The Role of ω-3 Fatty Acid Supplemented Parenteral Nutrition in Critical Illness in Adults: A Systematic Review and Meta-Analysis

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Objective: To determine whether the supplementation of parenteral nutrition with ω-3 fatty acids confers treatment benefits to critically ill adult patients.

Data Source: We performed computerized searches for relevant articles from 1996 to June 2011 on MEDLINE, EMBASE, and the Cochrane register of controlled trials and abstracts of scientific meetings from 2005 to 2011.

Study Selection: Randomized controlled trials of ω-3 fatty acid supplemented parenteral nutrition in critically ill adult patients admitted to the intensive therapy unit, given in addition to their routine care, compared with parenteral nutrition without ω-3 fatty acid supplementation.

Data Synthesis: Five fully published trials and three trials published in abstract form with 391 participants have been included. Overall trial quality was poor. Mortality data were pooled from eight studies with 391 participants. No differences were found with a risk ratio for death of 0.83 (95% confidence interval 0.57, 1.20; $p = 0.32$). Data for infectious complications were available from five studies with 337 participants. No differences were found, with a risk ratio for infection of 0.78 (95% confidence interval 0.43, 1.41; $p = 0.41$). Data for intensive therapy unit and hospital length of stay were available from six and three studies with 305 and 117 participants, respectively. With respect to intensive therapy unit length of stay, no differences were observed with a mean difference of 0.57 days in favor of the ω-3 fatty acid group (95% confidence interval −5.05, 3.90; $p = 0.80$). A significant reduction in hospital length of stay of 9.49 days (95% confidence interval −16.51, −2.47; $p = 0.008$) was observed for those receiving ω-3 fatty acid supplemented parenteral nutrition, but results were strongly influenced by one small study.

Conclusions: On the basis of this systematic review, it can be concluded that ω-3 fatty acid supplementation of parenteral nutrition does not improve mortality, infectious complications, and intensive therapy unit length of stay in comparison with standard parenteral nutrition. Although ω-3 fatty acids appear to reduce hospital length of stay, the poor methodology of the included studies and the absence of other outcome improvements mean they cannot be presently recommended. (*Crit Care Med* 2013; 41:307–316)

Key Words: critical illness; meta-analysis; parenteral nutrition; ω-3 fatty acids

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Dr. Palmer wrote the article, conducted a significant proportion of the literature search, reviewed primary studies, and extracted study data. Dr. Ho extracted study data. Olawunmi Ajibola contributed to the development of the search strategy and conducted a significant proportion of the literature search. Dr. Avenell had the original idea, developed the search strategy, conducted the search of the conference abstracts, extracted study data, reviewed primary studies, and was involved in the editing of the article.

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Critical illness can arise from a heterogeneous group of infectious and noninfectious etiologies. Despite this heterogeneity, many forms of critical illness are characterized by the systemic inflammatory response syndrome (SIRS). In this syndrome, the controlled response of the immune system is lost and uncontrolled release of cytokines leads to inappropriate systemic inflammation and widespread tissue injury (1). This results in the cardinal signs of inflammation appearing at sites distant to the original insult and with it, the clinical consequences of organ dysfunction (2). Later, SIRS is complicated by incongruous immune suppression, leaving patients vulnerable to sepsis.

Important secondary mediators of the SIRS include the eicosanoid fatty acids (FA), which are derived from the ω-6 FA,

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arachidonic acid. There is interest in the supplementation of parenteral lipid emulsions with ω-3 FA, as eicosanoids derived from ω-3 FA are less inflammatory, inactive, or even anti-inflammatory (3). Thus, ω-3 FA supplemented parenteral nutrition (PN), if required, could act to dampen the hyperinflammatory state that defines the SIRS, and improve patient outcomes (4).

Meta-analysis has suggested that ω-3 FA supplemented PN following elective surgery significantly reduced the risk of postoperative infections and shortened intensive therapy unit (ITU) and hospital length of stay (LOS) (5, 6). Hypothesis-formulating work by Heller and colleagues demonstrated a dose-response effect of ω-3 FA supplemented PN in a large cohort of critically ill patients, with significant reductions in mortality, antibiotic use, and hospital LOS (4, 7).

As such, an increasing number of randomized controlled trials (RCTs) looking at ω-3 FA supplemented PN in critically ill adult patients have been performed. Individually, however, they have been insufficiently powered to detect significant results. We therefore decided to systematically review the available evidence and perform a meta-analysis to examine the role of ω-3 FA supplemented PN in comparison with standard care PN in the critically ill adult patient.

METHODS

We undertook our review following a prespecified protocol (see Supplemental Digital Content 1, http://links.lww.com/CCM/A498).

