Curr Pulmonol Rep (2017) 6:113–123
DOI 10.1007/s13665-017-0171-2

Immunonutrition in Acute Respiratory Distress Syndrome

Masooma Aqeel[1] · **Shahryar Ahmad**[1] · **Jayshil J. Patel**[2] · **Todd W. Rice**[3]

Published online: 11 April 2017

Abstract
Purpose of Review Dietary supplementation with nutrients such as glutamine and omega-3 fatty acids to modulate/boost host immunity in critical illness is a new concept. We review current evidence (animal and human studies) on the role of immunonutrition in acute respiratory distress syndrome (ARDS).
Recent Findings Dietary supplementation during stress states (ARDS) with omega-3 fatty acids has been shown to attenuate inflammation and improve lung microvascular permeability in animals. In humans, omega-3 fatty acid supplementation has shown mixed results. While studies show improvement in oxygenation and lung mechanics, a recent study demonstrated increased mortality with omega-3 fatty acids. Similarly, animal studies suggest that lower glutamine levels are associated with worse outcomes in surgical and septic patients. But, a recent study in humans has shown an increased trend towards all-cause mortality.
Summary Current evidence is conflicting and does not support use of immune-modulating therapies (glutamine or omega-3 fatty acids) in ARDS.

Keywords Acute respiratory distress syndrome · Antioxidants · Arachidonic acid · Eicosanoids · Enteral nutrition · Immunonutrition · Immune modulation · Omega-3 fatty acids · Glutamine

Abbreviations

AA	Arachidonic acid
ALA	α-Linolenic acid
ALI	Acute lung injury
ARDS	Acute respiratory distress syndrome
BALF	Bronchial alveolar lavage fluid
BCAA	Branched chain amino acid
COPD	Chronic obstructive pulmonary disease
COX	Cyclooxygenase
DHA	Docosahexaenoic acid
DGLA	Dihomo-gamma-linolenic acid
EPA	Eicosapentaenoic acid
EN	Enteral nutrition
FiO2	Fraction of inspired oxygen
GLA	Gamma-linoleic acid
IL	Interleukin
ICAM	Intracellular adhesion molecule
LPS	Lipopolysaccharide
LPO	Lipoxygenase
LT	Leukotriene
LTVV	Low tidal volume ventilation
LX	Lipoxin
MOD	Multi-organ dysfunction
PaO2	Partial pressure of oxygen
PEEP	Positive end-expiratory pressure

Masooma Aqeel and Shahryar Ahmad Equally contributed as first authors

This article is part of the Topical Collection on *Nutrition and Critical Care*

✉ Jayshil J. Patel
jpatel2@mcw.edu

[1] Department of Medicine, Division of Pulmonary and Critical Care Medicine, Froedtert and Medical College of Wisconsin, 9200 West Wisconsin Avenue, Suite E5200, Milwaukee, WI 53226, USA

[2] Division of Pulmonary and Critical Care Medicine, Froedtert and Medical College of Wisconsin, Milwaukee, WI, USA

[3] Division of Pulmonary and Critical Care Medicine, Vanderbilt University Medical Center, Nashville, TN, USA

PG Prostaglandin
TNF-α Tumor necrosis factor alpha
TXA Thromboxane

Introduction

Modulation of the "immune response" to combat critical illness is a well-recognized concept. Recent efforts have been directed towards a modification of enteral/parenteral nutrition formulas for the benefit of altering, and even mitigating, a dysregulated immune response in critical illness. The addition of specific supplements to nutritional formulas with the aim of *boosting* the host immune response by increasing protein synthesis, stimulating an anti-inflammatory response, and accelerating the resolution of inflammation is coined "immunonutrition." These metabolic supplements include macronutrients (glutamine, arginine, polyunsaturated fatty acids such as ω-3 (omega-3) fatty acids), micronutrients (vitamins A, E and C, beta-carotene, nucleotides, taurine), and trace elements such as zinc and selenium [1]. Although these nutrients are available commercially for both enteral and parenteral use, this article will focus purely on the effects of these nutrients in acute respiratory distress syndrome (ARDS) when administered to patients via *an enteral route*.

In this review, we outline definitions of the ARDS as a dysregulated immune response and a pro-inflammatory state, explore the pathogenic mechanisms behind a proposed modulation of the inflammatory response via nutrition, examine the current evidence regarding the role of immunonutrition in ARDS, and discuss future insights using the current Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition (SCCM/ASPEN) critical care nutrition guidelines.

Acute respiratory distress syndrome is a life-threatening manifestation of lung dysfunction in the intensive care unit. Ashbaugh et al. first described ARDS in 12 patients who exhibited a clinical course similar to that of the infantile respiratory distress syndrome [2]. Treatment with positive end expiratory pressure (PEEP) was associated with a significant improvement in hypoxemia. Loss of lung compliance, non-hydrostatic pulmonary edema, and alveolar instability were recognized as important factors leading to respiratory collapse despite appropriate resuscitation [2]. The heterogeneity of disorders which cause ARDS and the lack of a concrete definition led to the first American-European consensus conference on ARDS (published in 1994) [3, 4]. Based on this 1994 publication, ARDS was defined as [1] acute onset hypoxemic respiratory failure with [2] partial pressure of oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) ratio (PaO_2/FiO_2) of <200 (regardless of PEEP level), [3] bilateral infiltrates on chest radiograph, and [4] pulmonary artery wedge <18 mmHg or no clinical evidence of left atrial hypertension. Acute lung injury was defined at a PaO_2/FiO_2 <300 [3, 4]. The Berlin criteria (published in 2012) [5] later replaced the American-European consensus conference's definition of ARDS allowing for standardization and uniformity in defining ARDS. The Berlin criteria for ARDS are (a) onset of symptoms within 1 week of clinical insult and (b) worsening bilateral infiltrates on chest radiography (exclusion of cardiogenic causes of pulmonary edema) and (c) and hypoxemia. When the PEEP is ≥5 cm of water, a PaO_2/FiO_2 ratio of 200–300 is considered mild, 100–199 moderate, and <100 severe ARDS [5].

Pathophysiology of Immunonutrition in ARDS

ARDS can result from a *direct* pulmonary insult as well as from an *indirect* injury from non-pulmonary etiologies. Regardless of the etiology, ARDS is characterized by a systemic inflammatory response resulting from the injury. The pathogenesis involves an exaggerated immune activation and cytokine production combined with endothelial dysfunction characterized by dysregulated coagulation and inflammation. The heightened inflammatory response culminates in loss of endothelial-alveolar barrier function and widespread and non-homogeneous proteinaceous (exudative) edema formation [6]. A potential role for specialized nutrition in ARDS becomes clear by understanding the three distinct stages in ARDS. The *exudative phase* represents the highly inflammatory phase, characterized pathologically as pulmonary edema with diffuse alveolar damage, the hallmark of which is hyaline membrane formation. This is followed by the *proliferative phase* (after 7–10 days) in which there is type II pneumocyte hyperplasia, squamous metaplasia, and myofibroblast infiltration with collagen deposition. The third and final *fibrotic phase* is marked by diffuse lung fibrosis and cyst formation leading to abnormal lung architecture [6].

