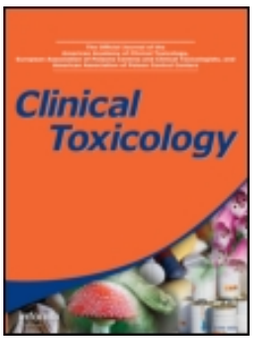

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REVIEW

Systematic review of clinical adverse events reported after acute intravenous lipid emulsion administration

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ABSTRACT

Background: Intravenous lipid emulsions (ILEs) were initially developed to provide parenteral nutrition. In recent years, ILE has emerged as a treatment for poisoning by local anesthetics and various other drugs. The dosing regimen for the clinical toxicology indications differs significantly from those used for parenteral nutrition. The evidence on the efficacy of ILE to reverse acute toxicity of diverse substances consists mainly of case reports and animal experiments. Adverse events to ILE are important to consider when clinicians need to make a risk/benefit analysis for this therapy. **Methods:** Multiple publication databases were searched to identify reports of adverse effects associated with acute ILE administration for either treatment of acute poisoning or parenteral nutrition. Articles were selected based on pre-defined criteria to reflect acute use of ILE. Experimental studies and reports of adverse effects as a complication of long-term therapy exceeding 14 days were excluded. **Results:** The search identified 789 full-text articles, of which 114 met the study criteria. 27 were animal studies, and 87 were human studies. The adverse effects associated with acute ILE administration included acute kidney injury, cardiac arrest, ventilation perfusion mismatch, acute lung injury, venous thromboembolism, hypersensitivity, fat embolism, fat overload syndrome, pancreatitis, extracorporeal circulation machine circuit obstruction, allergic reaction, and increased susceptibility to infection. **Conclusion:** The emerging use of ILE administration in clinical toxicology warrants careful attention to its potential adverse effects. The dosing regimen and context of administration leading to the adverse events documented in this review are not generalizable to all clinical toxicology scenarios. Adverse effects seem to be proportional to the rate of infusion as well as total dose received. Further safety studies in humans and reporting of adverse events associated with ILE administration at the doses advocated in current clinical toxicology literature are needed.

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Introduction

Intravenous lipid emulsion (ILE) has recently received much attention in the treatment of acute local anesthetic toxicity and a variety of other non-local anesthetic poisonings. Many clinicians may be unfamiliar with the likely adverse effects of ILE, particularly regarding its use in toxicological cases. While at least 90 published cases describe adverse effects associated with antidotal use of ILE for various toxins, reporting bias (whether bias favoring publication of a novel event or bias favoring not publishing the complications of therapy) may result in inconsistent or disproportionate representation of the clinical effects of ILE as represented by these cases. The use of ILE in various forms has occurred for decades in total parenteral nutrition (TPN), and this longer and broader clinical experience may indicate likely events that may also occur with acute antidotal use of ILE.[1]

After Intralipid® became readily available, reports of adverse reactions associated with its use began to surface, despite assumptions about its safety compared with previous ILE preparations. These adverse effects tended to be infrequent and non-life-threatening, but they complicated therapy. Reactions related directly to ILE can occur within minutes to hours after infusion, or they can be delayed for weeks to years with ongoing exposure to ILE, as is necessary with long-term parenteral nutrition.

Both the rate of infusion and the total dose infused are associated with reactions to ILE. Guidelines for maximum

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doses and rates of infusion have been established for nutrition support and are based on reported adverse events such as dyspnea, cyanosis, flushing, hypercoagulability, hypertriglyceridemia and chest pain.[2] In adults, infusion faster than the estimated maximum oxidation rate of 1.2–1.7 mg/kg/min (for ILE 20%, this is 0.35–0.51 mL/kg/h or 8.6–12.24 mL/kg/day) likely increases the risk of significant adverse events and is not recommended.[3–5]

Rapid reactions to ILE can transpire with any of the indication for its use (i.e., nutrition, drug carrier, or treatment of poisoning). ILE as an antidote was used initially to counter cardiac arrest induced by a local anesthetic. An increasing number of case reports have documented the use of ILE for less or non-life-threatening indications. Under emergency conditions, the amount of ILE given in a short period of time may exceed, by many fold, the daily limit usually given for TPN. If ILE is being considered for a non-life-threatening condition, the risk/benefit profile should be part of that consideration.

The purpose of this literature review is to characterize the adverse effects that have been reported after administration of ILE, irrespective of the purpose for ILE (i.e., nutrition, drug carrier, or treatment of poisoning), to assist clinicians in a risk/benefit assessment when ILE treatment for poisoning is considered.

Methods

The American Academy of Clinical Toxicology initiated a collaboration among the European Association of Poison Centers and Clinical Toxicologists, the Asia Pacific Association of Medical Toxicologist, the Canadian Association of Poison Control Centers, the American College of Medical Toxicology, and the American Association of Poison Control Centers to review the evidence and produce recommendations on the use of this novel therapy for drug toxicity. A working subgroup (the authors) formed to gather and review the evidence regarding clinical adverse events associated with short-term use of ILE. This subgroup comprised clinical experts and various stakeholders involved in the workgroup. It also included two medical librarians who assisted in conducting the systematic searches and the retrieval of potentially eligible publications, as well as an epidemiologist with specific methodological expertise in conducting systematic reviews. Subgroup members divulged all potential conflicts of interests prior to inclusion in the workgroup. All communication occurred by email exchanges and by telephone conferences.

Two medical librarians created a systematic search strategy for Medline (Ovid), which appears in the Appendix. The strategy comprised a combination of Medical Subject Headings, title/abstract key words, truncations, and Boolean operators, and included the concepts of ILE. The same search strategy was used for Embase (via Ovid), CINAHL (via EBSCO), BIOSIS Previews (via Ovid), Web of Science, Scopus, and the Cochrane Library/DARE. All databases searches ran from inception to 15 December 2014.

In addition, conference abstracts from the European Association for Poison Centers and Clinical Toxicologists, and the North American Congress of Clinical Toxicology (both from 2000 to 2014) and abstracts from the Asia Pacific Association of Medical Toxicology from 2007 to 2014 were searched. Group members hand-searched previous review articles. Group members also performed cross-referencing of full-text articles. No limits were applied for language, and candidate studies in languages not known to any of the authors were translated.

In summary, the criteria for publication inclusion in the evaluation of the effect of ILE include studies in humans and animals who received ILE for any indication. Rapidly occurring reactions to ILE from the parenteral nutrition literature were included. These cases are applicable to the evaluation of the safety profile for ILE used for acute poisonings and are appropriate to include in this review. Articles describing adverse events associated with long-term use (defined as >14 days) of ILEs for TPN were excluded. Other exclusion criteria were non-original data or animal studies with methods and results that cannot be extrapolated or are uninterpretable. A complete methodology of the larger project of which this systematic review is one part has been previously published and describes in detail all relevant methodological aspects such as clinical questions, search strategies, eligibility of publications, data extraction and summary, and assessment of the risk of bias.[151] The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used to appraise the quality of the evidence.

Results

The initial search identified 36,903 citations. A total of 36,933 citations were screened for relevance. Full text copies unavailable for five citations. This selection yielded 789 full text articles, of which 675 full text articles were excluded from analysis. Figure 1 lists the reasons for exclusion.

One hundred fourteen articles were analyzed for their report of acute adverse events that followed the therapeutic use of ILE for TPN or for the treatment of poisoning. The articles were divided into human (87 articles) and animal (27 articles) studies. We assigned each publication to an adverse event category to facilitate analysis. The final level of evidence was reported as per the GRADE system.[6–9] Table 1 summarizes the quality of the evidence. Most studies received low grades because they use animal models or are case reports of human patients. However, given the amount of animal data available and the tendency to rely on animal data for guidance in managing rare events that are difficult to randomize in humans, they were also included for analysis.

Human studies

The human studies were categorized according to the predominant effect of ILE administration: organ dysfunction (including cardiovascular, hematological, acute kidney injury [AKI], and metabolic acidosis); pulmonary effects (including acute respiratory distress syndrome [ARDS], acute lung injury [ALI], hypoxia, and ventilation/perfusion [V/Q]

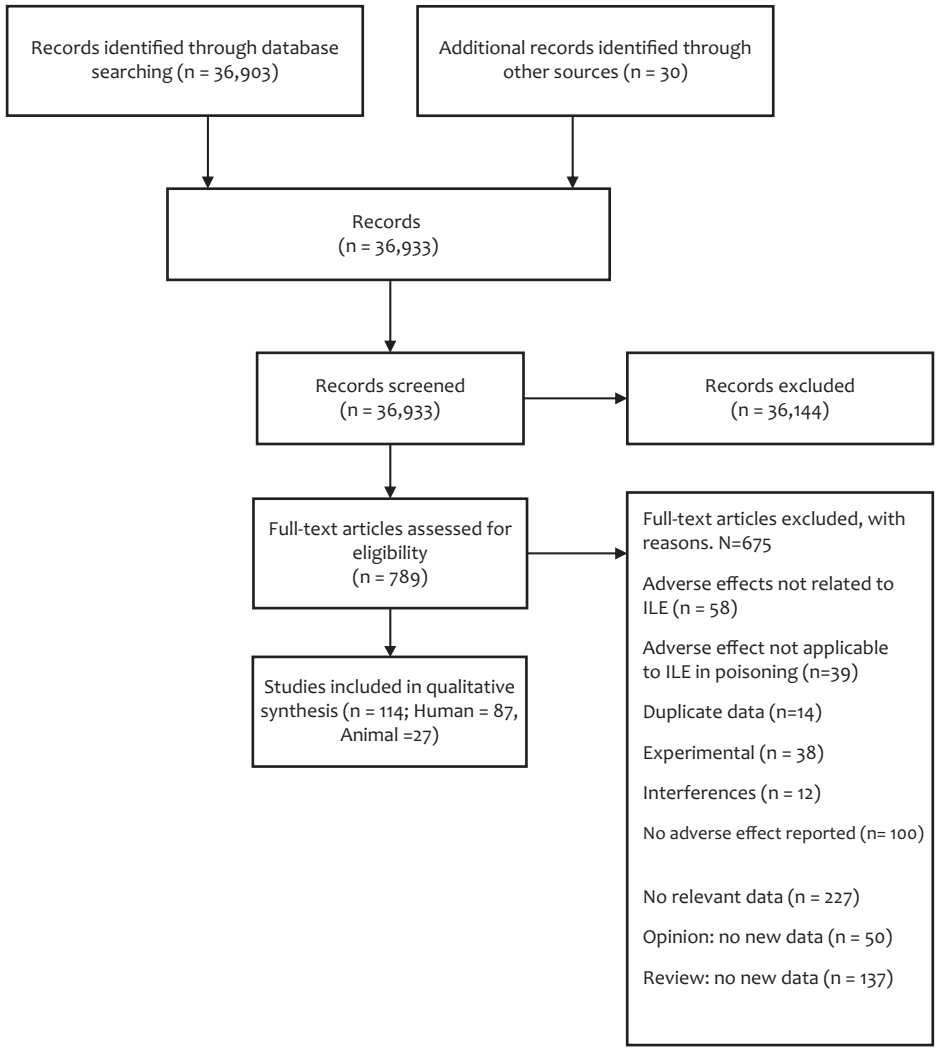

Figure 1. Selection of article flow diagram.

mismatch); hypersensitivity and allergic effects; vascular occlusion including priapism, deep vein thrombosis [DVT], phlebitis, coagulopathy, fat embolism, continuous veno-venous hemodiafiltration [CVVHF], and extracorporeal membrane oxygenation [ECMO] line interference; infection susceptibility and inflammatory effects; and fat overload syndrome, hypertriglyceridemia, lipemia, hyperamylasemia, pancreatitis, and cholestasis.

