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Parenteral Fish Oil Lipid Emulsions in the Critically Ill: a Systematic Review and Meta-analysis

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Abstract

Introduction—Polyunsaturated series-3 fatty acids (PUFAs n-3) contained in fish oils (FO) posess major anti-inflammatory, anti-oxidant, and immunological properties which could be beneficial during critical illness. We hypothesized that parenteral FO containing emulsions may improve clinical outcomes in the critically ill.

Methods—We searched computerized databases from 1980 to 2012. We included randomized controlled trials (RCTs) conducted in critically ill adults patients that evaluated FO containing emulsions, either in the context of parenteral nutrition (PN) or enteral nutrition (EN) fed patients.

Results—A total of 6 RCTs (n=390 patients) were included; the mean methodological score of all trials was 10 (range: 6–13). When the results of these studies were aggregated, FO containing emulsions were associated with with a trend towards a reduction in mortality (risk ratio RR= 0.71, 95% confidence intervals CI 0.49, 1.04, P=0.08, heterogeneity I^2=0%) and a tendency to reduce the duration of mechanical ventilation (weighted mean difference in days [WMD] −1.41, 95% CI −3.43, 0.61, P=0.17). However, this strategy had no effect on infections (RR= 0.76, 95% CI 0.42, 1.36, P= 0.35) and intensive care unit (ICU) length of stay (LOS) (WMD −0.46, 95% CI −4.87, 3.95, P=0.84, heterogeneity I^2=75%).

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Competing interests

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Conclusion—FO containing lipid emulsions may be able to decrease mortality and ventilation days in the critically ill. However, because of the paucity of clinical data, there is inadequate evidence to recommend the routine use of parenteral FO. Large, rigorously designed, RCTs are required to elucidate the efficacy of parenteral FO in the critically ill.

Keywords

fish oils; lipid emulsions; critically ill; meta-analyses

Introduction

Parenteral lipid emulsions (LE) are a dense source of energy and a source of essential fatty acids. As such, they lend themselves into strategic inclusion into parenteral nutrition (PN) formulation to avoid metabolic complications of glucose overfeeding [1]. Furthermore, the fatty acids composing LE are active with complex immunologic properties influencing biochemical pathways and signal transduction which is of particular significance during critical illness [2,3]. LE commonly used in critically ill patients are typically rich in long-chain triglycerides (LCT), especially linoleic acid (polyunsaturated series 6 fatty acid, PUFA n-6, 18:2 n-6) [4]. Nonetheless, over the last decade different alternative oil-based LE or “soy-bean sparing” strategies including FO, olive oil, and medium-chain triglycerides (MCT) have been developed [5].

The current literature suggests that intravenous soybean oil may adversely affect systemic inflammation, immune status and clinical outcomes [6]. In severe sepsis and trauma, parenteral LCT, derived from soybean oil, might promote production of pro-inflammatory eicosanoids and increase oxidative stress [7,8]. In 1998, a meta-analysis of PN suggested that inclusion of soybean oil-based lipid emulsions might be detrimental, at least in the most seriously ill patients [9]. Immunomodulation with the PUFAs n-3, eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA), is recognized for the ability to modify leukocyte activity, down-regulate expression of nuclear factor-kappa B (NF-κB), peroxisome proliferator-activated receptor γ (PPAR-γ), intracellular adhesion molecule 1 (ICAM-1) and E-selectin, and to decrease cytokine production [10]. In fact, intravenous infusion of FO leads to a rapid incorporation of n-3 fatty acids in leukocyte cell membrane phospholipids, increasing the ratio of n-3 to n-6 fatty acids in different cell types [11], and displacing n-6 fatty acids from the cell membranes of immune cells, which is a major cause of modulating systemic inflammation [12].