Search Strategy

Full details of our search strategy can be found in the prespecified protocol (see Supplemental Digital Content 1, http://links.lww.com/CCM/A498). In summary, we performed computerized searches in MEDLINE (1996 to June 2011), EMBASE (1996 to June 2011), and the Cochrane register of controlled trials (June 2011). We searched the abstract proceedings of scientific meetings from 2005 to 2010 for the British Association for Parenteral and Enteral Nutrition, European Society for Clinical Nutrition and Metabolism, and the American Society for Parenteral and Enteral Nutrition.

Inclusion Criteria

Two (A.J.P., A.A.) of us screened all citations and classified them into primary studies, reviewed articles or other. We then retrieved and reviewed independently all primary studies. Primary studies were selected for inclusion if they met the following criteria:

1. Research design: RCT.
2. Population: critically ill adults admitted to the ITU.
3. Intervention: ω-3 FA supplemented PN compared with standard-care PN containing another lipid.
4. Primary outcomes: mortality, hospital LOS, and ITU LOS.
5. Secondary outcomes: new infections, length of mechanical ventilation, adverse events (as defined by the included studies), quality of life, and economic outcomes.

Study authors who evaluated the impact of ω-3 FA on surrogate end points (e.g., cytokine levels) were contacted, and studies included if they could provide relevant outcome data.

Exclusion Criteria

Studies were excluded if:

- ω-3 FA were one of several immune-modulating nutrients given together (given the difficulty in attributing the treatment effects to ω-3 FA).
- ω-3 FA were given for < 24 hrs duration.
- The control intervention did not contain any FA.

In addition, we also excluded studies on elective surgical patients routinely admitted to the ITU.

Dealing With Missing Data

In the case of studies in which data were missing or incomplete, we contacted study authors to request these data. Where the information was unavailable due to data loss or nonresponse, we reported the available results as stated in the trial report.

TABLE 1. Criteria Used to Assess Methodological Quality of the Included Studies

	0	1	2
1. Randomization		Not concealed or not sure	Concealed randomization
2. Blinding	Not blinded	Single blinded	Double blinded
3. Analysis	Other		Intention to treat
4. Patient selection	Cannot tell	Consecutive eligible patients	
5. Comparability of groups at baseline	Not sure	Comparable	
6. Follow-up	< 100%	100%	
7. Treatment protocol	Poorly described	Reproducibly prescribed	
8. Cointerventions[a]	Not described	Described but not equal or not sure	Well described and all equal
9. Outcomes	Not described	Partially described	Objectively described

For questions 1–3 and 8–9, possible scores were 0, 1, or 2, for questions 4–7 possible scores were 0 or 1.

[a]Extent to which antibiotics, ventilation, oxygen, and transfusions were applied equally across all groups.

Assessment of Risk of Bias

We assessed the risk of bias in all selected articles in duplicate, independently, using a system (see **Table 1**) previously described (8). Disagreement was resolved in pairs by consensus.

Analysis

Details of the included studies are presented in **Tables 2** and **3** with denominators, means, and standard deviations.

We combined data from studies to estimate the common risk ratio (RR) and associated 95% confidence intervals (CI) for death and risk of new infections. We estimated mean difference and 95% CI for LOS. We used the more conservative random effects model due to anticipated heterogeneity. Heterogeneity was expressed as the I^2 statistic where ≥ 50% indicates significant heterogeneity. A conservative analysis was undertaken with all participants randomized to the intervention as the denominator when the total number of participants was available. All meta-analyses are presented as Forest plots with Review Manager (RevMan), Version 5.1, used to perform all statistical analyses.

RESULTS

Literature Search

The literature search identified 12,270 potentially eligible reports. Three non-English language publications were identified: two fully published RCTs in Chinese and one in German published in abstract form only. All were translated, allowing them to be considered for detailed eligibility review. Review of the abstracts (A.J.P., A.A.) resulted in 71 articles for eligibility review.

Study Selection

The results of the eligibility review are shown in **Figure 1** using the flow diagram recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) group (9).

Fourteen RCTs appeared to address the role of ω-3 FA supplemented PN in critically ill adults. Five were excluded for further consideration: one RCT examined the role of ω-3 FA supplemented PN in the first 24 hrs only (10); one RCT was examining PN composed primarily of medium-chain triglycerides in comparison with one containing only long-chain triglycerides (11); and three authors (two abstracts and one fully published article) were unable to provide us with relevant outcome data (12–14). This left nine RCTs to be included in the primary analysis; six fully published RCTs (15–20) and three RCTs published in abstract form only (21–23). On closer inspection, two of the fully published RCTs by Wang *et al* (19, 20), despite the differing number of study participants, were the same trial. We attempted to contact the lead author of the studies by e-mail to clarify this issue but received no response. We have therefore included the data from these studies as it is presented in the two articles, respectively. More precisely, ITU and hospital LOS are presented for 40 patients as published in the Wang 2008 article; and mortality and new infections are presented for 56 patients as published in the Wang 2009 article. Authors of all the abstracts included in the review provided further outcome data following contact via e-mail.