At a cellular level, the *exudative phase* is marked by recruitment, localization, retention, and activation of neutrophils. This coupled with disruption of normal neutrophil clearance mechanisms leads to excessive inflammation. The release of arachidonic acid (AA) metabolites (i.e., leukotrienes and prostaglandins), proteases (elastases), and reactive oxygen/nitrogen species results in a self-perpetuating cycle of lung injury [7]. The earliest response to lung injury is the release of tumor necrosis factor alpha (TNF-α) and interleukin-1 (IL-1), which act locally on cells, including macrophages, endothelial cells, fibroblasts, and epithelial cells to stimulate the production of other cytokines such as the neutrophil chemotactic factor IL-8. As balance between pro- and anti-inflammatory mediators is an important determinant of the overall inflammatory response, anti-inflammatory cytokines such as IL-10 and IL-11 are released to protect against lung injury. Recently, nuclear factor kappa-B (NF-κB), a transcription factor that upregulates the expression of intercellular

adhesion molecule-1 (ICAM-1), IL-1b, IL-6, IL-8, and TNF-α, among others, has been recognized as an important step in the initiation, amplification, and maintenance of the pro-inflammatory cytokine cascade in ARDS [7].

Both glutamine and ω-3 fatty acids are important ingredients of an immune-modulating diet in critical illness. Glutamine is the most abundant free amino acid in the body [8] and is depleted in times of stress [9]. It is central to cellular energy and proliferation and its supply in critical illness is maintained via deamination of branched chain amino acids (BCAAs). In addition to its contribution to meeting metabolic demands, it is a precursor to the antioxidant glutathione and also promotes heat-shock protein (HSP) responses [10, 11••]. Recent data suggests that administration of glutamine decreases circulating levels of IL-6 and TNF-α and reduces nuclear factor NF-κB activity following sepsis [12].

The ω-3 fatty acids are polyunsaturated fatty acids with a carbon-carbon double bond at the third carbon. They are inserted in cell membranes where they compete with ω-6 fatty acids stored predominantly in the form of AA. During cellular stress, fatty acids are released from cell membrane and are converted into powerful secondary messenger hormones, eicosanoids [11••]. Eicosanoids derived from ω-6 fatty acids are highly pro-inflammatory, while eicosanoids derived from ω-3 fatty acids are less inflammatory and may even have anti-inflammatory properties, as discussed in later section [11••, 13]. Figure 1 and Table 1 highlight these properties.

Anti-Inflammatory Role of ω-3 Fatty Acids

Fatty acids from cell membranes are released at the time of cellular stress and injury by phospholipases and are subsequently converted through cyclooxygenase (COX) and lipoxygenase pathways (LPO) into secondary messenger hormones, eicosanoids [11••, 14]. ω-3 fatty acids are isolated from cold-water fish species, flaxseed, and canola oil. Mammals cannot synthesize the carbon-carbon double bonds at either the third or sixth carbon, making these compounds essential in the diet [11••, 13]. The three most important ω-3 fatty acids are α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). The ω-3 fatty acids are inserted in cell membranes where they compete with AA (ω-6 fatty acid) [13]. Cellular membrane phospholipids contained a high concentration of AA, which is involved in inflammation and is a major substrate for pro-inflammatory eicosanoids. ω-6 fatty acids are found in animal fat and include linolenic acid (LA), dihomo-gamma-linolenic acid (DGLA), and AA [11••, 15•].

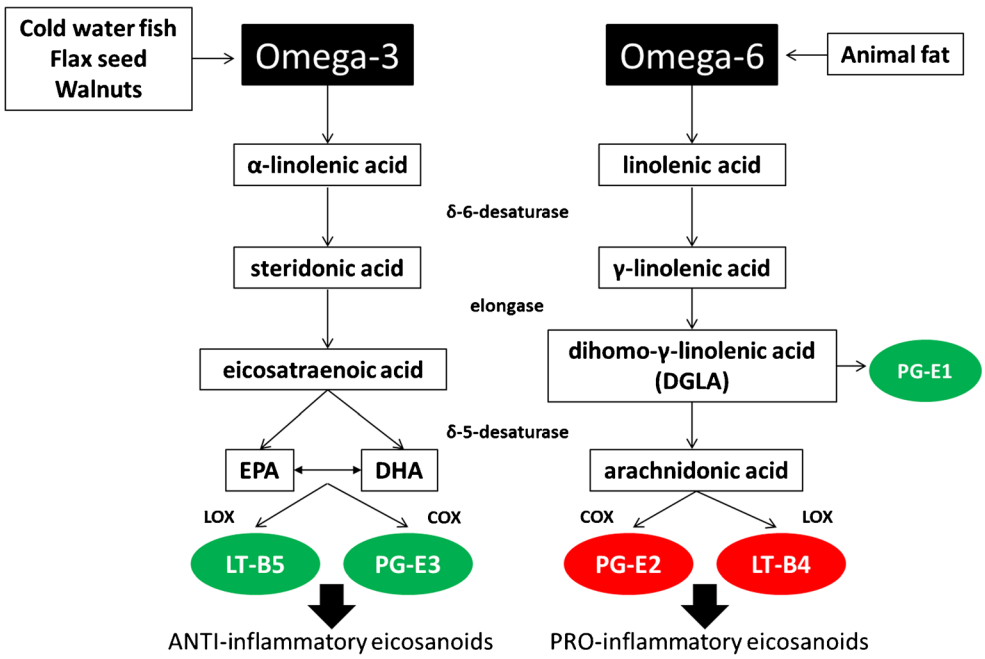

Fig. 1 Omega-3 and omega-6 fatty acid metabolism. The end-products of the omega-3 pathway include eicosanoids of the 3 and 5 series, which are anti-inflammatory and inhibit cytokine production and directly counteract the effect of 2 and 4 series eicosanoids. DGLA is an important intermediate in the omega-6 pathway which increases arachidonic acid levels; however, when DGLA is administered with EPA, δ-6-desaturase is inhibited, thus reducing arachidonic acid production and increasing PGE-1, a potent pulmonary vasodilator. The end-products of the omega 6-pathway are eicosanoids of the 2 and 4 series, which are pro-inflammatory, and lead to leukocyte adhesion, cytokine production, platelet coagulation, fever induction. *COX* cyclooxygenase, *DHA* docosahexaenoic acid, *EPA* eicosapentanoic acid, *LOX* lipoxygenase, *LTB* leukotriene, *PG* prostaglandin. Used permission from reference [53], with permission from Springer

Eicosanoid Pathway (Fig. 1 and Table 1)