Organ failure

Cardiovascular effects

Ten articles describing adverse effects were categorized as cardiovascular (Table 2).[10–19] Fatal cardiac arrest and death were reported in neonates receiving Intralipid® at 0.08–0.15 g/kg/h (0.4–0.75 mL/kg/h for ILE 20%) as part of TPN therapy.[13,20] It is unclear if the ILE administration caused the cardiac events or was simply associated with them. Pulmonary fat microemboli were found in the lung of one infant at autopsy.[13] One report described two adult patients who received Intralipid® for drug-induced shock in which asystole immediately followed the ILE bolus in both cases.[11] Both patients had refractory hypotension and bradycardia prior to ILE administration and the only conclusion that can be drawn is that there was a temporal relationship between ILE administration and onset of asystole. Kidney failure and cardiac arrest were reported in a TPN patient following the administration of 2580 mL of ILE (10 and 20%) over 24 h.[12]

Abel et al. studied 19 adult patients divided into two groups following uncomplicated isolated coronary artery bypass surgery.[10] One treatment group received a constant 60-min infusion of 2 mL/min of soy oil emulsion (20% Intralipid®) while the second group received 20% Intralipid at 1 mL/min for 1 h followed by an increase to 2 mL/min for an additional hour. Patients receiving the constant 2 mL/min infusion (averaging 5.25 mg/kg/min) had lower cardiac output and higher pulmonary wedge pressure than patients starting at 1 mL/min. No significant hemodynamic changes or adverse side effects occurred in the 1 mL/min group.[10] The authors concluded that the rate should not exceed the maximum clearance rate of 1 mL/min averaging 2.67 mg/kg/min in the study population. Marfella et al. studied the effect of 10% ILE plus heparin (to stimulate lipoprotein lipase activity) on cardiac repolarization in a controlled, crossover study with 32 healthy non-obese subjects.[15] Compared with saline, ILE plus heparin increased blood pressure, heart rate, QTc dispersion, and plasma concentrations of epinephrine and free fatty

Table 1. Summary estimates with associated GRADE ratings for controlled studies reporting adverse events.

		Comparison		Summary of finding		Quality of evidence	
No. of studies	Population	Intervention (No. of patients)	Comparator (No. of patients)	Summary estimate[a]	Interpretation	Quality assessment[b]	GRADE rating
Organ dysfunction							
Cardiovascular events							
N = 1 [10]	Post coronary artery bypass	Higher infusion rate (n = 12)	Slower infusion rate (n = 7)	RD (95% CI) in cardiac ischemia = +0.08 (NA)	No difference in cardiac ischemia events between groups.	Observational study; Downgrade: Imprecision due to small sample size (−1)	Very low
N = 1 [19]	Post major GI surgery	Liposyn™ II (n = 10)	Intralipid® (n = 10)	No cardiovascular events reported	No difference in cardiovascular events between groups.	RCT; Downgrade: Imprecision due to small sample size (−1) and absence of events reported (−1)	Low
Cardiac output							
N = 1 [10]	Post coronary artery bypass	ILE (n = 12)	No ILE (saline) (n = 7)	MD (95% CI) in cardiac output (L/min) = −1.79 (−3.10; −0.48)	ILE was significantly associated with lower cardiac index as compared to saline.	Observational study; Downgrade: Limitation due to potential selection bias (lower cardiac output at baseline in the ILE group) (−1); Indirectness due to surrogate marker (−1), Imprecision due to small sample size (−1)	Very low
N = 2 [10,17]	Post coronary artery bypass or critically ill	Higher infusion rate (n = 30)	Slower infusion rate (n = 25)	MD (95% CI) in cardiac output (L/min) = −1.57 (−2.79; −0.35) [10]; Reported comparative cardiac index- = lower in sepsis and higher in ARDS when comparing higher infusion rate groups to controls. (P = NR) [17]	Higher infusion rate was significantly associated with lower cardiac index in coronary artery bypass. Higher infusion rate was possibly associated with lower cardiac index in sepsis and with higher cardiac index in ARDS.	RCT crossover and Observational study; Downgrade: Limitation due to potential selection bias (lower cardiac output at baseline in the higher infusion rate in one study) (−1); Indirectness due to surrogate marker (−1), Imprecision due to small sample size in one study and indirect comparison between groups in the other (−1); Upgrade: Dose gradient response in one study (+1)	Very low
N = 1 [16]	Pancreatitis with ARDS	LCT/MCT (n = 9)	LCT (n = 9)	MD (95% CI) in cardiac output (L/min) = +0.5 (+0.12; +0.88)	LCT/MCT was significantly associated with higher cardiac output as compared to LCT.	RCT crossover; Downgrade: Indirectness due to surrogate marker (−1), Imprecision due to small sample size (−1)	Low
QT-c							
N = 1 [15]	Healthy volunteers	ILE (n = 32)	No ILE (saline) (n = 32)	Estimated MD (95% CI) in Q-Tc (ms) = +40 (NR) ($p < 0.01$) Estimated MD (95% CI) in Q-Tc dispersion (ms) = +27 (NR) ($p < 0.01$)	ILE was significantly associated with longer Q-Tc and Q-Tc dispersion as compared to saline.	RCT crossover; Downgrade: Indirectness due to surrogate marker (−1)	Moderate

(*continued*)

Table 1. *Continued*

		Comparison		Summary of finding		Quality of evidence	
No. of studies	Population	Intervention (No. of patients)	Comparator (No. of patients)	Summary estimate[a]	Interpretation	Quality assessment[b]	GRADE rating
Acute kidney injury							
N = 1 [29]	Premature infants needing artificial nutrition	ILE (n = 50)	No ILE (enteral nutrition) (n = 54)	MD (95% CI) in serum cystatin C (mg/L) = +0.3 (+0.20; +0.40)	ILE was significantly associated with higher levels of glomerular and tubular function biomarkers as compared to controls. No difference in renal function between groups.	Observational study; Downgrade: Limitation due to potential selection bias (confounding-by-indication) (−1) and absence of adjustment for potential confounders (−1), Indirectness due to surrogate markers (−1)	Very low
				MD (95% CI) in urinary β2 microglobulin (mg/L) = +6.5 (+4.35; +8.65) MD (95% CI) in gluthatione-S-transferase π (ng/mL) = +34.3 (+16.57; +52.23) MD (95% CI) N-acetyl- β-D glucosaminidase (μg/L) = +2.5 (+0.31; +4.69) MD (95% CI) in BUN (mg/dL) = +2.6 (−0.19; +5.39) MD (95% CI) in creatinine (mg/dL) = −0.05 (−0.11; +0.01)			
Pulmonary adverse effects							
Respiratory events/pneumonia							
N = 1 [32]	Polytrauma patients	ILE (n = 30)	No ILE (n = 27)	RD (95% CI) of pneumonia = +0.25 (+0.01; +0.50)	ILE was significantly associated with a higher risk of pneumonia as compared to controls.	RCT; Downgrade: Limitation due to potential reporting bias (unspecified duration to report clinical outcomes) (−1) and due to incomplete reporting of potential confounding factors (−1); Imprecision due to small sample size (−1)	Very low
N = 1 [19]	Post major GI surgery	Liposyn™ II (n = 10)	Intralipid® (n = 10)	No respiratory adverse events reported	No difference in respiratory adverse events between the two types of ILE.	RCT; Downgrade: Imprecision due to small sample size (−1) and absence of events reported (−1)	Low
Pulmonary vascular resistance							
N = 3 [35,38,43]	Various (premature low birth weight infants to adults; with or without ARDS)	ILE (n = 25) (32 infusions)	No ILE (n = 19) (19 infusions)	WMD (95% CI) in ratio of RVPEP/ET (Right ventricular pre-ejection period to ejection time) = +0.077 (+0.053; +0.101) [38,43]; Reported comparative pulmonary vascular resistance in ARDS = greater increase from baseline in ILE group as compared to no ILE group (p = NR). [35]	ILE was significantly associated with a higher pulmonary vascular resistance than controls. No difference in systemic vascular resistance between groups.	Observational studies; Downgrade: Limitation due to potential selection bias (−1), Indirectness due to surrogate markers (−1), Imprecision due to small sample size (−1)	Very low
		(n = 17) (24 infusions)	(n = 14) (14 infusions)	MD (95% CI) in ratio of LVPEP/ET (Left ventricular pre-ejection period to ejection time) = −0.041 (−0.091; +0.009) [38]; Reported NS [43]			

(*continued*)

Table 1. *Continued*

		Comparison		Summary of finding		Quality of evidence	
No. of studies	Population	Intervention (No. of patients)	Comparator (No. of patients)	Summary estimate[a]	Interpretation	Quality assessment[b]	GRADE rating
N = 1 [43]	Preterm infants either healthy or with ARDS	Higher dose (n = 11)	Lower dose (n = 11)	MD (95% CI) in ratio of RVPEP/ET = +0.079 (+0.042; +0.116); MD (95% CI) in ratio of LVPEP/ET = +0.011 (−0.003; +0.035)	Higher dose of ILE was significantly associated with a higher pulmonary vascular resistance. No difference in systemic vascular resistance between groups.	Observational study; Downgrade: Limitation due to potential selection bias (−1), Indirectness due to surrogate markers (−1), Imprecision due to small sample size (−1); Upgrade: Dose response gradient (+1)	Very low
N = 1 [49]	Preterm infants	Olive-based emulsion (n = 5)	Soy-oil based emulsion (n = 10)	MD (95% CI) in ratio of TVP/RVET (ratio of time to peak velocity to right ventricular ejection time) = +0.051 (−0.045; +0.147) Reported comparative pulmonary arterial pressure = greater decrease from baseline in the olive-oil based emulsion group as compared to controls (p = 0.02)	No difference in pulmonary arterial pressure between groups, but greater decrease from baseline in olive-based emulsion as compared to soy-oil based emulsion.	Observational study; Downgrade: Limitation due potential selection bias (groups not comparable at baseline) and no adjustment for potential confounders (−1), Indirectness due to surrogate markers (−1), Imprecision due to small sample size (−1)	Very low
Hypoxemia							
N = 1 [35]	Patients with or without ARDS	ILE (n = 8)	No ILE (n = 5)	Reported comparative PaO2/FIO2 in ARDS = greater decrease in ILE group as compared to controls (p = NR) Reported comparative compliance of respiratory system in ARDS = greater decrease from baseline in ILE group as compared to controls (p = NR)	ILE was possibly associated with a greater decrease in PaO2/FIO2 and compliance of respiratory system as compared to controls.	Observational study; Downgrade: Indirectness due to surrogate markers (−1), Imprecision due to small sample size (−1) and due to indirect comparison between groups (−1)	Very low
N = 1 [33]	Very low birth weight neonates	Higher dose (n = 12)	Lower dose (n = 15)	MD (95% CI) in A-aDO2 (mmHg) = +4.0 (−11.8; +19.2) RD (95% CI) of having pH <7.20 = +0.02 (−0.36; +0.39)	No difference in alveolar-arteriolar oxygen diffusion gradient or blood pH between groups.	RCT; Downgrade: Limitation due to potential selection bias (important lost to follow-up) (−1), Indirectness due to surrogate markers (−1), Imprecision due to small sample size (−1)	Very low

(*continued*)