However, clinical trials using parenteral FO have provided controversial results [13]. Because available research provides conflicting data on the effects of parenteral FO in critically ill patients, their influence on inflammatory processes and clinical outcomes remains unclear. In 2009, the Canadian guidelines [14] concluded that there were insufficient data to make a recommendation about FO containing emulsions. Nevertheless, the European Society in Parenteral and Enteral Nutrition (ESPEN) [15] suggest that the optimal PN regimen should include FO and concludes that FO-enriched lipid emulsions probably decrease length of stay in critically ill patients (Grade B) [15]. Over the past few years, there have been published several trials of parenteral FO containing LE in the

critically ill. Some of these trials have been included in prior meta-analyses, but these meta-analysis included trials of both elective surgical patients and critically ill patients [16,17] and also a more recent meta-analysis has included trials that reported only biochemical and immunologic outcomes [18]. To inform clinical recommendations pertinent to the critically ill, studies of elective surgery and critically ill patients should not be combined as the treatment effects of the nutritional strategies may differ [19].

The purpose of the current study was to provide an up-to-date systematic review and meta-analysis on all RCTs of FO containing LE on relevant clinical outcomes in the critically ill.

Methods

Study Identification

We conducted a systematic review of the published literature to identify all relevant clinical trials using text word or MeSH headings containing “randomized,” “blind,” “clinical trial,” “nutritional support”, “parenteral nutrition”, “omega-3 fatty acids”, “fish oils”, “lipid emulsions”, “critical illness” and “critically ill”. To locate these articles we performed computerized searches on MEDLINE, EMBASE, CINAHL the Cochrane Controlled Trials Register, and the Cochrane Database of Systematic Reviews from 1980 to May 2012. We also searched our personal files and comprehensive review articles were searched for additional original studies. No language restrictions were placed on the searches. Abstracts from scientific meetings had been accepted for inclusion into this systematic review if a copy of the manuscript was available to complete the data abstraction.

Study Selection Criteria

We only included original studies if they met the following inclusion criteria: a) study design: randomized clinical, parallel group, controlled trials (RCTs); b) population: critically ill adult patients (>18 years of age); c) intervention: parenteral FO LE versus placebo (either via enteral, parenteral, or both); d) study outcomes: pre-specified outcomes included one of the following: mortality, intensive care unit (ICU) and hospital LOS, infectious complications, and other clinically important complications. We excluded the clinical studies that reported only biochemical, metabolic, immunologic or nutritional outcomes. Furthermore, we excluded those trials performed in elective surgery patients cared for in an ICU. Critically ill patients were defined as patients admitted to an ICU who had an urgent or life-threatening complication (high baseline mortality rate ≥5%) to distinguish them from patients with elective surgery who are also cared for in some ICUs but have a low baseline mortality rate (<5%), low requirement for mechanical ventilation, and low incidence of infections including ICU acquired pneumonia

All original studies were abstracted in duplicate, independently by two reviewers, using a data abstraction form with a scoring system, which has been used previously. Disagreement in the individual scores of each of the categories was resolved by consensus between both reviewers. We attempted to contact the authors of included studies and requested additional information not contained in published articles. We scored the methodological quality of individual trials considering the following key features of high-quality studies: a) extent to

which randomization was concealed, b) blinding, c) analysis was based on the intention-to-treat (ITT) principle, d) comparability of groups at baseline, e) extent of follow-up, f) description of treatment protocol and co-interventions, and g) definition of clinical outcomes. Each individual study was scored from 0 to 14. We designated as a level 1 study if all of the following criteria are fulfilled: concealed randomization, blinded outcome adjudication and an intention to treat analysis. Meanwhile, a study was considered as level 2, if any one of the above characteristics was unfulfilled.

Data synthesis

The primary outcome of the systematic review was overall mortality. From all studies, we combined hospital mortality where reported (specified or assumed to be hospital if not specified). If hospital mortality was not reported, we used ICU mortality or if ICU mortality not reported, we used 28-day mortality. Secondary outcomes included infections, and ICU and hospital LOS (when reported). We included RCTs conducted in critically ill adults patients that evaluated parenteral FO containing emulsions, either in the context of parenteral nutrition (PN) or enteral nutrition (EN) fed patients. Given that PN based strategies contained a non-fish oil based emulsion and the EN based strategies did not, we did sensitivity analysis excluding the studies of EN based strategies.