Eicosanoids are short-acting potent hormones that act locally and play a major role in mediating and regulating the inflammatory response. Their major substrate is 20 carbon polyunsaturated fatty acid (AA) which is converted into prostaglandins (PG), thromboxanes (TX), leukotrienes (LT), and other oxidized derivatives (lipoxins (LX)) [14]. ω-6-derived eicosanoids are pro-inflammatory and mediate platelet aggregation, neutrophil activation and adhesion, cytokine production, and increased vascular permeability [15•]. These eicosanoids include series two prostaglandins, thromboxanes, and series four leukotrienes [15•]. Additionally, a ω-6 pathway intermediate product dihomo-γ-linolenic acid (DGLA) is produced in the reaction pathway leading to AA formation from dietary linoleic acid. The rate-limiting step in AA formation is controlled by enzyme Δ^5 desaturase which acts on DGLA to form AA [14]. Nutritional deficiencies, stress, and inflammation reduce the activity of Δ^5 desaturase, and instead of AA formation, DGLA is incorporated into cellular membranes [16]. This has important implications as eicosanoids formed by DGLA substrate (PGE_1) have anti-inflammatory properties [17]. Generally, series one and five eicosanoids have anti-inflammatory actions. Another intermediate product in the ω-6 pathway is gamma-linoleic acid (GLA). GLA is found in borage oil. When GLA is administered with eicosapentaenoic acid (EPA), the terminal enzyme is blocked resulting in less AA production [18]. EPA is subsequently converted via cyclooxygenase pathway into series five leukotrienes. ω-3-derived eicosanoids exhibit anti-inflammatory properties by reducing pro-inflammatory eicosanoid production through AA displacement, increase production of the anti-inflammatory lipids resolvins and protectins, decrease chemotaxis, and decrease adhesion molecule expression [11••, 15•]. Figure 1 and Table 1 summarize these important concepts.

Animal Studies on the Role of ω-3 and ω-Fatty Acids in ARDS

Animal studies have demonstrated the ability to alter eicosanoid balance in favor of anti-inflammatory metabolites by altering fatty acid profile of enteral nutrition formulas. Murray et al. [19] investigated the effects of adding EPA and GLA on hemodynamic parameters and lipid profile in porcine model of endotoxin-induced acute lung injury. Thirty-six pigs were divided in three groups to receive enteral diets composed of (a) LA, (b) EPA, and (c) EPA with GLA, given for 8 days before inducing endotoxemia. Baseline hemodynamic measurements as well as oxygen delivery were assessed. A reduction in cardiac index (after endotoxemia) was significantly attenuated with group (c), while the drop in blood pressure after endotoxemia was highest in group (a) and lowest in group (c). Thromboxane B_2, a stable metabolite of TXA_2, was significantly higher at baseline as well as at 4 h in group (a). Similar trends were noted for 6-keto PGF_{1a}, the stable metabolite of PGI_2. Fatty acid composition of lipid profile confirmed significantly lower levels of LA and AA as well as an increase in EPA and DHA levels in diet groups (b) and (c). DGLA levels were higher in group (c). Nutritional intervention by altering fatty acid composition resulted in attenuation of an early inflammatory response to endotoxemia. It was noteworthy that group (c) with EPA + GLA diet maintained the attenuation of inflammatory response through the 4-h study period. Simultaneous release of TXB_2 was significantly blunted in the same group. PGE_1 levels were not measured, but authors hypothesized that the improved response in group (c) may have been secondary to GLA supplementation, which augmented the synthesis of series one anti-inflammatory eicosanoids. Since PGE_1 is anti-inflammatory, the same authors proposed that substituting GLA for AA might increase the level of PGE_1 and substituting EPA would increase the formation of trienoic eicosanoids. Both mono- and trienoic eicosanoids have anti-inflammatory properties that can potentially

Table 1 Pro- and anti-inflammatory eicosanoids and their physiological effects in vivo

	Eicosanoids	Molecule(s)	Effects
Pro-inflammatory eicosanoids	Series 2 Prostaglandins (PG)	PGI_2, PGE_2, PGF_{2a}, PGD_2	Recruitment of inflammatory cells
	Thromboxanes (TX)	TXA_2, TXB_2	Promote leukocyte chemotaxis and aggregation
	Series 4 Leukotrienes (LT)	LTB_4, LTC_4, LTD_4, LTE_4	Promote platelet aggregation
			Induce vasoconstriction
			Enhance secretion of inflammatory cytokines
Inflammation resolving eicosanoids	Inflammation resolving Eiconsanoids	PGE_1, PGE_3, TXA_1	Induce vasodilatation
	Series 1 and 3 Prostaglandins (PG) and thromboxanes (TX)	LTB_5, LXA_4, LXB_4	Inhibit platelet aggregation
		RvD, RvE	Reduce neutrophil chemotaxis
	Series 5 leukotrienes (LT)	PD_1	Blocks inflammatory cytokine expression
	Lipoxins (LX)		Promotes phagocytosis and cell apoptosis
	Resolvins (Rv) and protectins (P)		

shift the eicosanoid balance from pro-inflammatory to anti-inflammatory state [19].

Mancuso et al. [20] evaluated lung microvascular protein permeability in a rat model of endotoxin-induced acute lung injury. Mean arterial pressure, platelets, and white blood cell count were measured in 40 rats randomized to receive enteral diets based with corn oil, fish oil, and 20% fish oil with 5 or 20% borage oil for 21 days. Protein microvascular permeability was increased in all dietary models; however, it was the highest in the corn oil-based diet group and this trend reached statistical significance in the 20% fish and 20% borage oil groups. Although no significant difference in mean arterial pressure was observed, further analysis did show an attenuated early and late response to blood pressure reduction after endotoxin administration for all dietary groups, as compared with the corn oil-fed group. In a different experiment, the same authors evaluated eicosanoid generation in stimulated alveolar macrophages and phospholipid fatty acid composition of lung and liver macrophage in 19 rats randomized to receive enteral feeding with corn oil, 20% fish oil, and 20% fish oil with 20% borage oil for 21 days. The release of LTB_4, TXA_2, and PGE_2 was significantly lower in the fish oil and fish + borage oil groups. Similarly the concentration of LTB_5 (anti-inflammatory derivative of EPA) was significantly higher in these groups. Also, the ω-6/ω-3 ratio was significantly lower in alveolar macrophages of rats fed with fish oil or fish + borage oil. The authors concluded that dietary supplements of fish and borage oil can potentially have protective effects as increased lung microvascular permeability is an important step in the pathogenesis of ARDS [20].

In a subsequent study, the same authors showed in vivo modulation of inflammatory eicosanoid pathway with fish + borage oil diet-fed rats [21]. Neutrophil accumulation as measured by lung myeloperoxidase activity was significantly lower in fish oil and fish + borage oil groups. LTB_4 and LTC_4/D_4 levels were significantly lower in fish oil and fish + borage oil groups. Similarly, levels of pro-inflammatory prostaglandins PGE_2 and TXB_2 following endotoxin administration were significantly lower in the fish oil and fish + borage oil groups. Overall, animal studies favor the anti-inflammatory effect of ω-3 fatty acid supplementation [20, 21]. Table 2 summarizes the results of these animal studies.