Table 1. *Continued*

		Comparison		Summary of finding		Quality of evidence	
No. of studies	Population	Intervention (No. of patients)	Comparator (No. of patients)	Summary estimate[a]	Interpretation	Quality assessment[b]	GRADE rating
N = 2 [17,33]	Various (very low birth weight neonates and critically ill adults)	Higher infusion rate (n = 32)	Lower infusion rate (n = 33)	MD (95% CI) in A-aDO2 (mmHg) = p = NS at different times (Brans1986) Reported comparative P/T ratio, pulmonary shunt fraction and P(A − a)O2/PaO2 = In ARDS with rapid infusion, greater increase in all parameters as compared to slow infusion; in sepsis with rapid infusion, greater decrease in pulmonary shunt fraction and P(A − a)O2/PaO2 only as compared to slow infusion (p = NR). Reported comparative PaO2/FiO2 = in ARDS with rapid infusion, greater decrease as compared to slow infusion; in sepsis with rapid infusion, greater increase as compared to slow infusion (p = NR). [17]	No difference in pooled oxygenation parameters between higher and lower rates of infusion, but possible opposite effects when stratifying for underlying diseases (ARDS versus sepsis).	RCTs (one being a crossover study); Downgrade: Limitation due potential selection bias in one study (important lost to follow-up) and lack of blinding in the other study (−1), Indirectness due to surrogate markers in both studies and due to indirect comparison between groups in the other (−1), Imprecision due to small sample size (−1)	Very low
		(n = 14)	(n = 15)	RD (95% CI) of having pH <7.20 = + 0.1 (−0.26; +0.46) [33]			
N = 2 [16,45]	Septic patients or with pancreatitis and ARDS	LCT (n = 19)	LCT/MCT (n = 20)	WMD (95% CI) in PaO2/FiO2 = −36.5 (−54.5; −18.6) WMD (95% CI) in VO2 (ml/min)- = −42.1 (−50.2; −33.9) WMD (95% CI) of Qva/Qt (%) = +9.2 (+5.4, +13.0)	LCT was significantly associated with lower PaO2/FiO2, VO2 and VCO2 as well as higher pulmonary venous admixture and DO2 as compared to LCT/MCT. No difference in pH between groups.	RCTs (one being a crossover study); Downgrade: Indirectness due to surrogate markers (−1), Imprecision due to small sample size (−1)	Low
		(n = 10)	(n = 11)	MD (95% CI) in pH = 0 (−0.78; 0.78) [45]			
		(n = 9)	(n = 9)	MD (95% CI) in VCO2 (ml/min)- = −30.0 (−43.6; −16.4) [16] MD (95% CI) in DO2 (ml/min)- = +140.0 (+43.9; +236.1) [16]			

(*continued*)

Table 1. *Continued*

		Comparison		Summary of finding		Quality of evidence	
No. of studies	Population	Intervention (No. of patients)	Comparator (No. of patients)	Summary estimate[a]	Interpretation	Quality assessment[b]	GRADE rating
Hypersensitivity and allergic adverse effects							
N = 1 [19]	Post major GI surgery	Liposyn™ II (n = 10)	Intralipid® (n = 10)	No allergic adverse events reported	No difference in allergic adverse events between groups.	RCT; Downgrade: Imprecision due to small sample size (−1) and absence of events reported (−1)	Low
Vascular occlusion adverse effects							
Coagulation parameters							
N = 2 [67,68]	Various (healthy subjects and patients with different diseases; children and adults)	ILE (n = 17)	No ILE (n = 17)	WMD (95% CI) in PAI-1 (ng/mL) = +84.05 (44.41; 123.71) [67,68]	ILE was associated with higher PAI-1 and TAT III complexes as compared to controls. No differences in PFi or PAP between groups while opposite effects are reported for TPA between groups.	Observational studies; Downgrade: Indirectness due to surrogate marker (−1), Imprecision due to small sample size (−1)	Very low
				Reported comparative tissue plasminogen activator = decreased with ILE compared to controls (P = NR) [67,120] and increased but NS [68]			
		(n = 5)	(n = 5)	MD (95% CI) in PFi (nM) = +1.95 (−3.58; +7.48) [68]			
				MD (95% CI) in TAT III complexes (μg/L) = +26.0 (+0.25; +51.75) [68]			
				Reported comparative PAP (nmol/L) = NS [68]			
ECMO line interference							
N = 1 [73]	Neonates on ECMO	Via ECMO circuit (n = 5)	Via a separate IV access (n = 4)	RD (95% CI) of patients needing circuit changes = −0.3 (−0.9; +0.3)	No difference in patients needing circuit changes or cloths in circuit between groups.	RCT; Downgrade: Limitation due potential selection bias (lack of comparability between groups at baseline) (−1), Indirectness due to surrogate marker (−1), Inconsistency between different measured parameters (−1), Imprecision due to small sample size (−1)	Very low
				RD (95% CI) of clots in circuit = +0.5 (NA)			

(*continued*)

Table 1. *Continued*

		Comparison		Summary of finding		Quality of evidence	
No. of studies	Population	Intervention (No. of patients)	Comparator (No. of patients)	Summary estimate[a]	Interpretation	Quality assessment[b]	GRADE rating
Infection susceptibility							
Infections							
N = 1 [32]	Polytrauma patients	ILE (n = 30)	No ILE (for the first 10 days only) (n = 27)	RD (95% CI) of pneumonia = +0.25 (+0.01; +0.50) RD (95% CI) of line infections = +0.25 (+0.02; +0.48) RD (95% CI) of bacteremia = +0.04 (−0.18; +0.27) RD (95% CI) of abdominal abscesses = +0.02 (−0.15; +0.19) RD (95% CI) of superficial wound infections = +0.12 (−0.07; +0.31) RD (95% CI) of other infections = +0.14 (−0.10; +0.38)	ILE was associated with a higher risk of pneumonia and line infections. No difference in other reported infections between groups.	RCT; Downgrade: Limitation due to potential reporting bias (unspecified duration to report clinical outcomes) (−1) and due to incomplete reporting of potential confounding factors (−1); Imprecision due to small sample size (−1)	Very low
Immune system alteration							
N = 1 [32]	Polytrauma patients	ILE (n = 30)	No ILE (for the first 10 days only) (n = 27)	The median ratio of LAK activity day 5/day 0 was lower in the ILE group than in the control group (p = 0.03) The median ratio of NK activity day 5/day 0 was lower in the ILE group than in the control group (p = 0.02)	ILE was significantly associated with a lower LAK and NK activity as compared to controls.	RCT; Downgrade: Limitation to incomplete reporting of potential confounding factors (−1), Indirectness due to surrogate markers (−1), Imprecision due to small sample size (−1)	Very low
N = 1 [78]	Various (healthy or critically ill patients)	Higher infusion rate (bolus) (n = 20)	Slower infusion rate (n = 8)	Reported comparative monocyte function (chemotaxis) = similar decrease in both groups following ILE (p = NR).	No difference in monocytes function decrease or lymphocytes function between two types of ILE administration.	Observational study; Downgrade: Limitation due potential selection bias (lack of comparability between groups at baseline) (−1), Indirectness due to surrogate markers (−1), Imprecision due to small sample size (−1)	Very low
N = 1 [79]	Gastric cancers	LCT (n = 10)	LCT/MCT (n = 10)	No change in lymphocytes function. Reported comparative neutrophil bacterial killing activity = lower in LCT group as compared to LCT/MCT group (p < 0.01). No change in phagocytosis index, chemotaxis, spontaneous migration, or oxidative metabolism.	LCT was associated with a lower neutrophil bacterial killing activity as compared with LCT/MCT. No difference in phagocytosis index, chemotaxis, spontaneous migration, or oxidative metabolism between groups.	RCT crossover; Downgrade: Indirectness due to surrogate markers (−1), Imprecision due to small sample size (−1)	Low

(*continued*)

Table 1. *Continued*

		Comparison		Summary of finding		Quality of evidence	
No. of studies	Population	Intervention (No. of patients)	Comparator (No. of patients)	Summary estimate[a]	Interpretation	Quality assessment[b]	GRADE rating
Inflammatory effects							
N = 1 [19]	Post major GI surgery	Liposyn™ II (n = 10)	Intralipid® (n = 10)	MD (95% CI) in CRP (mg/dL) = −1.9 (−10.4; 6.6)	No difference in CRP or C4 between groups.	RCT; Downgrade: Indirectness due to surrogate markers (−1), Imprecision due to small sample size (−1)	Low
				MD (95% CI) in C4 (mg/dL) = +2.5 (−8.8; +18.0)			
Fat overload syndrome/hypertriglyceridemia/lipemia/hyperamylasemia/pancreatitis/cholestasis							
Triglycerides/cholesterol/lipemia							
N = 1 [15]	Healthy volunteers	ILE (n = 32)	No ILE (saline) (n = 32)	MD (95% CI) in FFA (mmol/L) = +261 (+211; +311)	ILE was significantly associated with a higher level of FFA as compared to the control group.	RCT crossover; Downgrade: Indirectness due to surrogate marker (−1)	Moderate
N = 1 [33]	Very low birth weight neonates	Higher dose (n = 12)	Lower dose (n = 15)	RD (95% CI) in severe hyperlipidemia = +0.17 (NA)	No difference in severe hyperlipidemia between groups.	RCT; Downgrade: Limitation due to potential selection bias (important lost to follow-up) (−1), Indirectness due to surrogate markers (−1), Imprecision due to small sample size (−1)	Very low
N = 2 [33,94]	Very low birth weight and premature infants	Higher infusion rate (n = 22)	Slower infusion rate (n = 22)	MD (95% CI) in triglycerides (mg/dL) = +106.3 (+17.4; +195.3) [94]	Higher rate of infusion was significantly associated with higher levels of triglycerides and free fatty acids as compared to a slower rate of infusion. No difference in levels of cholesterol, HDL and LPL or in occurrence of severe hyperlipidemia between groups.	RCTs (one being a crossover study); Downgrade: Limitation due to potential selection bias (important lost to follow-up in one study and lack of comparability between groups at baseline in the other study) (−1), Indirectness due to surrogate markers (−1), Imprecision due to small sample size (−1)	Very low
				MD (95% CI) in FFA (μmol/L) = +0.64 (+0.15; +1.13) [94]			
				MD (95% CI) in cholesterol (mg/dL) = +13.6 (−15.0; +42.2) [94]			
				MD (95% CI) in hepatic lipase (U/mL) = +0.21 (−0.97; +1.39) [94]			
				MD (95% CI) in LPL (U/mL) = +0.72 (−0.22; +1.66) [94]			
		(n = 14)	(n = 15)	RD (95% CI) in severe hyperlipidemia = +0.07 (NA) [33]			
N = 2 [19,84]	Various (infants, adults post major GI surgery)	Liposyn™ or Lyposyn II (n = 28)	Intralipid® (n = 28)	WMD (95% CI) in triglycerides (mg/dL) = +39.0 (−21.6; +99.7)	No difference in triglyceride levels between groups.	RCTs (one being a crossover study); Downgrade: Indirectness due to surrogate marker (−1), Imprecision due to small sample size (−1)	Low

(*continued*)

Table 1. *Continued*

		Comparison		Summary of finding		Quality of evidence	
No. of studies	Population	Intervention (No. of patients)	Comparator (No. of patients)	Summary estimate[a]	Interpretation	Quality assessment[b]	GRADE rating
N = 1 [80]	Severe acute pancreatitis	MCT/LCT/Omega-3 (fish based) (n = 22)	MCT/LCT (n = 22)	Reported comparative triglycerides and cholesterol levels = slightly lower in the MCT/LCT/Omega-3 group (p = NS) RD (95% CI) of hypertriglyceridemia = −0.05 (NA)	No difference in levels of triglycerides and cholesterol, or in occurrence of hypertriglyceridemia between groups.	RCT; Downgrade: Limitation due to incomplete methodology reporting (−1), Indirectness due to surrogate markers (−1), Imprecision due to small sample size (−1)	Very low
N = 1 [73]	Neonates on ECMO	Via ECMO circuit (n = 5)	Via a separate IV access (n = 4)	Reported comparative triglycerides = similar between groups (P NR)	No difference in triglyceride levels between groups.	RCT; Downgrade: Limitation due potential selection bias (lack of comparability between groups at baseline) (−1), Indirectness due to surrogate marker (−1), Imprecision due to small sample size (−1)	Very low
Lipid deposits							
N = 1 [89]	Low birth weight infants who died	ILE (n = 9)	No ILE (human milk) (n = 12)	RD (95% CI) in pulmonary artery lipid deposits = +0.61 (+0.27; +0.96) RD (95% CI) in lipid deposits in macrophages = +0.19 (−0.19; +0.58) RD (95% CI) in lipid deposit in alveolar cells = +0.28 (−0.11; +0.67) Reported comparative lipid accumulation in brain capillaries = no difference (p = NR)	ILE was significantly associated with pulmonary artery lipid deposits as compared to controls. No difference in lipid accumulation in brain capillaries, macrophages or alveolar cells between groups.	Observational study; Downgrade: Limitation due to potential confounders (−1); Indirectness due to surrogate markers (−1), Imprecision due to small sample size (−1)	Very low
Cholesterol crystals							
N = 1 [95]	Pre-cholecystectomy	ILE (n = 8)	No ILE (n = 8)	RD (95% CI) in two types of cholesterol crystals = +0.63 (+0.25; +1.00) and +0.63 (NA) (p = 0.01)	ILE was significantly associated with a higher risk of cholesterol crystals than the control group.	RCT; Downgrade: Limitation due to a lack of reporting in patients' baseline characteristics (−1), Indirectness due to surrogate markers (−1), Imprecision due to small sample size (−1)	Very low
Liver abnormalities							
N = 1 [87]	Critically ill patients receiving artificial nutrition	ILE (n = 303)	No ILE (enteral nutrition) (n = 422)	Liver dysfunction was associated with the use of TPN at the univariate ($p < 0.001$), but also at the multivariate analysis (OR 1.96, 95% CI 1.3–2.97, $p < 0.001$), after adjusting for sepsis, multiple organ dysfunction score, early use of artificial nutrition, and energy requirements >25 kcal/kg/day.	ILE was significantly associated with liver dysfunction as compared to controls	Observational study: No serious limitation	Low