We used definitions of infections as defined by the authors in their original papers. If studies had more than one experimental intervention, these were each considered separately. We combined data from all trials to estimate the pooled risk ratio (RR) with 95% confidence intervals for death and infectious complications and overall weighted mean difference (WMD) with 95% confidence intervals for LOS data. All analyses, except the test for asymmetry, were conducted using RevMan 5.1 [20]. Pooled RRs were calculated using the Mantel-Haenszel estimator and WMDs were estimated by the inverse variance approach. The random effects model of DerSimonian and Laird was used to estimate variances for the Mantel-Haenszel and inverse variance estimators [21]. RRs are undefined and excluded for studies with no event in either arm. When possible, studies were aggregated on an intention-to treat basis. The presence of heterogeneity was tested by a weighted Mantel-Haenszel chi-square test and quantified by the I^2 statistic as implemented in RevMan. The possibility of publication bias was assessed by generating funnel plots and testing asymmetry of outcomes using methods proposed by Rucker and colleagues [22]. We considered $P< 0.05$ to be statistically significant and $P< 0.20$ as indicator of trend.

Results

Study identification and selection

A total of 44 relevant citations were identified from the search of computerized bibliographic databases and a review of reference lists from related articles. Of these, we excluded 38 due to the following reasons: 22 trials [23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44] did not include ICU patients (mostly elective surgery and cancer patients), 12 trials [45,46,47,48,49,50,51,52,53,54,55,56] did not evaluate clinically important outcomes; 2 trials [57,58] were published as abstracts and we were unable to obtain the data from the

author to complete our data abstraction process;1 trial [59] was conducted in a pediatric population; 1 trial [4] had a short duration of intervention (12 hours of lipid emulsion infusion during the first day); 1 trial included patients with poisoning and not representative of ICU patients [60], and one paper was a systematic review [16]. In the end, 6 RCTs [61,62,63,64,65,66] enrolling a total of 390 patients met the inclusion criteria and were included in this systematic review (see Tables 1 to 4). Among these trials, we found five level 1 studies [62,63,65,66,67] and one level 2 study [64]. Furthermore, among RCTs in PN fed patients, one trial compared LCT + MCT + FO emulsion to a MCT + LCT emulsion [66], 3 trials compared a FO containing emulsion mixed with LCT or LCT/MCT to a LCT or LCT+MCT mixture [62–64]. Meanwhile, among the two RCTs evaluating EN fed patients, one trial compared supplementation with intravenous FO to normal saline [65] and the other trial compared supplementation of EN with FO containing emulsion to standard EN alone [67].

The authors reached 100% agreement for inclusion of relevant trials in this review. The mean methodological score of all trials was 10 (range 9–12). Randomization was concealed in 5/6 (83%) trials, ITT analysis was performed in 6/6 (100%) trials and 5/6 (83%) trials were double blinded.

Meta-Analyses of Primary Outcome

Overall effect on Mortality—When the results of 5 RCTs [62,63,64,66,67] that evaluated mortality as one of the outcomes were statistically aggregated, fish oil containing lipid emulsions were associated with a trend towards a reduction in mortality (risk ratio [RR]= 0.71, 95 % confidence intervals [CI] 0.49–1.04, P= 0.08; see Figure 1). The test for heterogeneity was not significant (P= 0.89, I^2 = 0%). When a sensitivity analysis was done without the Gupta [67] study, a similar point estimate was observed but the 95% CI were considerably wider (RR 0.76, 95% CI 0.48, 1.21, P = 0.25, heterogeneity I^2=0%).

Secondary outcomes

Overall effect on infectious complications—When the data from 3 RCTs [64–66] of fish oil emulsions in PN fed patients which reported overall infections were aggregated, fish oil containing emulsion strategies had no effect in reducing infectious complications (RR= 0.76, 95% CI 0.42–1.36, P= 0.35, heterogeneity I^2 = 0%) (Figure 2).