Human Studies on the Role of ω-3 and ω-6 Fatty Acids in ARDS

Following the promising results from animal studies on the use of EPA + GLA in ARDS, several large-scale studies have since attempted to study these effects in humans [22–28]. With increasing evidence for the anti-inflammatory effects of long-chain ω-3 fatty acids, a commercial-based enteral formula enriched with ω-3 fatty acids was developed for use in ARDS [29]. This preparation provides 55% calories from fat and is a rich source of EPA, DHA, GLA, and other antioxidant vitamins. Low carbohydrate content was favored to minimize the hypothetical risk of high carbon dioxide production and resultant increase in minute ventilation requirements. Using this formula, Gadek et al., in 1999, pioneered a clinical trial in patients with severe ARDS [22] where 98 (of anticipated 146) patients were randomized to receive continuous EN enriched with EPA + GLA + antioxidant vitamins or control EN comprised of an isonitrogenous, isocaloric, high fat, ω-6 rich formula over 7 days. Arterial blood gas measurements and ventilator settings were recorded at study baseline and at days four and seven to enable calculation of PaO_2/FiO_2. Primary outcome variables were "time receiving ventilatory support," "time in the ICU," and "time on supplemental oxygen." Those who received EPA + GLA required significantly fewer days of ventilatory support (11 vs. 16.3 days, $p = 0.011$) and fewer ICU days (12.8 vs. 17.5 days, $p = 0.016$). Patients who received EPA + GLA also showed an improvement in arterial oxygenation (increase in PaO_2) and PaO_2/FiO_2 ratio by study day four ($p = 0.0011$) that was maintained on study day seven ($p = 0.0408$). Increase in PaO_2 was accompanied by a decrease in FiO_2, PEEP, and minute ventilation in the EPA + GLA group. In addition, there was a significant reduction in pulmonary neutrophil count and inflammation (i.e., bronchial alveolar lavage fluid (BALF) neutrophil counts) and a reduction in new onset organ failure in the study group. These results were similar to earlier observations in pig models with sepsis-induced ARDS [19].

Three subsequent clinical trials have studied the use of the same commercially prepared enteral formulation rich in EPA + GLA + antioxidant vitamins [24–26]. First, Singer et al. [26] randomized 100 ventilated patients with ALI in an

Table 2 Summary of animal studies on the role of omega-3 and omega-6 fatty acids in ARDS

Author/year	Study population	Main findings
Murray et al./1995 [19]	36 pigs with endotoxin-induced lung injury	Omega-3 diet ameliorates endotoxin induced ALI by suppressing pro-inflammatory eicosanoids in BAL fluid.
Mancuso et al./1997 [20, 21]	Randomized controlled trial on rats (pre-fed w/ omega-3 fatty acids vs omega-6 fatty acids)	° Severity of pulmonary vascular protein permeability and hypotension were less with omega-3 diet. ° Omega-3 diet ameliorates endotoxin induced ALI by suppressing pro-inflammatory eicosanoids in BAL fluid.

EPA eicosapentaenoic acid, *GLA* gamma-linoleic acid, *ALI* acute lung injury, *BAL* bronchial alveolar lavage fluid

open-label study design to receive EPA + GLA + antioxidant vitamin combination (study group) or an isonitrogenous, isocaloric, and high-fat, low-carbohydrate diet (control group). Lung-protective ventilator strategy or low tidal volume ventilation (LTVV) (maintain peak airway pressures <35 mmHg and tidal volume ~7 mL/kg) was employed. Primary outcomes of a change in oxygenation or change in breathing patterns at days four, seven, and 14 were measured. There was an improvement in oxygenation at day four ($p < 0.05$) and day seven ($p < 0.05$) as well as an improvement in respiratory mechanics (measured by static compliance and reduced resistance) from days one to seven in the study group. Patients who received EPA + GLA + antioxidants spent less time on the ventilator although there were no differences in mortality between the two groups. This study included patients with less severe lung injury than previously studied [22] and also measured parameters of lung injury (i.e., change in lung mechanics).

In 2006, Pontes-Arruda et al. used the same commercial enteral formula as the two previous studies [22, 26] and demonstrated a mortality benefit in the group that received EPA + GLA + antioxidant-enriched EN, 18 (33%) deaths vs 25 (52%) deaths, an absolute risk reduction of 19.4% ($p = 0.037$) [24]. In addition, as in prior trials, there were significant improvements in oxygenation, ventilator-free days, ICU-free days, and onset of new-organ dysfunction in the study group. This trial initiated all patients on continuous EN *promptly* within 6 h of enrollment although a total of 37 patients were excluded for being unable to meet caloric goals.

In 2012, Elamin et al. also used this commercial preparation in a randomized trial on 17 patients with ARDS and found a decrease in lung injury scores ($p < 0.003$) and lower ventilation variables (FiO2, PEEP, and minute ventilation) [25]. The study group also had a significant reduction in the onset of multi-organ dysfunction (MOD) and a shorter ICU stay.

These four trials essentially compared the effects of a high-fat diet rich in ω-3 fatty acids (EPA, DHA, and GLA) and antioxidant vitamins to that of a high-fat diet rich in ω-6 fatty acids [22, 24–26]. These earlier trials consistently demonstrated an improvement in oxygenation, lung mechanics, and fewer ventilator and ICU days with a ω-3 fatty acid-rich diet [22, 24–26]. A widespread implementation of this commercial formula was slow due to numerous concerns regarding these trials. For instance, the use of ω-6 fatty acid-rich formulas in the control arms raised the possibility that this simply worsened inflammation and shifted the scale for an improvement in outcome in the study group. Furthermore, intention-to-treat analyses were not undertaken as many of the studies excluded randomized patients from the analyses due to failure to tolerate adequate enteral nutrition.

When the administration pattern of the ω-3 fatty acid rich diet was modified, these results were not as consistent. In 2011, a phase III arm of the ARDSNet trial (OMEGA study) [27••] used the novel approach of a twice-daily bolus supplementation of EPA + GLA + DHA + antioxidants (in addition to continuous EN) in ALI. The rationale for this approach was the exclusion of large numbers of patients in prior trials due to their inability to tolerate continuous EN and meet caloric goals. The authors postulated that more patients would tolerate the supplementation in a bolus form. In addition, investigators questioned the true impact of a ω-3 fatty acid-rich diet in modulating the inflammatory response [27••, 29]. As stated earlier, it has been argued that the perceived benefits in prior studies [22, 24–26] may have been accentuated by the use of a pro-inflammatory (ω-6 and ω-9 fatty acid rich) diets in the control arm [29]. The OMEGA study eliminated this potential confounder by including an isocaloric control supplement comprising of *carbohydrate-based* calories instead of the commercial high-fat formulation (rich in ω-6 and ω-9 fatty acids) used in prior trials [22, 24–26] and randomized 272 adults to receive supplementation for up to 21 days [27••]. Lung-protective mechanical ventilation and conservative fluid management strategies were practiced and the primary end point was ventilator-free days (from randomization to day 28). The study was terminated after an interim analysis showed the study group clearly had worse outcomes with fewer ventilator-free days (14 vs. 17, p 0.02), fewer ICU-free days (14 vs. 16.7, p 0.04), and more deaths (26.6 vs. 33.8%, p 0.05). Twice-daily supplementation of EPA + GLA + DHA + antioxidants did not improve clinical outcomes and may even have been harmful. The authors surmised that the anti-inflammatory effects of ω-3 fatty acids may be offset by the more rigorous use of "low-tidal volume ventilation (LTVV) strategy" and more conservative fluid management that were widespread by the time of this study [30, 31].

