65]. Patients receiving lipid-free PN had the highest incidence of hepatic dysfunction. Including fish oil, a source of omega-3 PUFAs, at > 0.05 g/kg body weight per day was associated with lower incidence of hepatic dysfunction [65].

As mentioned earlier, omega-3 PUFAs normalize muscle mitochondrial function and oxidative stress through enhanced tissue mitophagy and protect from muscle wasting in experimental kidney disease [40*]. A trial in healthy young adults showed that oral omega-3 PUFAs (2.97 g EPA + 2.03 g DHA daily) maintain muscle protein synthesis during leg immobilization resulting in better maintenance of muscle mass [66]. Eighty three mechanically ventilated patients were allocated to receive in a RCT, a placebo, 2 g of EPA, 3 g of hydroxymethyl butyrate or both. Muscle strength and size of quadriceps and the diaphragm were evaluated at baseline and after 11 days. Ten days of EPA at 2 g/day did not affect muscle size and strength compared to placebo [67]. It may be that the dose of omega-3 PUFAs was too low to see an effect or that DHA, rather than EPA, is important in affecting muscle protein synthesis.

## Conclusions

This overview underlines the change from the concept of fish oil-derived omega-3 PUFAs (EPA and DHA) as immune-nutrients to nutrients preventing oxidative stress, reducing inflammation and promoting resolution of inflammation mainly through generation of SPMs. Multiple applications in ARDS, sepsis, COVID 19, and organ injury suggest that EPA and/or DHA may improve outcome in critically ill patients when administered with the right dosage and to the right population (Table 1). Future research needs to focus on the best dosages of omega-3 PUFAs to use, the optimal route(s) of administration and which patients are most likely to benefit. Future ESPEN guidelines may be inspired by these studies. Numerous promising therapeutic possibilities are suggested by recent research and meta-analyses and confirm the importance of omega-3 PUFAs from fish oil as a component of the medical nutritional therapy of the critically ill patient.

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## Conflicts of interest

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