Overall effect on ICU length of stay—When the data from the five RCTs [62,63,65–67] that reported on this outcome were aggregated (including the studies of EN fed patients), no effect on ICU LOS was observed (WMD −0.46, 95% CI −4.87, 3.95, p = 0.84, heterogeneity I^2=75%). Similarly, when a sensitivity analysis was done excluding the studies of EN fed patients [65,67], no effect on ICU LOS was observed (WMD −1.13, 95% CI −8.96, 6.69, P= 0.78; heterogeneity I^2 = 78%).

Overall effect on ventilator days—When the 5 RCTs [62,63,65–67] reporting ventilator days were aggregated, fish oil containing emulsions showed a trend towards reduction in the duration of mechanical ventilation days (WMD −1.41, 95% CI −3.43, 0.61, P=0.17); heterogeneity was not significant, P= 0.59, I^2 = 0%) (Figure 3). When a sensitivity

analysis excluding the 2 EN fed trials [65,67] was done there was still a trend towards a reduction in the duration of mechanical ventilation (WMD −1.81, 95% CI −3.98, 0.36, P=0.10; heterogeneity I^2= 0%).

Risk of Publication Bias in Included Trials—There was no indication that publication bias accounts for the effects of parenteral FO based LEs with respect to mortality (n= 5 RCTs, P= 0.55), infections (n= 3 RCTs, P= 0.39); ICU LOS (n= 5 RCTs, P= 0.30), and mechanical ventilation days (n= 5 RCTs, P= 0.28):

Discussion

Critical illness is characterized by hyperinflammation, immune dysfunction and multiple organ failure. In this context, anti-inflammatory and immunomodulatory effects of FO containing LE may represent an important therapeutic option for critically ill SIRS patients. Nonetheless, according to current evidence FO administration in the critically ill is still a subject of debate. Therefore, we have systematically reviewed six eligible RCTs [62–67] in ICU patients for evaluating the effects of parenteral FO-based strategies either in the context of PN or EN fed patients. In this meta-analysis we found that FO containing emulsions may be associated with a tendency to reduce mortality and ventilation days in the critically ill. At the same time, we did not observe any effect on infectious complications or the duration of ICU LOS. While no major benefit can be confirmed by our analysis, we observe no harm conferred by FO containing emulsions and given that the upper end of the confidence limit on the effect on mortality is 1.04, the probability of increased mortality is extremely small.

Our systematic review is the most updated and pertinent to critically ill patients as it contains only RCTs evaluating relevant clinical outcomes in the critically ill. Unfortunately, with the exception of one trial [63], most trials included in this systematic review were relatively small studies with a number of patients lower than 100, and thus inadequate to detect clinically important treatment effect of FO containing emulsions on mortality. However, the advantage of meta-analytic techniques is that it can combine across studies to gain a more precise effect of treatment effect. Furthermore, since the mortality effect seems to be greater than the effect on infectious complications, it is plausible that the mortality effect could be mediated by different mechanisms other than by reducing infection, although this is only a postulate and not supported by our data. According to our analysis, there is no indication of publication bias. However, the sample size was small because 3 to 5 RCTs were included in the analyses for each outcome; therefore, we should interpret these results with cautions because big p values may be due to lack of power.

Van der Meij et al [16] published the results of a systematic review of FO in cancer, surgery, and critical care on clinical effects, incorporation, and washout of oral or enteral compared with parenteral supplementation. In their report of critically ill patients, when the authors evaluated the effects of four RCTs supplementing FO containing emulsions in PN, they concluded that n-3 PUFAs did not demonstrate any beneficial effects on clinical outcomes. However, our systematic review is not comparable with the van der Meij [16] study in so far as they included RCTs which we excluded due to a short duration of intervention (12 hours) as well as another trial performed in elective surgical patients.