In a similar trial, Stapleton et al. demonstrated that a *single daily bolus* of fish oil (rich in ω-3 fatty acids; EPA + DHA) versus control saline did not lead to significant improvement in lung inflammation (IL-8 levels in BALF) or clinical outcome (including hospital mortality, 60-day mortality, ventilator-free days, or ICU-free days) [23]. IL-8 is a dominant neutrophil chemoattractant in ALI [32] and is reduced in patients who receive lung-protective mechanical ventilation [33]. Patients in this trial had less severe ARDS compared with other trials (i.e., higher baseline PaO_2/FiO_2). However, this study was unique in that it used *only ω-3 fatty acids*, as opposed to a combination of ω-3 fatty acids, GLA, and antioxidant vitamins in prior trials, thereby allowing for an analysis of the effect of ω-3 fatty acids *alone*.

Replicating this pattern of bolus supplementation, Parish et al. in 2014 randomized 58 patients to receive three times per day bolus EPA+ DHA supplementation (soft-gel capsules) for 14 days in patients with mild to moderate ARDS [28]. Low tidal volume ventilation strategy and conservative fluid management were used [30]. Contrary to the results of two

previous studies [23, 27••], oxygenation and lung mechanics were improved at 14 days (PaO_2; 81 vs. 67 mmHg, $p = 0.004$). The authors postulated that the differing outcomes may be related to the differences in formula supplementation and populations (trauma versus sepsis in other trials) [23, 27••].

The clinical benefits of ω-3 fatty acid supplementation are inconsistent based on these results. Where earlier trials [22, 24–26] have shown a clear benefit, these results have not been reproduced in more recent studies [23, 27••]. To date, there is only one trial that has studied the effect of ω-3 fatty acid-rich supplementation *alone* [23] without the effect of other co-nutrients such as ω-6 fatty acids (GLAs) or antioxidant vitamins—making it difficult to discern the effect of ω-3 fatty acid-rich supplementation *alone* versus the results of a *combination* or "*synergy*" effect between all the different nutrients used in these studies.

To dissect these effects, Santacruz et al. conducted a meta-analysis of seven major randomized trials (802 patients) [34•]. Overall, ω-3 fatty acid-rich supplementation in ARDS did not impact mortality outcomes (relative risk (RR) = 0.83, $p = 0.37$); however, when ω-3 fatty acid supplementation (immunonutrition) was compared with studies that had a high lipid content in their control groups (mostly earlier trials), there was a clear mortality benefit with ω-3 fatty acid supplementation (RR = 0.57, $p < 0.001$). When trials with lower-lipid content controls were considered, there seemed to be a trend towards higher mortality with ω-3 fatty acid supplementation (RR = 1.36, $p < 0.09$). There was no effect on ventilator-free days or ICU-free days and a minor reduction in ICU length of stay reported. It has been argued that the benefits seen in earlier trials were perhaps due to the prevention of lipid accumulation or toxicity/inflammation with ω-3 fatty acid supplementation. When later studies used lower lipid content formulas, this benefit was not present. In fact, critically ill patients receiving a diet with >40% calories from fat have had worse outcomes, as compared to those with a lower fat content [35].

Another potential reason that findings in more recent trials [23, 27••] are discordant with the results of older trials [22, 24–26] is that the benefits of a pharmacological (dietary) intervention may have been too weak or even lost in the face of a much more robust mechanical strategy of low tidal volume ventilation and conservative fluid management in ARDS—i.e., these practices were widely adopted by the time the later ω-3 fatty studies were conducted.

Table 3 showcases the important points from these large-scale human studies.

Glutamine in ARDS

Glutamine is the most abundant amino acid and is central to several important cellular processes in humans. It is a substrate for protein and nucleotide synthesis, maintains normal small intestinal health, acid-base balance, and glucose metabolism [36]. Most tissues synthesize glutamine hence it is not considered an *essential* amino acid. During periods of stress, however, utilization of glutamine by metabolically active tissues far exceeds the rate at which its synthesis can take place, and therefore, it is considered a *conditionally* essential amino acid.

Clinical interest in glutamine dates back to 1975, when trauma and post-operative patients were shown to have a marked reduction in levels of free intracellular glutamine in skeletal muscle [37]. Muscle glutamine concentration may discriminate between "survivors" and "non-survivors" after abdominal surgery [38], and plasma glutamine concentrations may predict hospital mortality in ICU patients [39]. Based on these findings, there has been a surge of interest in the potential role of exogenous supplementation of glutamine in critical illness.

Glutamine depletion has also been found in chronic respiratory illness. Chronic obstructive pulmonary disease (COPD) patients with muscle wasting may have reduced levels of arterial glutamine, and cystic fibrosis patients have a marked reduction in levels of glutamine in circulating neutrophils [40]. Glutamine is involved in several key processes of neutrophil function including motility, respiratory burst killing, secretion of proteolytic enzymes, and phagocytosis. The lungs play an important part in glutamine homeostasis in stress states. A study reported approximately 850% increase in lung glutamine production in septic surgical patients [41].

To date, there is little information about the role of glutamine in critically ill patients with ARDS. Most of our information currently comes from studies on models of indirect lung injury (extra pulmonary ARDS). For instance, in animal models of ARDS induced by cecal ligation and puncture [42], IV glutamine administration is shown to reduce mortality, attenuate lung injury via enhanced expression of heat-shock proteins in lung tissue, and reduce diaphragmatic damage and distal organ apoptosis [43••]. In a model of hind limb ischemia/reperfusion injury-induced ARDS, IV glutamine was shown to reduce local and systemic inflammation and attenuate lung injury [43••].