(*continued*)

Table 1. *Continued*

		Comparison		Summary of finding		Quality of evidence	
No. of studies	Population	Intervention (No. of patients)	Comparator (No. of patients)	Summary estimate[a]	Interpretation	Quality assessment[b]	GRADE rating
N = 2 [81,96]	Preterm infants	Various doses (n = 523)		TPN-associated cholestasis was associated with higher calorie intake, but also with longer duration of TPN, lower gestational age, lower birth weight, later enteric feeding and complications of prematurity (p = NR). [96]	Higher dose of ILE was significantly associated with higher unbound bilirubin and cholestasis as compared to lower dose.	Observational studies; Downgrade: Limitation due to incomplete methodology reporting in one study (−1) and due to potential confounders in both studies (−1); Upgrade: Dose response gradient in one study (+1)	Very low
		Various doses (n = 26)		Linear increase in unbound bilirubin of 0.62 μg/dL for each increase in 1 g/kg/d in ILE intake (p = 0.001). Association still statistically significant after adjustment for gestational age and glucose infusion (p = 0.003). [81]			
N = 1 [94]	Premature infants with ARDS	Higher infusion rate (over 15 h) (n = 22)	Lower infusion rate (over 24 h) (n = 22)	MD (95% CI) in unbound bilirubin (B/R) = +0.07 (−0.20; 0.34)	No difference in unbound bilirubin between groups.	RCT crossover; Downgrade: Limitation due to lack of comparability between groups at baseline) (−1), Indirectness due to surrogate markers (−1), Imprecision due to small sample size (−1)	Very low
N = 2 [96,98]	Preterm infants or neonates who died	Various duration (n = 523)		TPN-associated cholestasis was associated with longer duration of TPN, but also with higher calorie intake, lower gestational age, lower birth weight, later enteric feeding and complications of prematurity.[96]	Longer duration of ILE was significantly associated with higher risk of cholestasis and liver abnormalities as compared to shorter duration.	Observational studies; Downgrade: Limitation due to incomplete methodology reporting in one study (−1) and due to potential confounders in both studies (−1)	Very low
		Various duration (n = 24)		More severe liver abnormalities was associated not only with a longer duration of TPN (p = 0.0008), but also with smaller gestational age, bronchopulmonary dysplasia and direct hyperbilirubinemia. [98]			
N = 1 [97]	Post-hepatectomy	Olive (n = 15)	Soya (n = 16)	MD (95% CI) in total bilirubin (μmol/L) = −9.79 (−21.30; +1.72)	No difference in post-operative liver function between two groups.	RCT; Downgrade: Limitation due potential selection bias (lack of appropriate allocation) (−1), Indirectness due to surrogate marker (−1), Imprecision due to small sample size (−1)	Very low
				MD (95% CI) in direct bilirubin (μmol/L) = −5.41 (−11.53; +0.71)			
				MD (95% CI) in ALT (U/L) = −31.0 (−110.7; +48.7)			
				MD (95% CI) in AST (U/L) = −21.8 (−49.5; +5.9)			
				MD (95% CI) in ALP (U/L) = +28. 5 (−11.7; +68.8)			

As proposed by GRADE methodology, all other evidence was rated "very low" quality of evidence (this included pre/post intervention studies due to high risk of confounding, uncontrolled studies due to indirectness of comparisons, case reports/series due to very high likelihood of publication bias and animal studies due to lack of generalizability to humans and thus very serious indirectness).

[a]Summary estimate is expressed in difference between the "group intervention – group comparator". Either a risk difference (RD), a mean difference (MD) or weighted mean difference (WMD) was reported with 95% confidence interval (95% CI).

[b]Quality assessment according to GRADE methodology. Of note, since few studies were pooled together to answer a specific clinical question, inconsistency and publication bias were not evaluable.

Table 2. Organ dysfunction adverse effects reported in human studies.

References	Study type	Type of population (number)	Indication of ILE	Type of ILE	Total dose/duration of ILE	Timing of adverse events	Adverse events
Cardiovascular effects							
[15]	Randomized controlled crossover trial	32 healthy subjects randomized to either ILE (n = 32) or saline (n = 32), alternatively on 2 separate occasions	TPN	LCT 10% (Intralipid®)	Unknown amount of infusion given for 180 min.	Pre-infusion and at 180 min	*Pre-/post-comparison*: Increase in Q-Tc from 359 to 385 ms in the ILE/propranolol group ($p < 0.01$). No significant Q-Tc increase in the control groups (neither propranolol group nor saline group). *Group comparison*: Transient higher in mean blood pressure ($p < 0.05$), heart rate ($p < 0.05$), Q-Tc ($p < 0.01$), and Q-Tc dispersion ($p < 0.01$) in the ILE group.
[16]	Randomized controlled crossover trial	Nine patients with pancreatitis and ARDS randomized to either LCT (n = 9) or LCT/MCT (n = 9), alternatively for 24 h	TPN	LCT 20% (Intralipid®) & LCT/MCT 20% (Lipofundin®)	50% of daily non-protein caloric requirement given over 8 h	Pre-infusion, 30 min before the end of infusion and 4 h following the infusion	*Pre-/post-comparison*: Significant and transient increase in mean pulmonary artery pressure (from 28 to 35 mmHg) during LCT infusion. Significant increase in cardiac output (from 8.8 to 9.5 L/min) during LCT/MCT infusion. *Group comparison*: Transient higher mean pulmonary artery pressure during LCT infusion ($p < 0.05$). Transient higher cardiac output during LCT/MCT group ($p < 0.05$).
[17]	Randomized controlled crossover study	18 critically ill patients (stratified by diseases: 10 severe sepsis and 8 ARDS) randomized to either to receiving TPN over 6 h (n = 18) or 24 h (n = 18), alternatively	TPN	LCT 20% (Lipovenos)	1.1–1.3 g/kg in sepsis group and 1.29–1.31 g/kg in ARDS group	Pre-infusion and every 6 h for 24 h	*Subgroup comparison*: In the ARDS group with rapid infusion, there was an increase in cardiac index as compared to the sepsis group with rapid infusion.
[19]	Randomized controlled trial	20 patients post major gastrointestinal surgery randomized to Liposyn™ II (n = 10) or Intralipid® (n = 10)	TPN	LCT 10% Liposyn™ II versus Intralipid®	1.2 g/kg (12 mL/kg)	Baseline and 240 min after start of infusion	*Group comparison*: No cardiovascular adverse event.
[10]	Observational cohort study (prospective)	19 adult patients following an uncomplicated isolated coronary artery bypass receiving ILE at a rate of 2 mL/min (n = 12) versus 1 mL/min followed by 2 mL/min (n = 7)	TPN	LCT 20% (Intralipid®)	120 mL versus 60 mL + 120 mL	Pre-infusion, during infusion (5, 10, 15, 30, 45 and 60 min following its initiation) and 2 h after its termination	*Pre-/post-comparison*: An 8% decrease in cardiac index occurred at 30 min in the higher rate infusion ($p \leq 0.02$). An increase in pulmonary capillary wedge pressure occurred at 10–15 min in the control group. *Group comparison*: A significant decrease in cardiac output and increase in pulmonary wedge pressure in the higher rate infusion, while none occurred in the control group. Also, one case of cardiac ischemia after 30 min of infusion in the higher rate infusion n group.
[14]	Observational cohort (prospective pre-/post-intervention)	12 patients (7 critically ill patients and 5 healthy volunteers)	TPN	LCT 20% (Intralipid®)	500 mL	Pre-infusion, 2 and 4 h after start of infusion	*Pre-/post-comparison*: All patients experienced a significant rise in cardiac output (from 5.8 to 6.7 L/min, p = 0.05), HR remained unchanged, increased in pulmonary vascular resistance (from 64.7 dyne/s to 131.9 dyne/s, p = 0.05). No adverse effects on hemodynamics.
[11]	Case series	Two poisoned patients (1 with metoprolol + buproprion and 1 with diltiazem + propranolol)	Rescue	LCT 20% (Intralipid®)	100 mL of 20% ILE and 150 mL of 20% ILE	30 s–1 min after ILE given	Both critically ill patients received lipid rescue therapy for bradycardia and hypotension refractory to vasopressors and high-dose insulin. Both suffered brady/asystolic arrest shortly after ILE administration.

(*continued*)

Table 2. *Continued*

References	Study type	Type of population (number)	Indication of ILE	Type of ILE	Total dose/duration of ILE	Timing of adverse events	Adverse events
[12]	Case report	1 (70 years)	TPN	LCT 10–20% (Intralipid®)	2580 mL/24 h for 4 days	4 days after ILE started. ILE was stopped when the hemofiltration line was found to contain milky fluid, but patient had cardiac arrest soon after	Death (cardiac arrest)
[13]	Case report	1 (34 weeks)	TPN	ILE 10% (Intralipid®)	0.08 g/h (8 mL/h ILE) × 8 h = 0.64 g	8 h after ILE started	Cardiac arrest and death
[18]	Case report	1	TPN	NR	NR	NR	Tamponade from TPN infused into pericardium
Hematologic effects							
[21]	Descriptive cohort (retrospective)	Nine adult patients with cardiovascular drug toxicity	Rescue	LCT 20% (Intralipid®)	Bolus ± Infusion unknown amount	NR	1 out of 9 had DIC with fatal outcome (11.1%)
[22]	Case report	1 (34 years)	TPN	10% MCT/LCT	500 mL/day for 2 days	Just after second dose of ILE on day 2	Catatonia, thrombocytopenia, leukopenia noted after two doses of ILE.
[23]	Case report	1 (30 weeks)	TPN	LCT 20% (Intralipid®)	87 mL over 12 h (79 mL/kg)	Starting during the erroneous infusion	Dosing error in premature infant resulting in persisting hyponatremia (for the following 5 days), elevated liver enzymes and intraventricular hemorrhage.
[24]	Case report	1 (54 years)	TPN	LCT 10% (Intralipid®)	500 mL/day for 3 weeks	6 h after receiving 500 mL in 2 h instead of 8 h (250 mL/h)	Developed intravascular hemolysis. Abnormal bone marrow.
Acute kidney injury							
[29]	Observational cohort study (prospective)	104 premature infants receiving either TPN (n = 50) or EN (n = 54)	TPN	NR	0.5 g/kg/day (2.5 mL/kg/day using 20% ILE or 5 mL/kg/day using 10% ILE) for unknown duration	Between third day and 30th day of life	*Pre-/post-comparison*: Significant increase in serum cystatin C (from 1.2 to 1.6 mg/L), urinary β2 microglobulin (from 3.8 to 10.6 mg/L), gluthatione-S-transferase π (from 6.7 to 44.3 ng/mL) and N-acetyl-β-D glucosaminidase (from 2.9 to 7.3 μg/L) in TPN group (Ps all < 0.001), while the levels in the control group remained comparable. *Group comparison:* Significant decreased in glomerular and tubular function at 30th day of life in TPN group as compared to the EN (higher marker levels in TPN group, Ps all < 0.05). No statistical difference in BUN or creatinine.
[21]	Descriptive cohort (retrospective)	Nine patients with cardiovascular drug toxicity	Rescue	LCT 20% (Intralipid®)	Bolus ± Infusion	NR	Three out of nine patients had renal failure (33.3%). No value reported. All three survived.
[26]	Case report	One with amitriptyline OD	Rescue	LCT 20% (Intralipid®)	250 mL bolus, then 100 mL/h for 24 h, then 18 mL/h for 17 days	NR	Acute renal failure observed, no values reported.
[28][a]	Case report	One with Diltiazem OD refractory to standard therapy	Rescue	LCT 20% (Intralipid®)	1 mg/kg (5 mL/kg) bolus then 0.5 mg/kg/min (2.5 mL/kg/min) drip	NR	Renal failure no value reported