Characteristics of Included Studies

Table 2 summarizes the characteristics of the included studies (inclusion and exclusion criteria, details of the participants, and type of publication providing the data). All were single-center trials published between 2003 and 2010. Three were in Germany (16–18), two in Russia (21, 23), and one each in China (19, 20), Portugal (15), and Romania (22).

Only one study (18) demonstrated the passage of trial participants through the RCT using the flow diagram recommended by the Consolidated Standards of Reporting Trials group (24).

One study recruited participants from a medical ITU and therefore with a range of conditions (18). The remaining trials recruited participants with sepsis (15–17), trauma (23), abdominal sepsis (21, 22), and severe acute pancreatitis (19, 20). Severity of illness at baseline was objectively defined by all studies using internationally recognized scoring systems.

Clear details of the exact nutritional content of the PN were provided by five studies (15, 18–22) and are shown in Table 3. Only two studies objectively defined the reason for starting patients on PN (15, 18). No study reported failure of enteral nutrition prior to commencement of PN. Nutritional protocols and any deviation from this protocol were absent from all but one report (18). Where reported, the length of time patients received PN was between 5 and 10 days. The use of enteral nutrition during the intervention period and the subsequent introduction of enteral feeding while receiving PN were only clearly reported by one study (18).

The dose of ω-3 FA provided to the intervention group was provided by all studies and varied from 0.08 g/kg/d to 0.2 g/kg/d (see Table 3).

Risk of Bias in Included Studies

All studies reported on randomization to treatment allocation but only four studies described proper allocation concealment (15,18–21). Blinding of both participants and treatment providers was reported by only two studies (18–20). Three studies reported blinding only the participants (15, 21, 22). Two studies were open label (16, 17) and one failed to provide sufficient details and was therefore assumed to be nonblinded (23).

Intention-to-treat analysis was carried out by three studies (16, 18–20). After recruitment one study excluded two participants who failed to start PN (15).

The application of cointerventions, for example, the extent to which antibiotics, ventilation, oxygen, and transfusions were applied, was only partially described by one of the included studies (17).

No trial reported following up participants beyond this hospital admission, patients' perceived quality of life after discharge, or economic outcomes.

TABLE 2. Characteristics of Included Studies

Study	Publication Type	Inclusion Criteria	Exclusion Criteria
Barbosa et al (15)	Full	Systemic inflammatory response syndrome or sepsis and predicted to need total parenteral nutrition (SAPS, multiple organ failure, excisional surgery)	No details given
Friesecke et al (18)	Full	Medical intensive therapy unit patients; not possible for enteral nutrition to provide 25% calories and anticipated to remain impossible for > 6 days	Coagulopathy; acute liver failure; decompensated liver cirrhosis; HTG (>4 mmol/L)
Mayer et al 2003[a]	Full	Septic patients (systemic inflammatory response syndrome and infection in previous 24 hrs) intolerant of enteral nutrition.	< 18 yrs; cancer; steroids in last 48 hrs; immunosupressive drugs; human immunodeficiency virus; neutropenia other than due to sepsis; irreversible underlying disease
Mayer et al 2003[b]	Full	Sepsis, severe sepsis and septic shock	< 18 yrs; cancer; steroids in last 48 hrs; immunosuppressive drugs; human immunodeficiency virus; neutropaenia other than due to sepsis; irreversible underlying disease
Wang et al (19)	Full	Admission with SAP of < 72 hrs duration.	Pregnancy; obesity; alcohol or drug abuse; HTG; hypertension; chronic liver disease; human immunodeficiency virus; hepatitis; severe cardiac or renal disease; insulin, steroid or COX inhibitors use in previous two weeks
Wang et al (20)	Full	Admission with SAP of < 72 hrs duration.	Pregnancy; obesity; alcohol or drug abuse; HTG; hypertension; chronic liver disease; human immunodeficiency virus; hepatitis; severe cardiac or renal disease; insulin, steroid or COX inhibitors use in previous 2/52
Grecu et al (22)	Abstract	Sepsis from abdominal source (peritonitis, abscess, postop fistula)	No details given
Ignatenko et al (23)	Abstract	Trauma patients	No details given
Leiderman et al (21)	Abstract	Patients with abdominal sepsis	No details given

FA = fatty acid, SAP = severe acute pancreatitis, HTG = hypertriglyceridemia; SOFA = Sequential Organ Failure Assessment score; SAPS = Simplified Acute Physiology score. (*continued*)

[a]SOFA score.

[b]SAPS.

Impact of ω-3 FA Supplemented PN on Mortality, Infections, and ITU and Hospital LOS

Figures 2, 3, 4, and **5** show the Forest plots for the RR and associated 95% CI for the effect of ω-3 supplemented PN on mortality, infections, and ITU and hospital LOS, respectively.