The results are mixed for models of direct pulmonary injury causing ARDS. In 2009, Hou et al. [44] studied lung injury induced by intra-tracheal instillation of *Escherichia coli* (*E. coli*) lipopolysaccharide (LPS) in mice pretreated with 10 days of glutamine supplementation. The mice treated with glutamine had higher inflammatory response and increased neutrophil recruitment. However, in a rat model by Zhang et al. [45], immediate instillation of IV glutamine after LPS-induced pulmonary ARDS reduced lung damage, neutrophil infiltration, and BALF IL-8 levels. In a similar model of rats with lung injury induced by hydrochloric acid instillation and mechanical ventilation, Lai et al. [46] also demonstrated improved lung mechanics and reduced lung inflammation and

Table 3 Randomized controlled trials of omega-3 fatty acid supplementation in acute respiratory distress syndrome

Author/year	Study design	Intervention vs control (duration)	No. of patients	Primary outcome(s)	Main conclusions
Gadek et al./1999 [22]	RCT	EPA + GLA + antioxidants vs. high fat omega-6 control EN (7 days)	146	Duration of mechanical ventilation; time in ICU, and time on oxygen	1. More ventilator-free days 2. More ICU-free days 3. Improved oxygenation
Singer et al./2006 [26]	RCT (open abel)	EPA + GLA + antioxidants vs. high-fat omega-6 control EN (14 days)	100	Change in oxygenation or breathing patterns at days 4, 7, and 14	1. Improved oxygenation at days 4 and 7 2. Improved lung mechanics from day 1 to 7
Pontes-Arruda et al./2006 [24]	RCT	EPA + DHA + antioxidants vs high-fat omega-6 control EN (minimum 4 days); EN started w/in 6 h	165	28 day all-cause mortality	1. 28-day mortality benefit (18 vs 25 deaths) ($p = 0.037$) 2. Significantly improved oxygenation and ventilator- and ICU-free days and less new organ dysfunction
Stapleton et al./2011 [23]	RCT (Phase II)	EPA + DHA (single bolus) vs low fat control EN (14 days)	90	BAL fluid interleukin (IL-8) levels	1. No change in BALF IL-8 levels from day 0 to day 4 or 8
Elamin et al./2012 [25]	RCT	EPA + DHA + GLA + antioxidants vs high-fat omega-6 control EN (7 days)	17	Improvement in oxygenation and modified lung injury scores (LIS)	1. Decrease in LIS score 2. Lower FiO_2, PEEP and minute ventilation
Rice et al./2011 [27••]	RCT (Phase III; ARDSNet)	EPA + DHA + GLA + antioxidants (twice daily bolus) vs low fat EN formula (earliest of 21 days or extubation)	272	Ventilator-free days	Stopped early as study arm had 1. Fewer ventilator-free days 2. Fewer ICU-free days 3. More deaths
Parish et al./2014 [28]	RCT	EPA + DHA (three times daily) vs no supplementation (14 days)	58	Change in oxygenation	1. Improved oxygenation at 14 days 2. Improved lung mechanics at 14 days
Santacruz et al./2015 [34•]	Meta-analysis (7 RCTs)	Omega-3 fatty acid-rich EN vs control EN	802	Ventilator-free days, ICU LOS, ICU-free days	1. No overall impact on mortality 2. Mortality improved when omega-3 fatty acids compared with high lipid supplementation 3. No change in VFDs, ICU LOS or ICU-free days

RCT randomized clinical trial, *LOS* length of stay, *LIS* lung-injury score

damage with IV glutamine. In a recent study in 2015 [47], oral pretreatment with glutamine in rats with LPS induced lung injury and reduced lung damage, BALF protein, and lactate dehydrogenase levels. The proposed mechanisms by which glutamine may play an anti-inflammatory role in ARDS include increased heat-shock protein expression, reduced apoptosis, improved macrophage function, and reduced neutrophil infiltration among many other mechanisms [43••].

Several studies and meta-analysis have looked at the role of glutamine in critically ill patients. Results from these studies are conflicting. Older trials have shown a role for glutamine in reducing infections, particularly pneumonia, while more recent data have suggested harm with glutamine. In 2013, Heyland et al. [48•] randomized 1223 critically ill patients (not limited to those with ARDS) to glutamine supplementation and found glutamine was associated with an increased trend towards all-cause 28-day mortality (32.4 vs 27.2%, $p = 0.05$). A large systematic review is currently underway to review and critically appraise the role of immunonutrition versus standard non-immunonutrition formula supplementation in adult patients with ARDS [49]. Table 4 summarizes the salient points from the abovementioned animal studies on the use of glutamine.

Specialized SPMs in ARDS

More recently, attention has shifted from molecules that inhibit inflammation to molecules that accelerate resolution of inflammation. Specialized pro-resolving molecules (SPMs) are endogenously produced mediators responsible for *resolving* inflammation. These molecules are a diverse group of specialized lipid mediators and include lipoxins, resolvins, protectins, maresins, proteins (annexin), and even gaseous mediators such as hydrogen sulfide and carbon monoxide. Lipoxins and prostaglandins are derived from ω-6 fatty acids while EPA and DHA give rise to resolvins, protectins, and maresins. These molecules have been shown to alter neutrophil lifespan, modulate the adaptive immune system, and have analgesic actions [50].

While inflammation is vital for host survival, unregulated inflammation often leads to "collateral" host damage. Inflammatory mediator clearance is crucial once the inciting threat (e.g., infection) has been eliminated. SPMs such as resolvin RvD2 and RvE have been shown to help limit inflammation in the setting of *E. coli*, *Staphyloccocus aureus*, and *Streptococcus pneumoniae* infections in animal models [51]. There is also a growing body of literature on the role of SPMs in limiting macrophage migration, potentiating the effect of antibiotics, accelerating clearance of debris and in the resolution of inflammation in animal models [51]. Robust human studies, including those for SPMs in ARDS, are lacking.

Table 4 Studies on role of glutamine supplementation in patients with ARDS

Author/year	Study population (no. of patients)	Main Findings
Vinnars et al./1975 [37]	Post-operative and trauma (5 patients)	Marked reduction in skeletal muscle-free intracellular glutamine.
Roth et al./1982 [38]	Post-laparotomy for prolonged abdominal sepsis (14 patients)	"Non-survivors" demonstrated markedly decreased muscle glutamine levels.
Rodas et al./2012 [39]	Critically-ill (174 patients)	Low plasma glutamine at ICU admission is an independent predictor of ICU-mortality.
D'Eufemia et al./2006 [40]	Chronic pulmonary disease; cystic fibrosis (26 patients)	CF patients have significantly lower neutrophil glutamine levels.
Plumley et al./1990 [41]	septic surgical (31 patients)	850% increase in lung glutamine production during sepsis
Singleton et al./2005 [42]	ARDS induced by cecal-ligation and puncture in rats	IV glutamine reduced mortality and attenuated lung injury (enhanced heat-shock protein expression in lung tissue).
Hou et al./2009 [44]	Intra-tracheal instillation of LPS in mice pretreated w/ glutamine)	Glutamine pre-treatment allowed a higher inflammatory response and increased neutrophil recruitment in early acute lung injury.
Zhang et al./2009 [45]	IV glutamine after LPS induced ARDS in rats	Glutamine prevented neutrophil recruitment and infiltration and reduced BALF IL-8 levels during sepsis.
Lai et al./2014 [46]	Lung injury induced by acid in rats	IV glutamine improved lung mechanics and reduced lung inflammation.
Fernandez-Bustamante et al./2015 [47]	Pretreatment w/ oral glutamine in rats w/ LPS induced lung injury	Oral glutamine reduced lung damage, BALF protein, and lactate dehydrogenase levels.
Heyland et al./2013 [48•]	RCT; mechanically ventilated ICU patients w/ multi-organ failure (1223 patients)	Glutamine administration increased trend towards all-cause 28-day mortality and did not improve clinical outcomes.