(*continued*)

Table 2. *Continued*

References	Study type	Type of population (number)	Indication of ILE	Type of ILE	Total dose/duration of ILE	Timing of adverse events	Adverse events
[27][a]	Case report	1	TPN	LCT 20% (Intralipid®)	100 mL of 20%	NR	Iatrogenic OD in premature infant, elevation in blood urea nitrogen.
[12]	Case report	1 (70 years man with complicated post-operative course after emergency surgery)	TPN	LCT 10–20% (Intralipid®)	2580 mL/24 h	NR	Renal failure required hemofiltration. BUN 20.4 mmol/L (57 mg/dL), creatinine 300 mmol/L (3.4 mg/dL.
Metabolic acidosis							
[21]	Descriptive cohort (retrospective)	Nine patients with cardiovascular drug toxicity	Rescue	LCT 20% (Intralipid®)	Bolus ± Infusion	NR	One out of nine had metabolic acidosis resulting in death (11.1%)
[30]	Case report	1 (32 weeks old infant)	TPN	LCT 20% (Intralipid®)	250 mL of 20% – 24 g Lipid/kg body weight	On day 5 of life immediately after infusion	*Massive OD of TPN*: Patient developed metabolic acidosis, among other effects – Treated with exchange transfusion, full recovery

AE: Adverse events; AKI: acute kidney injury; AMS: altered mental status; ARDS: acute respiratory distress syndrome; BB: beta blocker; BM: bone marrow; CCB: calcium channel blocker; CVC: central venous catheter; CVVHF: continuous veno-venous hemofiltration; DIC: disseminated intravascular coagulation; CO: carbon monoxide; DKA: diabetic ketoacidosis; DLCO: carbon monoxide diffusion capacity; DVT: deep vein thrombosis; ECMO: extracorporeal membrane oxygenation; FiO_2: fraction of inspired oxygen; FOBLE: fish oil-based lipid emulsion; GA: gestational age; HPF: high powered field; ICU: intensive care unit; ILE: intravenous lipid emulsion; LCT: long chain triacylglycerols; LFT: liver function tests; LPL: lipoprotein lipase; MCT: medium chain triacylglycerols; MODS: multiorgan dysfunction syndrome; NA: not available; NICU: neonatal intensive care unit; NR: not reported; OD: overdose/poisoning; PAP: pulmonary artery pressure; $P(A–a)O_2$: Alveolar Arterial gradient; PaO_2: arterial partial pressure of oxygen; PAI-1: plasminogen activator inhibitor type I; Pt: patient; PVR: peripheral vascular resistance; R/Q: respiratory quotient; SVC: superior vena cava; TAT: thrombin antiothrombin; TCA: tricyclic antidepressants; TG: triacylglycerols; TPN: total parenteral nutrition; Tx: treatment; V/Q: ventilation perfusion; VCO_2: carbon dioxide production; VO_2: oxygen consumption.

[a]A study available in abstract only.

Table 3. Pulmonary adverse effects reported in human studies.

References	Study type	Type of population (number)	Indication of ILE	Type of ILE	Total dose/ duration of ILE	Timing of adverse events	Adverse events
ARDS/ALI/Hypoxia/V/Q Mismatch							
[32]	Randomized controlled trial	60 polytrauma patients randomized to receive 10 days of either standard TPN with ILE (n = 30) or TPN without ILE (n = 27)	TPN	LCT 10 or 20%	10 or 20% ILE for 12 h	Duration of hospitalization	*Group comparison*: Total number of pneumonia during hospitalization was 27 in the ILE group as compared to 14 in the control group (p = 0.05) The ILE group also experienced a longer course of mechanical ventilation (p = 0.01).
[33]	Randomized controlled trial	41 very low birth weight neonates randomized to either 1 g/kg/day on 24 h with subsequent increasing dosage (n = 15), or same intervention on 16 h (n = 14), or 4 g/kg/day on 24 h (n = 12)	TPN	LCT 10% or 20% (Intralipid®)	Max dose 4 g/kg/day (40 mL/kg/day) × 8 days	At baseline and every 12 h for 8 days	*Pre/post and group comparisons*: Various regimens and rates of infusion had no effect on blood pH and alveolar-arteriolar oxygen diffusion gradient.
[45]	Randomized controlled trial	21 septic patients with ARDS randomized to either LCT (n = 10) or LCT/MCT (n = 11)	TPN	LCT 20% (Intralipid®) & LCT/MCT 20% (Lipofundin®)	50% of daily non-protein caloric requirement given over 8 h	Pre-infusion, 30 min before the end of infusion and 4 h following the infusion	*Pre-/post-comparison*: Significant and transient increase in pulmonary venous admixture (from 24% to 37%) and a decrease in PaO_2/FiO_2 (from 240 to 180) during LCT infusion. Significant increase in VO_2 (from 329 to 396 mL/min) during LCT/MCT infusion. *Group comparison*: Transient higher pulmonary venous admixture and VO_2 and lower PaO_2/FiO_2 during LCT infusion ($p < 0.05$).
[16]	Randomized controlled crossover trial	Nine patients with pancreatitis and ARDS randomized to either LCT (n = 9) or LCT/MCT (n = 9), alternatively for 24 h	TPN	LCT 20% (Intralipid®) & LCT/MCT 20% (Lipofundin®)	50% of daily non-protein caloric requirement given over 8 h	Pre-infusion, 30 min before the end of infusion and 4 h following the infusion	*Pre-/post-comparison*: Significant and transient increase in pulmonary venous admixture (from 26% to 36%) and a decrease in PaO_2/FiO_2 (from 210 to 170) during LCT infusion. Significant increase in VO_2 (from 340 to 398 mL/min) and VCO_2 (from 247 to 282 mL/min) during LCT/MCT infusion. *Group comparison*: Transient higher pulmonary venous admixture and VO_2, and lower PaO_2/FiO_2 during LCT infusion ($p < 0.05$). Transient higher VCO_2 during LCT/MCT infusion ($p < 0.05$).
[17]	Randomized controlled crossover study	18 critically ill patients (stratified by diseases: 10 severe sepsis and 8 ARDS) randomized either to receiving TPN over 6 h (n = 18) or 24 h (n = 18), alternatively	TPN	LCT 20% (Lipovenos)	1.1–1.3 g/kg in sepsis group and 1.29–1.31 g/kg to ARDS group	Pre-infusion and every 6 h for 24 h	*Pre/post and group comparison*: In the ARDS group with rapid infusion, there was an increase in P/T ratio, in pulmonary shunt fraction and in $P(A-a)O_2/PaO_2$ while there was a decrease in pulmonary vascular resistance and PaO_2/FiO_2. The opposite occurred in the ARDS group with slow infusion as well as in the sepsis group with rapid infusion (in which P/T ratio remained unchanged at either infusion rate).
[19]	Randomized controlled trial	20 patients post major gastrointestinal surgery randomized to Liposyn™ II (n = 10) or Intralipid® (n = 10)	TPN	LCT 10% Liposyn™ II versus Intralipid®	1.2 g/kg (12 mL/kg)	Baseline and 240 min after start of infusion	*Group comparison*: No respiratory adverse event.
[38]	Observational cohort study (prospective)	12 premature low birth weight infants either receiving ILE (n = 6 on 13 infusions) versus not receiving ILE (n = 6)	TPN	LCT 10% (Intralipid®)	0.2–0.9 g/kg (2–9 mL/kg) over 2 h	Baseline and 90 min after start of infusion	*Pre-/post-comparison*: In ILE infusion, increase in the ratio of right ventricular pre-ejection period to ejection time (from 0.232 to 0.285; p = 0.0001), from which 43% of patients had pulmonary hypertension. No change in the control group. *Group comparison*: ILE infusion was associated with echocardiographic pulmonary hypertension.

(*continued*)

Table 3. *Continued*

References	Study type	Type of population (number)	Indication of ILE	Type of ILE	Total dose/ duration of ILE	Timing of adverse events	Adverse events
[35]	Observational cohort study (prospective)	19 adult patients: 8 with ADRS and receiving TPN with ILE; 5 with ARDS receiving TPN without ILE; 6 without ARDS receiving TPN with ILE (n = 6)	TPN	LCT & MCT 20% (Lipofundin®)	0.21 g/kg (1.05 mL/kg) over 1 h	Pre-infusion and at the end of the infusion	*Pre-/post-comparison*: Decrease in PaO_2/FiO_2 (from 129 to 95) and in compliance of respiratory system (from 39.2 to 33.1 mL/cm H_2O), and an increase in pulmonary vascular resistance (from 258 to 321 dyne × s × cm (−5)) in the ARDS with ILE group. No significant change was observed in the two other groups. *Group comparison*: ILE bolus in ARDS group resulted in deterioration in pulmonary gas exchange and increased pulmonary vascular resistance as compared with controls.
[43]	Observational cohort study (prospective)	19 preterm infants either with respiratory distress with 1.5 g/kg/day for 24 h followed by 3 g/kg/day for 24 h (n = 11) or healthy preterm infants (n = 8)	TPN	LCT 20% (Intralipid®)	1.5–3 g/kg/day (7.5–15 mL/kg/day) for 2 days	At baseline and after 24 h of infusion	*Pre-/post-comparison*: Increased ratio of right ventricular pre-ejection period to ejection time in the 1.5 g/kg/day infusion group (from 0.225 to 0.287) and in the 3 g/kg/day infusion group (up to 0.326). No significant change was observed in the controls. *Group comparison*: Continuous 24 h ILE infusion caused significant dose and time dependent increases in pulmonary vascular resistance.
[49]	Observational cohort study (prospective)	15 preterm infants receiving either olive-oil based emulsion (n = 5) or soy-oil based emulsion (n = 10)	TPN	LCT 20% (Clinoleic & Intralipid®)	1–3 g/kg/day (5–15 mL/kg/day)	At baseline and at maximum lipid infusion	*Pre-/post-comparison*: Estimated PAP fell in both groups: olive-oil-based emulsion group (83%) and soy-oil based emulsion (12%) *Group comparison*: Estimated fall in PAP was greatest in the olive-oil-based emulsion group than in the soy-oil based emulsion ($p = 0.02$).
[14]	Observational cohort (prospective pre-/post-intervention)	12 patients (7 critically ill patients and 5 healthy volunteers)	TPN	LCT 20% (Intralipid®)	500 mL	Pre-infusion, 2 and 4 h after start of infusion	*Pre-/post-comparison*: All patients experienced an increase in VO_2 and in VCO_2 (19% and 17% In healthy volunteers, and 31 and 37% in critically ill patients). RQ remained constant. No adverse effects on pulmonary gas exchange and blood gases.
[39]	Observational cohort (prospective pre-/post-intervention)	Seven infants with hyaline membrane disease or bronchopulmonary dysplasia	TPN	LCT 20% (Intralipid®)	0.05–0.027 g/kg/h (0.25–0.135 mL/kg/h) for 10 h/day	Pre-infusion and after lipid infusion	*Pre-/post-comparison*: Significant decrease in transcutaneous PO_2 after lipid infusion (mean decrease of 10%). No change in transcutaneous PCO_2
[41]	Observational cohort (prospective pre-/post-intervention)	Three normal fasting patients	TPN	LCT 20% (Intralipid®)	200 mL over 30 min	Before and after infusion	*Pre-/post-comparison*: No significant difference in diffusion of CO
[42]	Observational cohort (prospective pre-/post-intervention)	16 premature neonates	TPN	LCT 10% (Intralipid®)	1 g (10 mL) over 4 h	Baseline, at 4 and 8 h	*Pre-/post-comparison*: Decrease in PaO_2 (from 80.6 to 59.1 and to 65.3 mmHg). Infants less than a week old had significant decline in PaO_2 after lipid, while those aged 2–3 weeks did not. Other blood gas parameters were not altered.
[47]	Observational cohort (prospective pre-/post-intervention)	Eight premature infants	TPN	LCT 10% (Intralipid®)	1 g/kg (10 mL/kg)	Baseline and 15 min after start of ILE infusion	*Pre-/post-comparison*: Decrease in umbilical artery oxygen tension (from 70.9 to 62.0 mmHg), from which 6 had greater than 10 mmHg drop
[48]	Observational cohort (prospective pre-/post-intervention)	Five full term neonates	TPN	NR	2 g/kg (10 mL/kg using 20% ILE or 20 mL/kg using 10% ILE)	Baseline and after 6 h of ILE infusion	*Pre-/post-comparison*: Significant decrease in alveolar oxygen tension (from 107 to 97 mmHg) and respiratory quotient (from 1.0 to 0.8), but not in alveolar-arterial O_2 gradient.
[21]	Descriptive cohort (retrospective)	Nine patients with cardiovascular drug toxicity	Rescue	LCT 20% (Intralipid®)	Bolus ± Infusion	NR	Acute Lung Injury reported in three out of nine patients (33.3%). All three survived