In another meta-analysis including RCTs performed with elective surgery and critically ill patients, Pradelli et al [17] demonstrated that parenteral FO enriched LE were associated with a statistically and clinically significant reduction in infections (RR =0.61; 0.45, 0.84) and the LOS, both in the ICU (−1.92; −3.27, −0.58) and in hospital (−3.29; −5.13, −1.45) [17]. Notwithstanding, these results cannot be compared with our findings because our meta-analysis is the first and more pertinent to critically ill patients, as it contains only trials evaluating relevant clinical outcomes for intensive care.

“More recently, Palmer et al [18] in another meta-analysis on the role of ω-3 FA supplemented PN in critically ill adults, concluded that parenteral FO does not improve mortality, infectious complications, and ICU LOS in comparison with standard PN. These results are slightly different from our findings. In fact, we found a trend to reduce mortality and our other major finding was a tendency toward a reduction in mechanical ventilation days. Furthermore, we believe that these differences were largely due to the difference in the papers included in the different reviews. In fact, Palmer et al [18] included trials that did not evaluate relevant clinical outcomes in the critically ill. In addition, they include both papers published by Wang et al in 2008 [37] and 2009 [63]. However, we have decided to include the study published in 2009 [63] and exclude the previous study because it did not include ICU patients and did not report on relevant clinical outcomes. Similarly, with respect to the Mayer study [50], we excluded it because they did not report on clinically important outcomes.

Moreover, we excluded two unpublished studies Liderman et al [57] and Ignatenko et al [58], due to both are published as abstracts and we have not had any response from the reviewers, which was needed to complete our data abstraction form. Finally, we included two trials on parenteral FO based emulsions performed in enterally fed patients which were excluded in the Palmer systematic review.

Nonetheless, although papers included in both systematic reviews are different, current evidence derived from both meta-analyses conclude that there is insufficient evidence to recommend the supplementation of PN in critically ill adult patients with ω-3 FA.

The parenteral route may be a more reliable strategy to provide FO than the enteral route due to better bioavailability, but the optimal dose and timing are still unknown. Most trials supplementing parenteral FO have used between 0.1 and 0.2 g/kg/d FO and lipids were started within the first 24–48 hours after admission to the ICU. A daily dose of 0.1 and 0.2 g/kg/d has been supported by the analysis of a database in 661 critically ill patients [67], including patients with severe sepsis, where best outcome data were found in this dose range. Furthermore, this dose would be able to decrease available arachidonic acid (derived from omega-6 fatty acids) and produce balanced pro-/anti-inflammatory effects influencing physiological endpoints [68].

The anti-inflammatory properties of FO have been described and exhaustively studied in many experimental and clinical studies [69]. The involved mechanisms include the following: a) inhibition of the PUFAs n-3 on the toll like receptor (TLR)-nuclear factor kappa-B (NF-κB) axis, controlling gene expression and thus down-regulating the synthesis

of pro-inflammatory cytokines [70]; b) synthesis of DHA-derived lipid mediators such as Resolvin D1 and Protectin D1 which are able to attenuate neutrophil migration [71] and, finally c) modulation of vagal tone restoring parasympathetic activity which demonstrated potential anti-inflammatory effects [72].

Clinical trials included in our systematic review have evaluated mechanistic effects of parenteral FO. In fact, Barbosa et al [66] demonstrated significant reduction in plasma interleukin (IL-6) and interleukin 10 (IL-10) levels in the FO group ($P < 0.001$). Similarly, Wang et al [64] in severe acute pancreatitis patients demonstrated an increase in the IL-10 levels and HLA-DR expression, and concomitantly a significant reduction in C- reactive protein levels. In contrast, Friesecke et al [63] reported that administration of a mixed MCT/LCT/FO LE in critically ill SIRS patients had no effect on inflammatory markers such as IL-6 and monocyte HLA-DR expression.

Meanwhile, in two randomized, open label studies in septic patients Mayer et al [49,51] reported a significant reduction on TNF-α, IL-1β, IL-6, IL-8 and IL-10 production by cultured monocytes, in septic patients receiving a soybean oil-FO mix compared to those receiving soybean oil alone. Unfortunately, both trials [49,51] did not report any relevant clinical outcomes, and therefore they were not included in our review.