BALF bronchial-alveolar lavage fluid, *LPS* lipopolysaccharide

Conclusion

Over the past 30 years, substantial strides have been made in the area of nutrition in critical illness. The concept of *nutritional support* has essentially evolved into a concept of *nutritional therapy*. Despite the enthusiasm for immunonutrition, the current level of evidence does not support widespread use of immune-modulating therapies such as ω-3 fatty acids, glutamine, or antioxidants such as vitamins in critically ill patients with ARDS or ALI [52]. Current data are marred by the heterogeneity of both immune-enhancing formula preparations and the populations studied. Results from clinical trials are conflicting. While it may still be too soon to write off the role of these fatty acids in modulating inflammation, the discovery of newer molecules such as SPMs represents an exciting area for immunonutrition research.

Compliance with Ethical Standards

Conflict of Interest Todd Rice reports personal fees from Avisa Pharma, personal fees from Cumberland Pharmaceuticals, Inc., and personal fees from GlaxoSmithKline, LLC. Jayshil Patel reports personal fees from Nestle Corporation, outside the submitted work. Shahryar Ahmad and Massoma Aqeel declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

*Special thanks are given to Dr. Shirin Shafazand for reviewing this manuscript.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Mariette C. Immunonutrition. J Visc Surg. 2015;152(Suppl 1):S14–7.
2. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. Lancet. 1967;2(7511):319–23.
3. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, et al. Report of the American-European consensus conference on acute respiratory distress syndrome: definitions, mechanisms, relevant outcomes, and clinical trial coordination. Consensus Committee J Crit Care. 1994;9(1):72–81.
4. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, et al. The American-European consensus conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med. 1994;149(3 Pt 1):818–24.
5. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: the Berlin definition. JAMA. 2012;307(23):2526–33.
6. Tomashefski JF. Pulmonary pathology of acute respiratory distress syndrome. Clin Chest Med. 2000;21(3):435–66.
7. Ware LB. Pathophysiology of acute lung injury and the acute respiratory distress syndrome. Semin Respir Crit Care Med. 2006;27(4):337–49.
8. Brosnan JT. Interorgan amino acid transport and its regulation. J Nutr. 2003;133(6 Suppl 1):2068S–72S.
9. Planas M, Schwartz S, Arbós MA, Farriol M. Plasma glutamine levels in septic patients. JPEN J Parenter Enteral Nutr. 1993;17(3):299–300.
10. Wischmeyer PE, Musch MW, Madonna MB, Thisted R, Chang EB. Glutamine protects intestinal epithelial cells: role of inducible HSP70. Am J Phys. 1997;272(4 Pt 1):G879–84.
11. •• Pierre JF, Heneghan AF, Lawson CM, Wischmeyer PE, Kozar RA, Kudsk KA. Pharmaconutrition review: physiological mechanisms. JPEN J Parenter Enteral Nutr. 2013;37(5 Suppl):51S–65S. **This review comprehensively explains the pharmacological effects of various macronutrients and micronutrients on the immune-system**
12. Singleton KD, Beckey VE, Wischmeyer PE. Glutamine prevents activation of NF-kappa B and stress kinase pathways, attenuates inflammatory cytokine release, and prevents acute respiratory distress syndrome (ARDS) following sepsis. Shock. 2005;24(6):583–9.
13. Calder PC. Omega-3 fatty acids and inflammatory processes. Nutrients. 2010;2(3):355–74.
14. King MW. The Medical Biochemistry Page: eicosanoid synthesis and metabolism: prostaglandins, thromboxanes, leukotrienes, lipoxins 1996–2016 [Available from: http://themedicalbiochemistrypage.org/.
15. • García de Acilu M, Leal S, Caralt B, Roca O, Sabater J, Masclans JR. The role of omega-3 polyunsaturated fatty acids in the treatment of patients with acute respiratory distress syndrome: a clinical review. Biomed Res Int. 2015;2015:653750. **This review covers recent data and trials on the use of omega-3 polyunsaturated fatty acids in ARDS patients**
16. de Alaniz MJ, Marra CA. Glucocorticoid and mineralocorticoid hormones depress liver delta 5 desaturase activity through different mechanisms. Lipids. 1992;27(8):599–604.
17. Pontes-Arruda A, Demichele S, Seth A, Singer P. The use of an inflammation-modulating diet in patients with acute lung injury or acute respiratory distress syndrome: a meta-analysis of outcome data. JPEN J Parenter Enteral Nutr. 2008;32(6):596–605.
18. Barham JB, Edens MB, Fonteh AN, Johnson MM, Easter L, Chilton FH. Addition of eicosapentaenoic acid to gamma-linolenic acid-supplemented diets prevents serum arachidonic acid accumulation in humans. J Nutr. 2000;130(8):1925–31.
19. Murray MJ, Kumar M, Gregory TJ, Banks PL, Tazelaar HD, DeMichele SJ. Select dietary fatty acids attenuate cardiopulmonary dysfunction during acute lung injury in pigs. Am J Phys. 1995;269(6 Pt 2):H2090–9.
20. Mancuso P, Whelan J, DeMichele SJ, Snider CC, Guszcza JA, Claycombe KJ, et al. Effects of eicosapentaenoic and gamma-linolenic acid on lung permeability and alveolar macrophage eicosanoid synthesis in endotoxic rats. Crit Care Med. 1997;25(3):523–32.
21. Mancuso P, Whelan J, DeMichele SJ, Snider CC, Guszcza JA, Karlstad MD. Dietary fish oil and fish and borage oil suppress intrapulmonary proinflammatory eicosanoid biosynthesis and attenuate pulmonary neutrophil accumulation in endotoxic rats. Crit Care Med. 1997;25(7):1198–206.
22. Gadek JE, DeMichele SJ, Karlstad MD, Pacht ER, Donahoe M, Albertson TE, et al. Effect of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in patients with acute respiratory distress syndrome. Enteral nutrition in ARDS study group. Crit Care Med. 1999;27(8):1409–20.
23. Stapleton RD, Martin TR, Weiss NS, Crowley JJ, Gundel SJ, Nathens AB, et al. A phase II randomized placebo-controlled trial of omega-3 fatty acids for the treatment of acute lung injury. Crit Care Med. 2011;39(7):1655–62.