On the basis of the meta-analysis from eight studies with 391 participants, it was found that mortality was not different for patients receiving ω-3 FA supplemented PN (RR 0.83; 95% CI 0.57, 1.20; $p = 0.32$). The test for heterogeneity was nonsignificant ($I_2 = 0\%$; $p = 0.96$).

TABLE 2 (Continued).

No. Randomized		Sex Male/Female		Mean Age (SD)		Mean Acute Physiology and Chronic Health Evaluation II, SOFA, or SAPS II Score (SD)	
ω-3 FA	Control	ω-3 FA	Control	ω-3 FA	Control	ω-3 FA	Control
13	10	5/8	4/6	70 (7.2)	57 (15.8)	9.3 (3.2)[a]	8.9 (3.8)[a]
83	83	55/28	47/35	63 (13)	66 (11)	49 (18)[b]	54 (17)[b]
10	11	8/3	7/3	58.5 (11.1)	59.9 (14.0)	19.6 (4.7)	15.2 (6.6)
5	5	3/2	2/3	51 (no SD)	56.4 (no SD)	21	15
20	20	15/5	13/7	37 (9)	40 (10)	13 (4)	12 (3)
28	28	20/8	19/9	40 (13)	42 (11)	15(4)	13(4)
28	26	–	–	–	–	17.5 (5.5)	16.0 (6.3)
17	17	14/3	14/3	30.9 (10.2)	32.7 (12.9)	18.2 (3.6)	18.0 (4.8)
13	14	–	–	17.1 (4.3)	19.6 (3.6)	17.1 (4.3)	19.6 (3.6)

In meta-analysis of five studies with 337 participants, the frequency of new infections was not different for patients receiving ω-3 FA supplemented PN (RR 0.78; 95% CI 0.43, 1.41; $p = 0.41$). The test for heterogeneity was nonsignificant ($I_2 = 51\%$; $p = 0.09$).

On the basis of the meta-analysis of six studies with 305 participants, there was no difference in ITU LOS for patients receiving ω-3 FA supplemented PN (−0.57 days; 95% CI −5.05, 3.90; $p = 0.80$). The test for heterogeneity was nonsignificant ($I_2 = 49\%$; $p = 0.08$).

TABLE 3. Composition of Parenteral Nutrition Used in the Included Studies

	Total Energy Intake (kcal/kg/d)		Amino Acid Intake (g/kg/d)		Glucose Intake (g/kg/d)		Total Lipid Intake (g/kg/d)		Ω-3 FA (g/kg/d)		Control Emulsion
Study	ω-3 FA	Control	ω-3 FA	Control	ω-3 FA	Control	ω-3 FA	Control	Brand	ω-3 FA	Brand
Barbosa et al (15)	29.3	25.3	1.17	1.22	4.1	3.1	0.91	0.9	Lipoplus	0.09	Nutriflex lipid special[a]
Friesecke et al (18)	22.2	21.6	1.1	1.1	2.3	2.2	0.91	0.93	Omegaven	0.1	Lipofundin[a]
Mayer et al 2003a (16)	Unclear	Unclear	0.7	0.7	3	3	Unclear	Unclear	Omegaven	0.2	Lipoven
Mayer et al 2003b (17)	Unclear	Unclear	0.7	0.7	3	3	Unclear	Unclear	Omegaven	0.2	Lipoven
Wang et al (19)	28	28	1.1	1.1	2.8	2.8	0.96	0.96	Omegaven	0.19	Lipoven
Wang et al (20)	28 25	28 25	1.1	1.1	2.8	2.8	0.96	0.96	Omegaven	0.19	Lipoven Intralipid
Grecu et al (22)	25	25	1.0–1.2	1.0–1.2	2.0–2.5	2.0–2.5	1.4	1.4	Omegaven	0.15–0.2	
Ignatenko et al (23)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Leiderman et al (21)	28–30	28–30	0.8–1.0	0.8–1.0	3–4.5	3–4.5	0.8–1.0	0.8–1.0	Unclear	0.08–0.15	Unclear[a]

FA = fatty acid; MCT = medium chain triglycerides; LCT = long chain triglycerides.
[a]MCT/LCT mixture.

On the basis of the meta-analysis of three studies with 117 participants, there was a significant reduction of 9.49 days in hospital LOS for patients receiving ω-3 FA supplemented PN (95% CI –16.51, 2.47; $p = 0.008$). The test for heterogeneity was nonsignificant ($I_2 = 0\%$; $p = 0.37$).

Impact of ω-3 Supplemented PN on Length of Mechanical Ventilation and Adverse Events

No significant differences in the number of days on a ventilator between the ω-3 FA and control group were reported by Barbosa et al (10 [SD 14.4] vs. 11 [SD 12.6]), Friesecke et al (22.8 [SD 22.9] vs. 20.5 [SD 19]), and Ignatenko et al (12.5 [SD 7.7] vs. 13 [3.1]). One of the studies conducted by Mayer and colleagues reported a longer ventilator time ($p = 0.007$) in those infused with the control emulsion.