(*continued*)

Table 3. *Continued*

References	Study type	Type of population (number)	Indication of ILE	Type of ILE	Total dose/ duration of ILE	Timing of adverse events	Adverse events
[34][a]	Descriptive cohort (prospective)	Nine patients with cardiovascular collapse (with poor response to vasopressors) secondary to lipo-soluble agents poisoning	Rescue	LCT 20% (Intralipid®)	500–1000 mL Bolus	NR	One case of ARDS in severe verapamil toxicity. Outcome not reported.
[26]	Case report	One patient with amitriptyline OD	Rescue	LCT 20% (Intralipid®)	250 mL bolus, then 100 mL/h for 24 h, then 18 mL/h for 17 days	NR	ARDS and respiratory failure reported no details given. Survival without sequelae
[37]	Consecutivecase series	Nine patients with lipophilic drug toxicity	Rescue	LCT 20%	Various	NR	Three developed ARDS
[40]	Case report	One patient with verapamil OD	Rescue	LCT 20%	100 mL bolus then 0.2 mL/kg/min	NR	ARDS from Intralipid® used for verapamil toxicity. Survival.
[44]	Case report	One (3 yo) patient with Bupivacaine toxicity	Rescue	LCT 20%	170 mL	NR	Resuscitated successfully. VQ mismatch noted after resuscitation
[31]	Case report	One patient	TPN	LCT 10% (Intralipid®)	NR	NR	ARDS from Intralipid®. Care withdrawn and patient expired.
[30]	Case report	One patient	TPN	LCT 20% (Intralipid®)	250 mL of 20% – 24 g Lipid/kg body weight	NR	Massive OD of TPN in 32 weeks old infant - respiratory distress, Treated with exchange transfusion, full recovery
[36]	Case series	Eight premature infants	TPN	LCT 20% (intralipid®)	Total NR- rate from 0.07 g/kg/h to 0.44 g/kg/h (0.35–2.2 mL/kg/h) for 4 h–27 days	NR	Autopsies showed fat accumulation in pulmonary vasculature consistent with V/Q mismatch, inconsistent with fat overload syndrome or embolism.
[46][a]	Case report	One premature infant	TPN	LCT 20% (Intralipid®)	14.5 mL over 1.75 h	NR	Received an accidental OD of Lipid, was hypoxic for 12 h but returned to normal without sequelae

AE: Adverse events; AKI: acute kidney injury; AMS: altered mental status; ARDS: acute respiratory distress syndrome; BB: beta blocker; BM: bone marrow; CCB: calcium channel blocker; CVC: central venous catheter; CVVHF: continuous veno-venous hemofiltration; DIC: disseminated intravascular coagulation; CO: carbon monoxide; DKA: diabetic ketoacidosis; DLCO: carbon monoxide diffusion capacity; DVT: deep vein thrombosis; ECMO: extracorporeal membrane oxygenation; FiO_2: fraction of inspired oxygen; FOBLE: fish oil-based lipid emulsion; GA: gestational age; HPF: high powered field; ICU: intensive care unit; ILE: intravenous lipid emulsion; LCT: long chain triacylglycerols; LFT: liver function tests; LPL: lipoprotein lipase; MCT: medium chain triacylglycerols; MODS: multiorgan dysfunction syndrome; NA: not available; NICU: neonatal intensive care unit; NR: not reported; OD: overdose/poisoning; PAP: pulmonary artery pressure; $P(A–a)O_2$: Alveolar Arterial gradient; PaO_2: arterial partial pressure of oxygen; PAI-1: plasminogen activator inhibitor type I; Pt: patient; PVR: peripheral vascular resistance; R/Q: respiratory quotient; SVC: superior vena cava; TAT: thrombin antiothrombin; TCA: tricyclic antidepressants; TG: triacylglycerols; TPN: total parenteral nutrition; Tx: treatment; V/Q: ventilation perfusion; VCO_2: carbon dioxide production; VO_2: oxygen consumption.

[a]A study available in abstract only.

acids. The authors suggested that the increased plasma catecholamine level could have been the mechanism by which ILE affected cardiac repolarization. Eighteen critically ill patients (stratified by disease – 10 with severe sepsis and with eight with ARDS) were randomized to receive TPN over either 6 h or 24 h.[17] In the ARDS group with rapid infusion, a decrease in pulmonary vascular resistance and systemic vascular resistance occurred, while there was an increase in cardiac index. The authors attributed these effects to ILE administration and concluded that linoleic acid administration, regardless of infusion rate, may be unwanted in patients with pulmonary organ failure. One patient experienced tamponade from TPN infused into the pericardium.[18] After major gastrointestinal surgery, 20 patients were randomized to Liposyn™ II or Intralipid®.[19] No cardiovascular events were noted. Liposyn II is a 50% soy/50% safflower oil emulsion.

Smyrniotis et al. studied nine patients with pancreatitis and ARDS who were randomized to receive either long-chain triacylglycerols (LCT) or LCT/medium-chain triacylglycerols (MCT) alternately for 24 h in a crossover trial.[16] An example of LCT is Intralipid®, while Lipofundin® represents a LCT/MCT mixture. When comparing the two treatment conditions, there was a transient higher mean pulmonary artery pressure from 28 to 35 mm Hg during LCT infusion ($p < 0.05$) and a transient higher cardiac output from 8.8 to 9.5 L/min during LCT/MCT infusion ($p < 0.05$). In an observational cohort, 12 patients (5 volunteers, 7 critically ill) received Intralipid® 2.1 mL/min for 4 h (500 mL total volume).[14] All of the critically ill patients experienced a significant rise in cardiac output (5.8–6/7 L/min) and an increase in pulmonary vascular resistance (64.7–131.9 dyne/sec/cm^5). No adverse effects on hemodynamics were reported.

Hematological effects

Four articles described hematological effects after administration of TPN containing lipid.[21–24] McGrath and associates described a patient in whom intravascular hemolysis developed following an infusion of 500 mL of Intralipid® 10% over 2 h.[24] For 3 weeks, the patient had received the same daily amount infused over 8 h without any symptoms. The reaction to the faster administration indicated that the reaction was likely due to the rate of infusion. The authors speculated that Intralipid® might cause changes in the phospholipid composition of the red cell membrane; or alternatively, a product of Intralipid® breakdown (e.g., lysolecithin) might have acted as a direct hemolysin. Two other author groups reported thrombocytopenia in the setting of lipid administration for TPN.[22,25] Geib and colleagues described the emergence of disseminated intravascular coagulation (DIC), which had a fatal outcome.[21] Low and Ryan determined that a dosing error in a premature infant resulted in persistent hyponatremia (for 5 days), elevated liver enzymes, and intraventricular hemorrhage.[23]

Acute kidney injury

Six articles focused on adverse effects classified under AKI.[12,21,26–29] Three of them involved the use of ILE for poisoning,[21,26,28] and three described patients receiving TPN.[12,27,29] AKI requiring continuous renal replacement therapy (CRRT) was noted in a patient who received 20% ILE for 18 h as treatment for tricyclic antidepressant overdose.[26] A serum creatinine was not reported. AKI occurred in three of nine patients receiving various doses of 20% Intralipid® for overdose of various cardiotoxic medications, though AKI was not defined and no laboratory markers were reported.[21] AKI developed in an 47-year-old female after Intralipid® administration in the setting of diltiazem poisoning.[28] A serum creatinine was not reported.

Crook reported AKI in a patient who received 2580 mL of ILE (combined dose for 10% and 20% ILE) over 24 h.[12] An elevation in blood urea nitrogen from 7 to 28 mg/dL was detected in a premature infant after an iatrogenic overdose of Intralipid® intended for TPN.[27] No change in serum creatinine was observed. In the largest of the reports, reduced glomerular and tubular function, manifested by increased urine protein markers, was detected in 50 premature infants receiving TPN, including 0.5 g/kg/day (equivalent to 2.5 mL/kg/day of 20% ILE) of a lipid emulsion that was not specifically described.[29] The two groups were significantly different at baseline in this non-randomized, observational study. 80% of the neonates in the TPN group were born at 28–30 weeks gestation; 80% of the enterally-fed infants were older than 30 weeks. Likewise, the mean birth weight for the enteral group was 30% higher than the mean birth weight of the TPN group. Mothers of the TPN-fed babies were more likely to have hypertension or eclampsia.

Metabolic acidosis

Two articles addressed metabolic acidosis after ILE administration.[21,30] One case series reported metabolic acidosis in one of nine patients being treated with ILE in response to drug-induced cardiotoxicity.[21] The magnitude of this acidosis and the amount of lipid received were not reported. Fairchild and associates described the clinical course of a preterm infant who received an overdose of Intralipid® 20% (24 g/kg or 250 mL) over 60 min.[30] The child had laboratory values of a pH of 7.25, a PCO_2 of 35 mm Hg, and a PaO_2 64 of mm Hg, which improved with administration of sodium bicarbonate, 2 mEq/kg. The patient's oxygen saturation was 92%, with evidence of ARDS. It is unclear how, or if, ILE administration and the metabolic acidosis were related.