24. Pontes-Arruda A, Aragão AM, Albuquerque JD. Effects of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in mechanically ventilated patients with severe sepsis and septic shock. Crit Care Med. 2006;34(9):2325–33.
25. Elamin EM, Miller AC, Ziad S. Immune enteral nutrition can improve outcomes in medical-surgical patients with ARDS: a prospective randomized controlled trial. J Nutr Disord Ther. 2012;2:109.
26. Singer P, Theilla M, Fisher H, Gibstein L, Grozovski E, Cohen J. Benefit of an enteral diet enriched with eicosapentaenoic acid and gamma-linolenic acid in ventilated patients with acute lung injury. Crit Care Med. 2006;34(4):1033–8.
27.•• Rice TW, Wheeler AP, Thompson BT, de Boisblanc BP, Steingrub J, Rock P, et al. Enteral omega-3 fatty acid, gamma-linolenic acid, and antioxidant supplementation in acute lung injury. JAMA. 2011;306(14):1574–81. **This large-scale randomized (phase III ARDSNet) clinical trial had to be terminated early after it showed worsened outcomes in ARDS patients supplemented with omega-3 fatty acids.**
28. Parish M, Valiyi F, Hamishehkar H, Sanaie S, Asghari Jafarabadi M, Golzari SE, et al. The effect of omega-3 fatty acids on ARDS: a randomized double-blind study. Adv Pharm Bull. 2014;4(Suppl 2): 555–61.
29. Calder PC. A matter of fat. JPEN J Parenter Enteral Nutr. 2015;39(7):756–8.
30. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med. 2000; 342(18):1301–8.
31. Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, de Boisblanc B, et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006;354(24): 2564–75.
32. Goodman RB, Pugin J, Lee JS, Matthay MA. Cytokine-mediated inflammation in acute lung injury. Cytokine Growth Factor Rev. 2003;14(6):523–35.
33. Ranieri VM, Suter PM, Tortorella C, De Tullio R, Dayer JM, Brienza A, et al. Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. JAMA. 1999;282(1):54–61.
34.• Santacruz CA, Orbegozo D, Vincent JL, Preiser JC. Modulation of dietary lipid composition during acute respiratory distress syndrome: systematic review and meta-analysis. JPEN J Parenter Enteral Nutr. 2015;39(7):837–46. **An important meta-analysis of current randomized clinical trials showcasing the role of omega-3 fatty acid supplementation. It highlights that benefits were more pronounced when omega-3 fatty acids were compared to a high lipid supplementation rather than benefits from omega-3 fatty acid use alone.**
35. Mesejo A, Sánchez Álvarez C, Arboleda Sánchez JA, (SEMICYUC-SENPE) SSoICMaCU-SSoPaEN. Guidelines for specialized nutritional and metabolic support in the critically ill-patient. Update. Consensus of the Spanish Society of Intensive Care Medicine and Coronary Units-Spanish Society of Parenteral and Enteral Nutrition (SEMICYUC-SENPE): obese patient. Med Int. 2011;35(Suppl 1): 57–62.
36. Newsholme P, Procopio J, Lima MM, Pithon-Curi TC, Curi R. Glutamine and glutamate—their central role in cell metabolism and function. Cell Biochem Funct. 2003;21(1):1–9.
37. Vinnars E, Bergström J, Fürst P. Influence of the postoperative state on the intracellular free amino acids in human muscle tissue. Ann Surg. 1975;182(6):665–71.
38. Roth E, Funovics J, Mühlbacher F, Schemper M, Mauritz W, Sporn P, et al. Metabolic disorders in severe abdominal sepsis: glutamine deficiency in skeletal muscle. Clin Nutr. 1982;1(1):25–41.
39. Rodas PC, Rooyackers O, Hebert C, Norberg Å, Wernerman J. Glutamine and glutathione at ICU admission in relation to outcome. Clin Sci (Lond). 2012;122(12):591–7.
40. D'Eufemia P, Finocchiaro R, Celli M, Tote J, Ferrucci V, Zambrano A, et al. Neutrophil glutamine deficiency in relation to genotype in children with cystic fibrosis. Pediatr Res. 2006;59(1):13–6.
41. Plumley DA, Souba WW, Hautamaki RD, Martin TD, Flynn TC, Rout WR, et al. Accelerated lung amino acid release in hyperdynamic septic surgical patients. Arch Surg. 1990;125(1): 57–61.
42. Singleton KD, Serkova N, Beckey VE, Wischmeyer PE. Glutamine attenuates lung injury and improves survival after sepsis: role of enhanced heat shock protein expression. Crit Care Med. 2005;33(6):1206–13.
43.•• Oliveira GP, de Abreu MG, Pelosi P, Rocco PR. Exogenous glutamine in respiratory diseases: myth or reality? Nutrients. 2016;8(2): 76. **Comprehensive review article for readers on the current evidence of use of glutamine in acute lung injury (mostly animal studies)**
44. Hou YC, Pai MH, Chiu WC, Hu YM, Yeh SL. Effects of dietary glutamine supplementation on lung injury induced by lipopolysaccharide administration. Am J Physiol Lung Cell Mol Physiol. 2009;296(3):L288–95.
45. Zhang F, Wang X, Pan L, Wang W, Li N, Li J. Glutamine attenuates lipopolysaccharide-induced acute lung injury. Nutrition. 2009;25(6):692–8.
46. Lai CC, Liu WL, Chen CM. Glutamine attenuates acute lung injury caused by acid aspiration. Nutrients. 2014;6(8):3101–16.
47. Fernandez-Bustamante A, Agazio A, Wilson P, Elkins N, Domaleski L, He Q, et al. Brief glutamine pretreatment increases alveolar macrophage CD163/heme oxygenase-1/p 38-MAPK dephosphorylation pathway and decreases capillary damage but not neutrophil recruitment in IL-1/LPS-insufflated rats. PLoS One. 2015;10(7):e0130764.
48.• Heyland D, Wischmeyer PE, Day AG, Group CCCT. Glutamine and antioxidants in critically ill patients. N Engl J Med. 2013;369(5):484–5. **Randomized controlled trial on ICU-patients in multi-organ failure. Glutamine supplementation increased all cause mortality at 28 days**
49. Dushianthan A, Cusack R, Grocott M. Immunonutrition for acute respiratory distress syndrome (ARDS) in adults (Protocol).Cochrane Database of Systematic Reviews 2016. [Systematic Review]. In press 2016.
50. Headland SE, Norling LV. The resolution of inflammation: principles and challenges. Semin Immunol. 2015;27(3):149–60.
51. Martindale RG, Warren MM, McClave SA. Does the use of specialized proresolving molecules in critical care offer a more focused approach to controlling inflammation than that of fish oils? Curr Opin Clin Nutr Metab Care. 2016;19(2):151–4.
52. McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr. 2016;40(2):159–211.
53. Patel JJ, Kha V, Butler D, Kozeniecki M, Martindale R, Allen K. Organ-specific nutrition: one for the history books or still an active player? Curr Surg Rep 2016; 4 (28).