DISCUSSION

We investigated the effect of ω-3 FA supplemented PN in the critically ill adult patient on clinically meaningful outcomes. We found no statistically significant results with respect to mortality, infections, and ITU LOS. However, we did find weak evidence that ω-3 FA supplemented PN shortens the hospital LOS.

The evidence for this meta-analysis is weak for a number of reasons. First, relative to other meta-analyses, there were few trials involving ω-3 FA supplemented PN in critically ill adults. Furthermore, these studies were small, single-center studies, with six of the eight trials containing < 50 participants. In addition, the availability of clinically meaningful outcome data was limited. Indeed, our finding of a significant reduction for hospital LOS was based on three studies, totalling 117 participants; uncommon events in a small number of studies are more likely to produce erroneous and/or unstable estimates.

Second, there is a high risk of bias as a result of missing data and the selective reporting of outcomes by the included trials. This is a particularly important point with respect to the duplicate publications by Wang *et al*. The publication in 2008 provides ITU and hospital LOS data; however, this is absent from the report in 2009, which also includes an additional 16 patients. We attempted to clarify this issue with the corresponding author by e-mail but received no response. Given that these data are included in our only significant finding, we urge readers to be vigilant in their interpretation of this result.

Our significant finding for hospital LOS is worth further consideration. As the weight attributed to each study is determined by the precision of its estimate of effect, which is equal to the inverse of the variance, the study by Grecu *et al* ends up contributing considerably more due to the huge relative variance of the other included studies. This is important as the study by Grecu *et al*

pertains to the only significant difference. The main influence is the considerably larger standard deviation in the control group compared with the intervention group in the study by Grecu *et al*, implying that there are cases in the control group with very long LOS dragging the mean upward. As such, we would further reiterate our recommendation that this result be treated with extreme caution.

Other features of the poor methodological quality of the trials are also likely to have biased our findings. Appropriate blinding and clear reporting of allocation concealment are important as failure has been shown to exaggerate treatment effects by up to 26% and 40%, respectively (25). Intention to treat is important as it preserves randomization, thereby reducing bias, maintaining external validity, and making the results generalizable. In addition, no study reported long term follow-up, failing to account for the prolonged recovery of patients from critical illness.

Individually, the included studies were underpowered to demonstrate a significant effect of ω-3 FA supplemented PN in the critically ill adult patient on outcomes. The advantage of a meta-analysis is that it provides a higher statistical power to detect a significant effect than is possible with any one individual study. However, even the aggregation of insufficiently powered studies may be at the limit to detect a significant result. Given that the upper limit of our 95% CI for mortality was > 1 , we cannot conclude with reasonable confidence that ω-3 FA supplemented PN in the critically ill adult patient is safe (i.e., exclude harm). Given that the conclusions drawn from any meta-analysis can only be as strong as its constituent parts, our work should be viewed as hypothesis generating only.

Meta-analysis of ω-3 FA supplemented PN in patients undergoing elective surgery has suggested benefit, with reductions in the frequency of postoperative infections and ITU and hospital LOS (5) attributed to reductions in the production of pro-inflammatory eicosanoids and cytokines (26). Such effects have also been observed in critically ill patients, with suppression of cytokines by endotoxin-stimulated mononuclear cells *ex vivo* (17). Given that critically ill individuals and patients undergoing elective surgery both share a SIRS response, it is notable that we failed to show similar benefit. However, dichotomous effects in these two patient groups should perhaps not be unexpected, with the immune response of patients undergoing elective surgery differing from that of critically ill subjects. In critical illness there is a dramatic overamplification of the inflammatory