Pulmonary adverse effects

26 articles addressed pulmonary adverse effects, including ARDS, ALI, hypoxia, and V/Q mismatch (Table 3).[14,16,17,19,21,26,30–49] Six of these cases were reported in the context of rescue ILE, while the remaining 20 were in the context of TPN. The articles reporting ARDS after administration of ILE for poisoning describe a total of nine cases.[26,34,37,40,50] All patients were critically ill prior to receiving rescue ILE, so the authors could not implicate ILE as a single direct causative factor in development of ARDS. Four of the TPN articles cited or speculated a mechanism of Intralipid®-induced ARDS in which fatty acid precursors to arachidonic acid resulted in inflammatory cascade and prostaglandin production.[16,35,45,51] One patient of particular

interest was a 68-year-old man who developed ARDS and died after receiving a first dose of lipid for TPN.[31] Another article described a premature infant who received an unintentional overdose of almost 30 mL/kg of 20% Intralipid® over 1.75 h and then became dusky and hypoxic. Echocardiography demonstrated pulmonary hypertension. The effect was transient and self-resolved, so TPN with ILE was eventually resumed.[46]

Several articles specifically addressed V/Q mismatch as a complication of ILE.[17,36,44] The earliest one describes eight preterm infants who died after administration of Intralipid®.[36] The dose did not exceed 3 g/kg/day (15 mL/kg/day of 20% ILE). Signs of lipid deposits could be seen as early as 4 h after the first infusion. At autopsy, the lungs of these babies were found to have significantly greater lipid deposits than a matched group of infants who had not received ILE. One of the eight infants died within 3 days after ILE administration. Another child presented with perfusion mismatch 4 h after cardiac arrest induced by a local anesthetic.[44] The dose of ILE given was 3 g/kg/h (15 mL/kg/h of 20% ILE) instead of 0.125 g/kg/h, as recommended by the American Society for Parenteral and Enteral Nutrition (ASPEN). Nonetheless, the causes of this child's pulmonary dysfunction are likely multifactorial.[52] A prospective controlled randomized crossover study of 10 ARDS and eight septic adult patients reported an increased prostaglandin/thromboxane ratio matching and an increase in pulmonary shunting with either slow (24 h) or rapid (6 h) ILE infusion given for nutritional support at rates of 0.050–0.054 g/h (0.25–0.27 mL/h for 20% ILE) over 24 h or 0.2–0.217 g/h (1–1.09 mL/h for 20% ILE) over 6 h.[51] The authors of this study recommended caution in using ILE in patients with pulmonary disease. In a prospective, observational cohort of 12 patients receiving TPN, all patients experienced an increase in VO_2 (oxygen consumption) and in VCO_2 (carbon dioxide excretion) (19% and 17% in healthy volunteers; 31% and 37% in critically ill patients).[14] No adverse effects on pulmonary gas exchange or blood gases were reported. Conversely, three articles cited no adverse pulmonary effects from lipid used for TPN.[19,33,41] Forty-one very-low-birth weight neonates were randomized to either 1 g/kg/day over 24 h with subsequent increasing doses (n = 15), the same intervention over 16 h (n = 14), or 4 g/kg/day over 24 h (n = 12). The various regimens and rates of infusion had no effect on blood pH or alveolar-arteriolar oxygen diffusion gradient.[33] Following major gastrointestinal surgery, Tomassetti and associates randomized 20 patients to receive Intralipid® or Liposyn™ II for TPN. No adverse respiratory events were reported.[19] Partridge and colleagues found no significant difference in diffusion of carbon monoxide in three normal, fasting volunteers who received 200 mL of 20% Intralipid® over 30 min.[41]

Hypersensitivity and allergic adverse effects

Eight articles addressed hypersensitivity, a reaction with an incidence of less than 1% in clinical trials (Table 4).[31,53–58] Published reports of hypersensitivity involve 1–3 cases and include adult and pediatric patients. Reaction severity includes diffuse pruritus[56]; diffuse urticaria and dyspnea[55]; urticarial rash[54,59]; skin blistering[53]; and diffuse erythema, shortness of breath, and tachypnea with subsequent development of ARDS and death.[31] In most cases, the reactions resolved when ILE was stopped and without treatment with antihistamines and/or glucocorticoid therapy. One report indicated hypersensitivity to ILE containing LCT in three cancer patients. Re-exposure to LCT and exposure to marginally different formulations of MCT solutions without soybean lecithin were well tolerated.[57] One out of 48 patients receiving ILE rescue was reported to have bronchospasm after administration.[60] In the study by Tomassetti et al., mentioned above, no adverse allergic events were reported in twenty patients who were randomized to receive Intralipid® or Liposyn™ II for TPN after major gastrointestinal surgery.[19]

Vascular occlusion

Priapism

Five articles addressed priapism (Table 5).[61–65] Klein and colleagues reported the development of priapism in two patients after infusion of 500 mL of Intralipid® 20% or Liposyn™ (a safflower oil emulsion) during long-term TPN therapy.[63] Hebuterne and associates described their management of a man who experienced priapism as a reaction to parenteral nutrition, and summarized four other cases from previously published articles.[64] Chapuis and Stratt reported priapism in a 70-year-old man who received 1500 mL of Intralipid® 20% daily following emergency surgery.[62] Priapism occurred at the end of his daily infusion on the 34th day of TPN therapy. While this interval exceeded the criterion for the article selection process, it is reasonably likely that this adverse effect may be attributable to a single infusion of ILE and not to the cumulative dosage of the previous 34 days. The rate of infusion was not reported. Collectively, these five articles present eight cases of priapism associated with TPN. Half of them had received heparin in addition to ILE. The reaction occurred under a range of circumstances: at a wide range of intervals (45 min to 11 days) and doses (between 500 and 1500 mL daily).

Deep vein thrombosis/phlebitis/coagulation biomarkers

Four articles addressed DVT in a context that could apply to the use of ILE in toxicology.[21,66–68] Phlebitis was developed at the site of ILE administration shortly after the onset of infusion during resuscitation from a diphenhydramine poisoning; DVT was confirmed on a return visit.[66] Geib and colleagues diagnosed DVT in 3 of 9 patients who received ILE for poisoning. Two of them received a bolus with a subsequent infusion, and one patient received three boluses. The total doses of ILE were not reported.[21] In a prospective, observational cohort study in patients receiving TPN, Altomare and co-workers found that tissue plasminogen activator concentrations were significantly lower in a group receiving 500 mL ILE over 5–6 h than in a control group.[67]

Table 4. Hypersensitivity and allergic adverse effects reported in human studies.

References	Study type	Type of population (number)	Indication of ILE	Type of ILE	Total dose/ duration of ILE	Timing of adverse events	Adverse events
[19]	Randomized controlled trial	20 patients post major gastrointestinal surgery randomized to Liposyn™ II (n = 10) or Intralipid® (n = 10)	TPN	LCT 10% Liposyn™ II versus Intralipid®	1.2 g/kg (12 mL/kg)	Baseline and 240 min after start of infusion	*Group comparison*: No allergic adverse event.
[60]	Descriptive cohort (prospective)	48 patients with drug toxicity (online lipid registry): 10 with LA, 38 other OD)	Rescue	Multiple preparations	Variable	NR	Bronchospasm 1/48 cases (2.1%)
[53]	Case report	One patient	TPN	NR	Unknown	NR	Severe skin erythema, edema, and blistering at site of infusion. Resolution after 2 months with steroids and antibiotics.
[54]	Case report	One patient	TPN	LCT 20% (Intralipid®)	650 mL total	NR	Urticarial rash, resolution with diphenhydramine
[55]	Case report	One patient	TPN	LCT 10% (Intralipid®)	500 mL	NR	Prior history of allergy to legume and bean products developed urticaria and dyspnea that responded to diphenhydramine.
[59]	Case report	1 (9 years)	TPN	LCT 20% (Intralipid®)	NR	NR	After 19 days of TPN, developed urticarial rash that resolved with cessation and recurred with rechallenge. Disparity noted between skin testing and intravenous challenge.
[56][a]	Case report	1 (2 years)	TPN	LCT 20% (Intralipid®)	NR	NR	Developed allergic reaction, resolved with cessation. Subsequent positive egg white allergy.
[57]	Case series	Three patient	TPN	MCT & LCT? %	NR	NR	Hypersensitivity to LCT but not MCT in cancer patients. Symptoms resolved with steroids and termination of infusion.

AE: Adverse events; AKI: acute kidney injury; AMS: altered mental status; ARDS: acute respiratory distress syndrome; BB: beta blocker; BM: bone marrow; CCB: calcium channel blocker; CVC: central venous catheter; CVVHF: continuous veno-venous hemofiltration; DIC: disseminated intravascular coagulation; CO: carbon monoxide; DKA: diabetic ketoacidosis; DLCO: carbon monoxide diffusion capacity; DVT: deep vein thrombosis; ECMO: extracorporeal membrane oxygenation; FiO_2: fraction of inspired oxygen; FOBLE: fish oil-based lipid emulsion; GA: gestational age; HPF: high powered field; ICU: intensive care unit; ILE: intravenous lipid emulsion; LCT: long chain triacylglycerols; LFT: liver function tests; LPL: lipoprotein lipase; MCT: medium chain triacylglycerols; MODS: multiorgan dysfunction syndrome; NA: not available; NICU: neonatal intensive care unit; NR: not reported; OD: overdose/poisoning; PAP: pulmonary artery pressure; $P(A–a)O_2$: Alveolar Arterial gradient; PaO_2: arterial partial pressure of oxygen; PAI-1: plasminogen activator inhibitor type I; Pt: patient; PVR: peripheral vascular resistance; R/Q: respiratory quotient; SVC: superior vena cava; TAT: thrombin antiothrombin; TCA: tricyclic antidepressants; TG: triacylglycerols; TPN: total parenteral nutrition; Tx: treatment; V/Q: ventilation perfusion; VCO_2: carbon dioxide production; VO_2: oxygen consumption.
[a]A study available in abstract only.

Fat embolism

Six articles addressed fat embolism in patients receiving TPN.[13,20,69–72] The majority occurred after at least 7 days of therapy. No cases were associated with administration of ILE in the treatment of poisoning. It is unknown if the risk of fat embolism occurs with each infusion or is a cumulative risk.

CVVHF circuit and ECMO line interference

Three case reports or series described line complications.[40,73,74] Rodriguez et al. described a 26-year-old man with refractory hypotension and bradycardia following an intentional overdose of amlodipine, metoprolol, and lisinopril. He received a bolus of ILE 20% followed by a continuous infusion after other treatments had failed.[74] He continued to deteriorate, and he underwent continuous veno-venous hemofiltration. Lipemic blood appeared immediately in the CVVHF filter, and the filter become completely obstructed and unusable. The patient died despite ongoing resuscitation efforts. Buck and colleagues conducted a prospective study that identified nine neonates who received ILE for nutrition and were on simultaneous extracorporeal membrane oxygenation (ECMO). Five patients received ILE through the ECMO circuit and four patients received ILE through a separate line. All five patients receiving ILE through the ECMO circuit developed clots in the circuit. Two of the four patients in the IV access group developed blood clots, though it is not mentioned if clotting in the circuit occurred.[73]

Table 5. Vascular occlusion adverse effects reported in human studies.