Unfortunately, the current evidence from RCTs and our systematic review and meta-analysis is too weak and sparse to make definitive and conclusive recommendations about the role of FO containing emulsions in the treatment of critically ill adult patients. Currently, the superiority of FO to MCT/LCT for ICU patients cannot be asserted. Undoubtedly, more research is needed to clarify the role of FO containing emulsions in the critically ill population. As a first step in a prospective study, it would be needed to determine the optimal dose able to optimize the effects on underlying inflammatory, immunologic, and metabolic processes and at the same time is safe and well tolerated by SIRS patients. Currently, Fish OIL optimal dosE Determination study (FOILED - ClinicalTrials.gov NCT01146821) is evaluating the safety and efficacy of parenteral FO doses of 0.20 g/kg and 0.50 g/kg, compared to a control group, in critically ill septic patients [73].

The strength of our meta-analysis is based on the fact that we have used several methods to reduce bias (comprehensive literature search, duplicate data abstraction, specific criteria for searching and analysis) and have focused on clinically important primary outcomes for ICU patients. Nevertheless, we are aware that our meta-analysis has several limitations including the small number of trials included to evaluate different outcomes and the heterogeneity of the included ICU study populations, which may limit the reliability of the analysis and the strength of our conclusions.

Conclusion

In this meta-analysis, we have demonstrated that FO containing LE may be able to decrease mortality and ventilation days in the critically ill. However, because of the paucity of clinical data, there is inadequate evidence to recommend the routine use of FO containing emulsions in PN and/or as a therapeutic strategy in an EN-fed patient population. Large,

rigorously designed, randomized controlled trials are required to elucidate the efficacy of parenteral FO in this patient population are clearly warranted.

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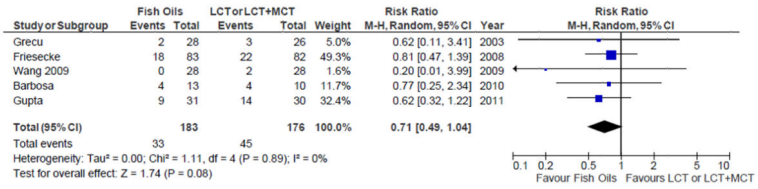

Figure 1. Effects of fish oil lipid emulsion strategies on mortality (n= 5)

Abbreviations: LCT: long chain triglycerides; MCT: medium chain triglycerides; 95% CI: 95% confidence intervals

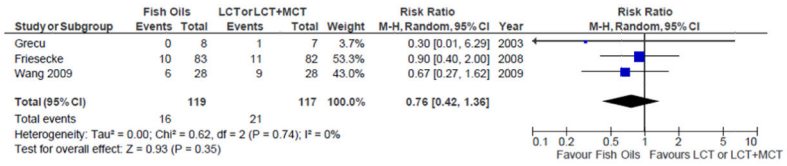

Figure 2. Effects of parenteral fish oil lipid emulsions on infections (n= 6)

Abbreviations: LCT: long chain triglycerides; MCT: medium chain triglycerides; 95% CI: 95% confidence intervals

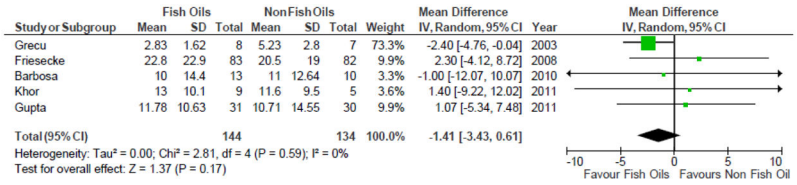

Figure 3. Effects of parenteral fish oil lipid emulsions on ventilation days (n= 4)
Abbreviations: 95% CI: 95% confidence intervals

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Table 1

Details and clinical outcomes of included trials on fish oil containing emulsions in PN fed patients