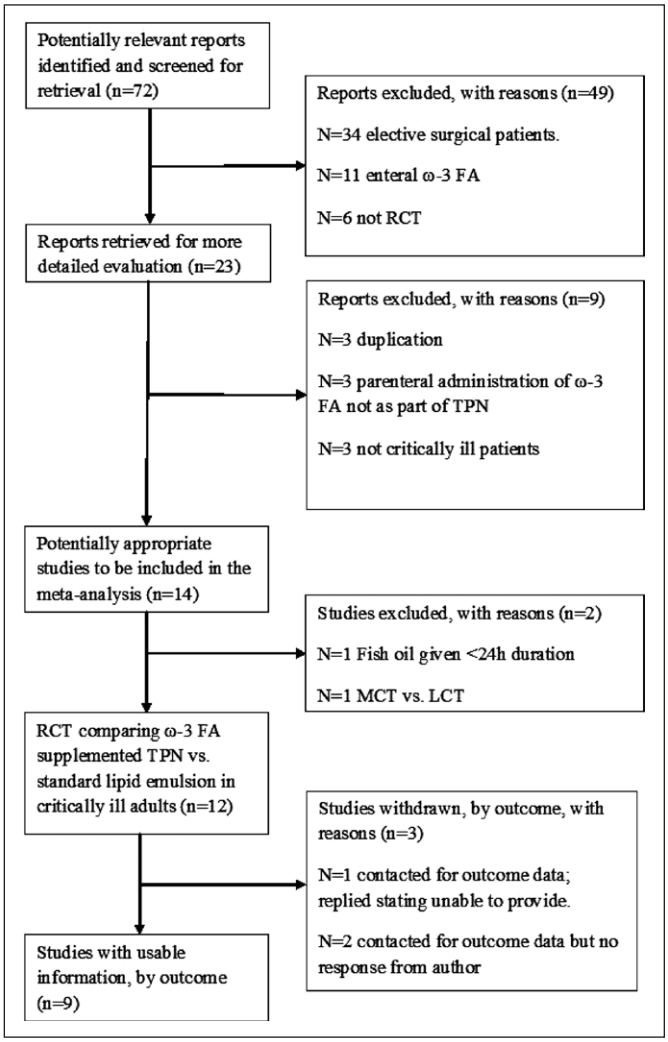

Figure 1. Results of the literature review. RCT = randomized controlled trials; FA = fatty acids; TPN = total parenteral nutrition; MCT = medium chain triglycerides; LCT = long chain triglycerides.

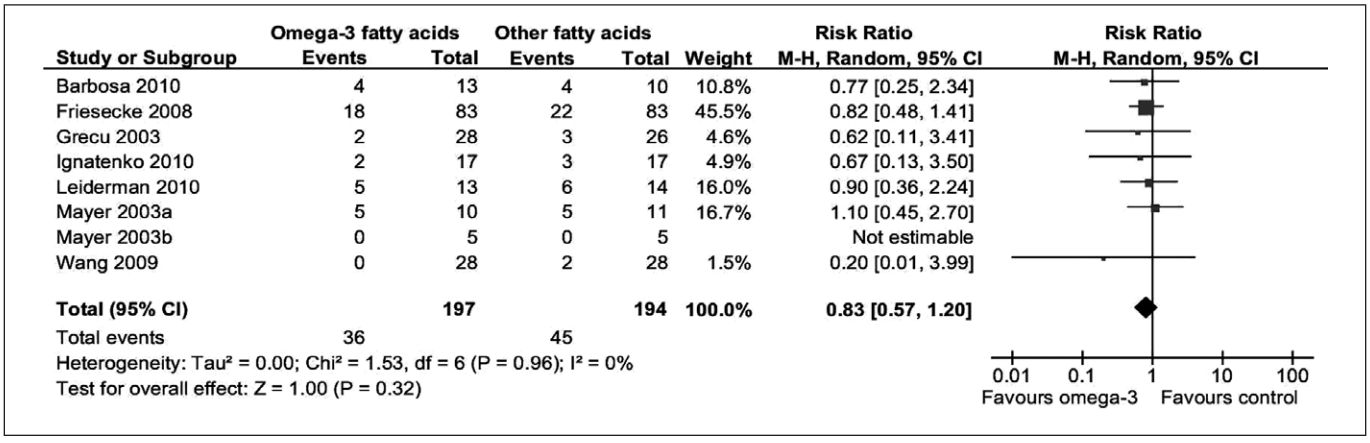

Figure 2. Impact of ω-3 fatty acid supplemented parenteral nutrition on mortality. MH = Mantel-Haenszel; CI = confidence interval.

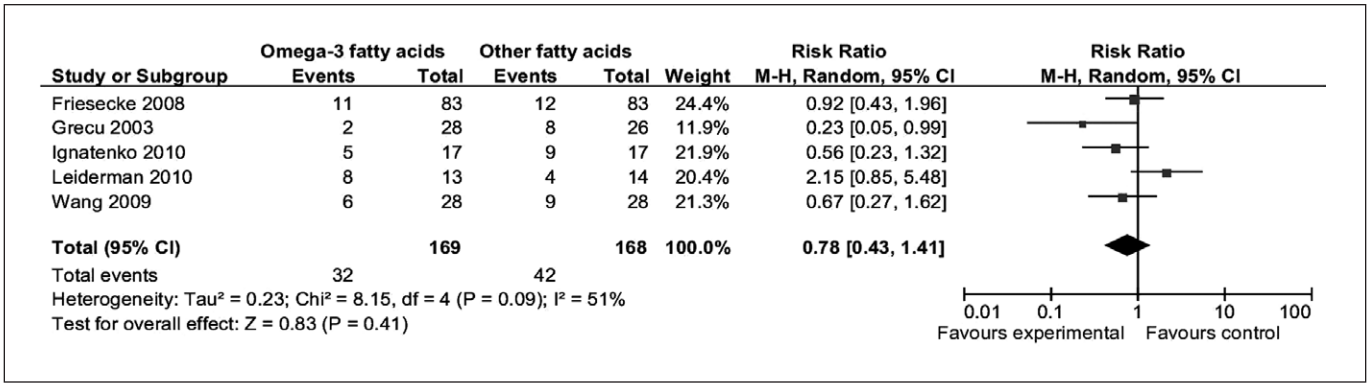

Figure 3. Impact of ω-3 fatty acid supplemented parenteral nutrition on new infections. MH = Mantel-Haenszel; CI = confidence interval.