Fish oil containing emulsions in PN fed patients vs. LCT or LCT+MCT							
Study	**Population**	**Methods (score)**	**Intervention**	**Mortality**		**Infections**	
Grecu [62] **2003**	Patients with abdominal sepsis N = 54 (15/54 in ICU)	C.Random: yes ITT: yes Blinding: double (12)	PN + FO based LE (10% FO) plus LCTs vs. PN with LCT	**FO based LE + LCT ICU 2/28 (7)**	**LCT ICU 3/26 (12)**	FO based LE **VAP 0/8**	**LCT VAP 1/7 (14)**
Friesecke [63] **2008**	Medical ICU patients N= 166	C.Random: yes ITT: yes Blinding: double (10)	PN + Lipofundin MCT (50% LCT + 50% MCT) + FO based LE (10% FO) vs. Lipofundin MCT (50% LCT + 50% MCT)	**LCT + MCT + FO 28 day 18/83 (22)**	**LCT+MCT 28 day 22/82 (27)**	**LCT+ MCT+ FO 10/83 (12)**	**LCT + MCT 11/82 (13)**
Wang [64] **2009**	Severe acute pancreatitis patients in ICU N = 56	C.Random: no ITT: yes Blinding: double (11)	PN + FO based LE (10% FO) plus Lipovenos (LCTs, soybean oil) (ω3:ω6 ratio was 1:4) vs. PN with Lipovenos (LCTs, soybean oil). Both received same amounts of lipids (1 gm/kg/day)	FO based LE **ICU 0/28 (0)**	**LCT ICU 2/28 (7)**	FO based LE **6/28 (21)**	**LCT 9/28 (32)**
Barbosa [66] **2010**	ICU patients with SIRS or sepsis requiring PN N=25	C.Random: yes ITT: yes Blinding: single (10)	PN + Lipoplus (50% MCT, 40% LCTs soybean oil, 10% fish oil) vs. Nutriflex LipidSpecial (50% MCT, 50% LCT, soybean oil). Both received same amounts of lipids (~1 gm/kg/day)	**MCT+LCT+FO 5 day 2/13 (15) 28 day 4/13 (31)**	**MCT+LCT 5 day 1/10 (10) 28 day 4/10 (40)**	**MCT+LCT+FO NA**	**MCT+LCT NA**

Abbreviations: ARDS: acute respiratory distress syndrome; C.Random: concealed randomization; DHA: docosahexaenoic acid; EN: enteral nutrition; EPA: eicosapentaenoic acid; C.Random: concealed randomization; EN: enteral nutrition; FO: fish oil; ICU: intensive care unit; ITT: intention to treat; IV: intravenous; LCT: long chain triglycerides; LE: lipid emulsion; MCT: medium chain triglycerides; N: number of patients; NA: non attribuible; PN: parenteral nutrition; SIRS: systemic inflammatory response syndrome.

Table 2

Details and clinical outcomes of included trials on fish oil containing emulsions in EN fed patients

Fish oil containing emulsions in EN fed vs. none							
Study	**Population**	**Methods (score)**	**Intervention**	**Mortality**		**Infections**	
Gupta [67] **2011**	ICU patients with suspected ARDS N=61	C.Random: yes ITT: yes Blinding: double (9)	EN (standard diet) + FO based LE 10% (ω3:ω6 ratio was 1:4) vs EN (standard diet)	FO based LE **ICU 7/31 (23) Hospital 9/31 (29)**	**Standard EN ICU 13/30 (43) Hospital 14/30 (47)**	FO based LE **NA**	**Standard EN NA**
Khor [65] **2011**	ICU patients with severe sepsis/septic shock N = 28	C.Random: yes ITT: yes Blinding: double (9)	Supplementation with 100 ml 10% FO based LE (10g refined fish oil, EPA 12.5–28.2 g/L, DHA 14.4–30.9 g/L) vs. 100 ml 0.9% normal saline	**Omegaven NA**	**Saline NA**	FO based LE **NA**	**Saline NA**

Abbreviations: ARDS: acute respiratory distress syndrome; C.Random: concealed randomization; DHA: docosahexaenoic acid; EN: enteral nutrition; EPA: eicosapentaenoic acid; FO: fish oil; ICU: intensive care unit; ITT: intention to treat; LE: lipid emulsion; N: number of patients; NA: non attribuible.