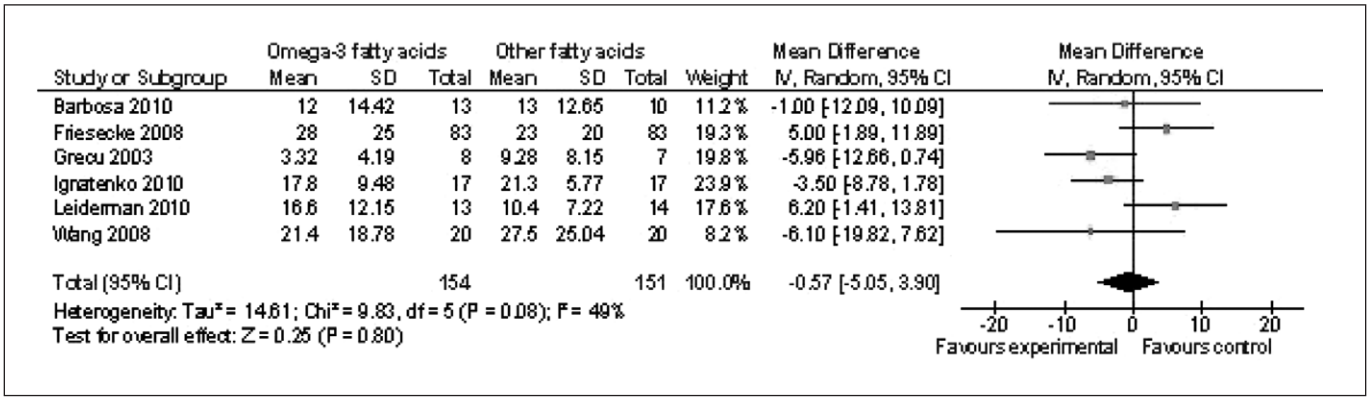

Figure 4. Impact of ω-3 fatty acid supplemented parenteral nutrition on length of intensive therapy unit stay. IV = inverse variance; CI = confidence interval.

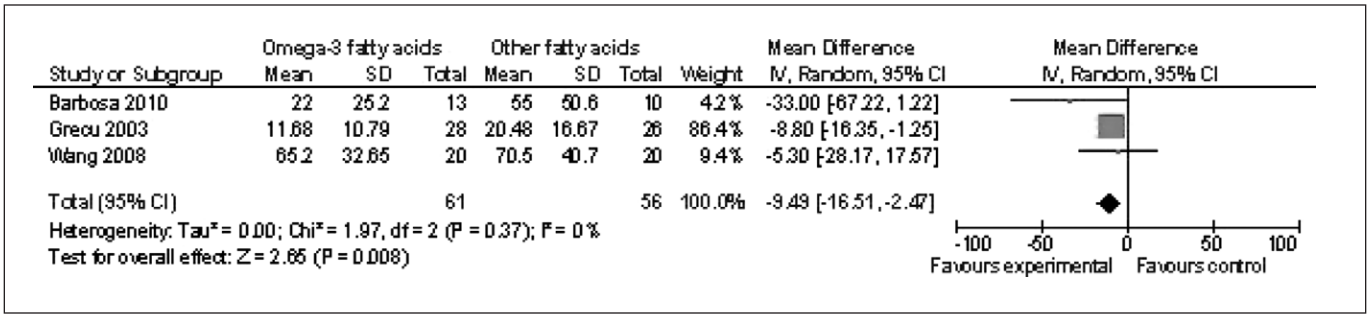

Figure 5. Impact of ω-3 fatty acid supplemented parenteral nutrition on length of hospital stay. IV = inverse variance; CI = confidence interval.

response, together with cellular immune dysfunction; after surgery patients experience less cytokine activation but some suppression of cell-mediated immunity (27). It is for this reason that we also decided to exclude trials of elective surgical patients routinely admitted to the ITU.

Failure to show benefit may be an issue of timing. A retrospective analysis of patients undergoing abdominal surgery demonstrated lower mortality rates in those who received preoperative ω-3 FA supplemented PN; this was not found in those who received only postoperative supplementation (28). This suggests the immune-modulating functions of ω-3 FA is greatest at the beginning of the SIRS response. As five of the included studies recruited patients with sepsis/septic shock, it is worth noting that the prompt administration of interventions in sepsis is crucial in improving outcomes (29). Thus if the "window of opportunity has passed" the ability of ω-3 FA to clinically alter the SIRS response in critical illness may be limited as the excessive cytokine production that characterizes this syndrome is already established.