Table 3

Outcomes of included trials on fish oil containing emulsions in PN fed patients

Fish oil containing emulsions in PN fed patients vs. LCT or LCT+MCT										
Study	**LOS days**				**Ventilation days**		**Other**			
Grecu [62] **2003***	FO based LE *10%* **ICU** 3.32 ± 1.48 (8) **Hospital** 11.68 ± 2.04 (28)		**LCT** **ICU** 9.28 ± 3.08 (7) **Hospital** 20.46 ± 3.27 (26)		FO based LE 2.83 ± 1.62 (8)	**LCT** 5.23 ± 2.80 (7)	**FO based LE**	**LCT**		
							Patients undergoing reoperation for septic episode			
							2/28 (7)	8/26 (31)		
Friesecke [63] **2008**	**FO**		**LCT**		**LCT + MCT + FO**	**LCT+MCT**	**LCT + MCT + FO** **LCT+MCT**			
	ICU	**28 ± 25 (83)**	ICU	**23 ± 20 (82)**	**22.8 ± 22.9 (83)**	**20.5 ± 19.0 (82)**	**Urinary Tract Infections**			
							6/83 (7)	4/82 (5)		
							Catheter-related infections			
							1/83 (1)	3/83 (4)		
							Total EN Energy Intake (kcal/kg)			
							22.2 ± 5.5	21.6 ± 5.6		
Wang [64] **2009**	**NA**		**NA**		**NA**	**NA**	**FO based LE**	**LCT**		
							Surgery of infected pancreatic necrosis			
							3/28 (11)	**6/28 (21)**		
Barbosa [66] **2010**	**MCT+LCT+FO** **ICU** 12 ± 14.4[a] (13) **Hospital** 22 ± 25.2 [a] (13)		**MCT+LCT** **ICU** 13 ± 12.6 [a] (10) Hospital **55 ± 50** [a] **.6 (10)**		**MCT+LCT+FO** 10 ± 14.4 (13)	**MCT+LCT** 11 ± 12.64 (10)	**MCT+LCT+ FO** **MCT+LCT** **2057± 418 kcals** **1857 ± 255 kcals**			

Abbreviations: EN: enteral nutrition; FO: fish oil; ICU: intensive care unit; LCT: long chain triglycerides; LE: lipid emulsion; LOS: length of stay; MCT: medium chain triglycerides; NA: non attribuible

Table 4

Outcomes of included trials on fish oil containing emulsions in EN fed patients

Fish oil containing emulsions in EN fed patients vs. none						
Study	**LOS days**		**Ventilation days**		**Other**	
Gupta [67] **2011**	FO based LE **ICU** 15.96 ± 7.57 (31) **Hospital** 21.5 ± 13.49 (31)	**Standard EN** **ICU** 15.88 ± 6.47 (30) Hospital **26.63 ± 18.22 (30)**	FO based LE 11.78 ± 10.63 (31)	**Standard EN** 10.71 ± 14.55 (30)	**FO based LE** **NA**	**Standard EN** **NA**
Khor [65] **2011**	FO based LE **ICU** 10.3 ± 8.4 (14) **Hospital** 19.6 ± 7.4 (14)	**Saline** **ICU** 8.4 ± 6.5 (13) **Hospital** 17.5 ± 6.0 (13)	FO based LE 13.0 ± 10.1 (9)	**Saline** 11.6 ± 9.5 (5)	**FO based LE** **NA**	**Saline** **NA**

Abbreviations: EN: enteral nutrition; FO: fish oil; ICU: intensive care unit; LE: lipid emulsion; LOS: length of stay; NA: non attribuible