The dose of ω-3 FA is also worth some consideration. Work on a large cohort of critically ill patients by Heller *et al* demonstrated a significantly lower rate of infection and ITU and hospital LOS in those patients receiving ≥ 0.05 g/kg/d of ω-3 FA (4). Furthermore, mortality was significantly reduced with doses > 0.1 g/kg/d. Given that the studies included in this review used comparable doses of ω-3 FA, why have we not observed clinical

benefit? First, the work by Heller *et al* must be interpreted with caution due to the lack of randomization and blinding. However, a key problem is the use of the original Simplified Acute Physiology Score II database as a "historical control" group, as the application of Simplified Acute Physiology Score II to more contemporary data may overpredict mortality (30, 31).

Another salient issue is the choice of lipid emulsion used as the control by the studies. A number of studies used a control lipid emulsion that was lower in ω-6 FA, due to the presence of medium-chain triglycerides. This resulted in the average daily dose of ω-6 FA being reduced, potentially resulting in a control formula that was less inflammatory. This raises the possibility that PNs supplemented with ω-3 FA are not in fact immunomodulating, but less inflammatory. Given that attempts to manipulate the immune system in sepsis/disease with severe SIRS have had little success, we would argue that one needs to be extremely cautious in attempting to alter the inflammatory response of critically ill individuals with such large doses of ω-3 FA. Indeed, the presence or absence of potential complications, for example bleeding, were infrequently reported. If benefits do exist in lowering the ω-6 FA component of lipid emulsions, and it does make biological sense, then if the same benefit can be obtained by substituting a proportion of the ω-6 FA with immunologically inert medium-chain triglycerides, then the need to use large doses of ω-3 FA is questionable. To our knowledge the exact requirement for ω-3 FA in critical illness is unknown. Given that in ischemic heart disease most, if not all, benefit in primary prevention is obtained by consuming 250 to 500 mg of ω-3 FA per day (32), why have the included studies used such large doses? Future work needs to address these issues, namely: the optimal requirement for ω-3 FA in critical illness; the risk of hemorrhagic complications; and the potential benefits of lipid emulsions rich in medium-chain triglycerides and/or oleic acid over pure soya bean emulsions.

Recently, the benefits of enteral feeds containing ω-3 FA, γ-linolenic acid, and antioxidants in the critically ill patient have been questioned. Meta-analysis of these formulae in adults with acute lung injury had suggested a reduction in mortality, mechanical ventilation, and a shorter ITU LOS (33). As with the trials included in this review, the trials included in the meta-analysis were small and potentially prone to bias. It is therefore noteworthy that the OMEGA study was stopped early because of a significant increase in mortality, time on a ventilator, longer duration of nonpulmonary organ failure, and ITU LOS (34). Although it is difficult to attribute these effects to ω-3 FA, this study highlights the problem of relying on meta-analyses of small, underpowered, and methodologically poor RCTs to make evidence-based recommendations.

A strength of our meta-analysis was the comprehensive literature search we undertook. We identified three non-English language RCTs, reducing the possibility of language bias. In addition, we included three conference abstracts of unpublished studies, reducing the possibility of publication bias. We also identified two further conference abstracts but were unable to include these in our meta-analysis as both reported surrogate end points. Contact with leading experts did not yield any unpublished studies.

The main limitation of the study is the heterogeneity of the patient groups. We had originally planned to perform subgroup analyses to explore studies with better methodology to those with lesser methodology and studies evaluating higher ω-3 FA doses compared with those with lower ω-3 FA doses; however, there were insufficient data. We acknowledge that studying an anti-inflammatory intervention in a broad spectrum of critically ill patients increases the likelihood of negative findings. Ideally, we would have performed further subgroup analyses for specific pathologies (e.g., sepsis) in order to try and limit heterogeneity and potential confounding factors, but again this was not possible due to there being insufficient data. At the same time however, it could be argued that the heterogeneous nature of the study population means that our results could be considered generalizable to ITU populations, as has been suggested in other meta-analyses of nutritional interventions in critically ill patients (35). The considerable statistical heterogeneity we observed for risk of new infection and ITU LOS, although failing to reach statistical significance, reflects the small nature of the included studies, with small studies more susceptible to one outlying observation, which affects the mean and variance, as well as cultural differences in defining critical illness.

In conclusion, there is insufficient evidence to recommend the supplementation of PN in critically ill adult patients with ω-3 FA except as an intervention being investigated in the setting of a RCT. Although ω-3 FA appear to reduce hospital LOS, the poor methodology of the included studies and the absence of other outcome improvements means that this result must be interpreted with caution. In short large, high-quality RCTs are required.

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