References	Study type	Population (number and type)	Indication of ILE	Type of ILE	Total dose of ILE	Timing of adverse events	Adverse events
Priapism							
[62]	Case report	One patient	TPN	LCT 20% (Intralipid®)	1500 mL/day × 34 days	At the very end of 1500 mL ILE on the 34th day	Priapism, remained impotent at 3-year follow up
[61]	Case series	Three patient	TPN	LCT (20% Intralipid®)	500–1000 mL/day	One patient developed priapism after 5 days, two patients after 11 days	Priapism developed 5–11 days following TPN. Treated surgically. One out of three patients remained impotent at 6-month follow up.
[64]	Case report	One patient	TPN	LCT 20%	500 mL/12 h	Within 24 h of the onset of ILE	Priapism, continued impotence at 3-year follow up
[63]	Case series	Two patient	TPN	LCT (Liposyn™) 20%	Unclear within 1 h of 500 mL infusion rate not reported	45 min after start of ILE infusion	Two patients with priapism, one remained impotent, one had resolution after treatment. Incidence of 5.7% (from an 8-year TPN program including 35 males).
[65]	Case report	One patient	TPN	LCT 20% (Intralipid®)	500 mL for 5 days then 1000 mL for 1 day	12 h after infusion on the 6th day of ILE	Priapism, treated surgically. No erections at 2 months follow up
Deep vein thrombosis/phlebitis/coagulation biomarkers							
[67]	Observational cohort study (prospective)	24 patients with various diseases receiving ILE (n = 12) versus no ILE (n = 12 matched controls)	TPN	LCT 10% (Intralipid®)	500 mL over 5–6 h	Baseline, at the end of the infusion and 24 h later	*Pre-/post-comparison*: Tissues plasminogen activator levels were significantly lower at the end of the infusion and 24 h later (Ps < 0.001 and <0.05), while they were increased in the controls at the end of the infusion only ($p < 0.01$). *Group comparison*: Tissue plasminogen activator levels were significantly lower in the ILE group than in the control group, while PAI-1 levels were comparable at all times between the two groups.
[68]	Observational cohort study (prospective)	10 healthy men received IV endotoxin after either ILE (n = 5) or dextrose 5% (n = 5)	TPN	LCT 20% (Intralipid®)	500 mL	Pre-infusion and every hour for 6 h	*Pre/post and group comparison*: Peak levels of prothrombin fragment Fi + 2, TAT complexes and PAI-1 increased to 6.88 nM, 63.1 μg/L, and 622.3 μg/L in the ILE group as compared to 4.93 nM, 37.1 μg/L, and 337.7 μg/L in the control group, which was statistically higher in the ILE group (Ps all < 0.05). Infusion of lipid emulsion potentiated endotoxin induced coagulation activation in compared to controls
[21]	Descriptive cohort (retrospective)	Nine patients with cardiovascular drug toxicity	Rescue	LCT 20% (Intralipid®)	Bolus ± Infusion	NR	Three out of nine had DVT (33.3%). Two survived.
[66]	Case report	One patient with Diphenhydramine OD	Rescue	LCT 20%	8 mL/kg	2 weeks after ILE	Observed phlebitis during administration. On 2-week follow-up the patient was found to have a deep vein thrombosis in the brachial vein and a superficial thrombosis in the proximal basilic vein.
Fat embolism							
[20]	Case series	Four infants	TPN	LCT 20% (Intralipid®)	0.08–0.15 g/kg/h (0.4–0.75 mL/kg/h) for 11–18 days	No specific timing	Autopsies showed evidence of fat emboli at autopsy. All had received prolonged ILE.

(*continued*)

Table 5. *Continued*

References	Study type	Population (number and type)	Indication of ILE	Type of ILE	Total dose of ILE	Timing of adverse events	Adverse events
[69]	Case report	One patient	TPN	LCT? % (Intralipid®)	500 mL/15 min	Immediately after ILE	Developed fever, Vision Loss, Seizure and coma after lipid infusion – Complete resolution by 2 weeks
[13]	Case report	One premature infant	TPN	ILE 10% (Intralipid®)	0.08 g/h (8 mL/h ILE) × 8 h = 0.64 g	8 h after the beginning of infusion	Pulmonary microemboli found at autopsy death 12 h post-ILE
[70]	Case series	Two patients (aged 22 and 76)	TPN	NR	Unknown	NR	Suspected cerebrovascular fat emboli due to development of permanent neurological deficits while receiving ILE
[71]	Case report	One child	TPN	LCT 20% (Lipofundin®)	60.7 g/kg (303.5 mL/kg) over 7 weeks	NR	Autopsy showed fat embolism of pulmonary small arteries and giant-cell reaction in lumen.
[72]	Case report	One pediatric patients	TPN	LCT 20% (Intralipid®)	5.1 mg/kg/day (25.5 mL/kg/day) for 1 day	24 h after infusion	Fat emboli in multiple capillaries and arterioles in organs including the brain, spleen, liver, kidney, and lymph nodes
CVVHF circuit clot or ECMO line interference							
[73]	Randomized controlled trial	Nine neonates on ECMO randomized to TPN either by the ECMO circuit (n = 5) or separate IV access (n = 4)	TPN	LCT 20% (Intralipid®)	3 g/kg (15 mL/kg) max	During the 24 h following the start of infusion	Group comparison: 100% developed clots in the ECMO circuit versus 50% in the IV access (p = NR). Clot formation trended to occur more frequently when ILE is administered by the ECMO circuit.
[40]	Case report	One patient with Verapamil OD with ARDS, treated with VA-ECMO and CVVH	Rescue	LCT 20% (Intralipid®)	100 mL if ILE with infusion 0.2 mL/kg duration unknown	NR	Filter needed to be changed three times
[74]	Case report	One patient with BB and CCB refractory to standard therapy treated with CVVHF for volume overload and acidosis	Rescue	LCT 20% (Intralipid®)	1.5 mg/kg (7.5 mL/kg) bolus × 2	NR	CVVHF unsuccessful due to lipemic blood and filter obstruction

AE: Adverse events; AKI: acute kidney injury; AMS: altered mental status; ARDS: acute respiratory distress syndrome; BB: beta blocker; BM: bone marrow; CCB: calcium channel blocker; CVC: central venous catheter; CVVHF: continuous veno-venous hemofiltration; DIC: disseminated intravascular coagulation; CO: carbon monoxide; DKA: diabetic ketoacidosis; DLCO: carbon monoxide diffusion capacity; DVT: deep vein thrombosis; ECMO: extracorporeal membrane oxygenation; FiO_2: fraction of inspired oxygen; FOBLE: fish oil-based lipid emulsion; GA: gestational age; HPF: high powered field; ICU: intensive care unit; ILE: intravenous lipid emulsion; LCT: long chain triacylglycerols; LFT: liver function tests; LPL: lipoprotein lipase; MCT: medium chain triacylglycerols; MODS: multiorgan dysfunction syndrome; NA: not available; NICU: neonatal intensive care unit; NR: not reported; OD: overdose/poisoning; PAP: pulmonary artery pressure; $P(A–a)O_2$: Alveolar Arterial gradient; PaO_2: arterial partial pressure of oxygen; PAI-1: plasminogen activator inhibitor type I; Pt: patient; PVR: peripheral vascular resistance; R/Q: respiratory quotient; SVC: superior vena cava; TAT: thrombin antiothrombin; TCA: tricyclic antidepressants; TG: triacylglycerols; TPN: total parenteral nutrition; Tx: treatment; V/Q: ventilation perfusion; VCO_2: carbon dioxide production; VO_2: oxygen consumption.

Infection susceptibility and inflammation adverse effects

Nine articles discussed the adverse effect of immune modulation in the context of ILE administration (for rescue therapy in only one case) (Table 6).[19,21,22,32,75–79] Battistella and associates conducted a prospective, randomized trial of 57 trauma patients randomized to receive 20% ILE or no ILE as part of the TPN during the first 10 days of TPN. The group that received ILE had a higher rate of infectious complications.[32] This scenario may not apply to the short courses of ILE for acute poisoning. In acute poisoning, treatment with ILE seldom continues for many days, although Agarwala and colleagues describe a patient with a massive and severe amitriptyline overdose treated with ILE at 18 mL/h for a total of 19 days with no complication other than lipemia.[26]

In a study of the effect on neutrophil function, Cury-Boaventura and colleagues gave volunteers a single infusion of 500 mL of a 20% soybean oil over 6 h.[76] The obtained-blood sample before, immediately after, and 18 h after infusion, and then cultured lymphocytes and neutrophils for 0, 24, or 48 h after sampling. Compared with samples taken prior to ILE infusion, samples taken immediately after the end of ILE infusion had decreased levels of lymphocytes and neutrophils. The authors pointed to mitochondrial membrane

Table 6. Infection susceptibility/inflammation adverse effects reported in human studies.

References	Study type	Population (number and type)	Indication of ILE	Type of ILE	Total dose of ILE	Timing of adverse events	Adverse events
[32]	Randomized controlled trial	60 polytrauma patients randomized to standard TPN with ILE (n = 30) or TPN without ILE for the first 10 days (n = 27)	TPN	LCT 10 or 20%	10 or 20% ILE for 12 h	Clinical outcomes: duration of hospitalization. T-cell function: baseline and day 5	*Pre-/post-comparison*: T-cell function improved in the control group contrary to the ILE group which deteriorated by day 5. *Group comparison*: Total number of infectious episodes was 72 (from which 27 pneumonia and 15 line sepsis) in the ILE group and 39 (from which 14 pneumonia and 6 line sepsis) in the control group. ILE group had more frequent infectious complications (pneumonia ($p = 0.05$) and line sepsis ($p = 0.04$)) than the control group.
[19]	Randomized controlled trial	20 patients post major gastrointestinal surgery randomized to Liposyn™ II (n = 10) or Intralipid® (n = 10)	TPN	LCT 10% Liposyn™ II versus Intralipid®	1.2 g/kg (12 mL/kg)	Baseline and 240 min after start of infusion	*Pre/post and group comparison*: No change in inflammatory C4 CRP
[79]	Randomized controlled crossover trial	10 patients with gastric cancer randomized to either LCT (n = 10) or MCT/LCT (n = 10) emulsion, alternatively for 48 h each	TPN	LCT 10% (Lipovenos) & LCT/MCT 10% (Lipofundin®)	0.8 g/kg/h (8 mL/kg/h) for 48 h	Before and after lipid infusion	*Pre-/post-comparison*: Neutrophil bacterial killing was reduced after LCT emulsion (from 79% killed bacteria to 67%, $p<0.05$), although remaining in normal range for 80% of the patients. *Group comparison*: LCT alone had decreased neutrophil bacterial killing activity as compared with LCT/MCT ($p<0.01$), without any difference in phagocytosis index, chemotaxis, spontaneous migration, or oxidative metabolism
[78]	Observational cohort study (prospective)	Seriously ill general surgery patients receiving ILE infusion (n = 8) versus healthy volunteers receiving ILE bolus (n = 20)	TPN	LCT 20% (Intralipid®)	In seriously ill patients: 500 mL over 8 h versus healthy volunteers: bolus	Baseline and after 3 h of infusion on seriously ill patients or 15 min after bolus in healthy volunteers	*Pre/post comparison*: Decrease in monocyte chemotaxis from 150 to 94 cells/hpf in seriously ill patients after 3 h of infusion ($p < 0.05$) versus 96–60 cells/hpf in healthy volunteers 15 min after bolus ($p = 0.0002$). Preserved lymphocytes function. *Group comparison*: Similar decreased monocyte function (chemotaxis) in both groups following Intralipid®. Also, heparin prevented the changes in monocytes function.
[76]	Observational cohort (prospective pre-/post-intervention)	11 healthy volunteers	TPN	LCT 60% (Soybean oil emulsion)	500 mL over 6 h	Baseline, immediately post-infusion and 18 h post-infusion	*Pre-/post-comparison*: Various neutrophils and lymphocytes biomarkers showed significant alteration immediately post-infusion, with a persistent effect in many biomarkers 18 h post-infusion. Decrease in lymphocyte proliferation and enhanced lymphocyte and neutrophil apoptosis after infusion
[21]	Descriptive cohort (retrospective)	Nine patients with cardiovascular drug toxicity	Rescue	LCT 20% (Intralipid®)	Bolus ± Infusion	NR	One case of sepsis survived.
[77]	Descriptive cohort (prospective)	103 TPN bottles were collected at completion of 5–12 h infusions and 5–10 mL cultured for measurement of bacterial contamination	TPN	LCT 10% (Travalmulsion)	NA	After completion of infusion	7.8% were positive for bacterial growth with various bacterial contaminant. No reported cases of bacteremia

(*continued*)

Table 6. *Continued*

References	Study type	Population (number and type)	Indication of ILE	Type of ILE	Total dose of ILE	Timing of adverse events	Adverse events
[75]	Case report	One neonate	TPN	(Intralipid®)	NR	Unclear but during first 6 weeks unknown when scalp vein inserted	ILE infusion into brain matter (accidental). Died 62 days later. No local immune response on pathology.
[22]	Case report	One patient	TPN	MCT/LCT 10%	500 mL/day	Symptoms started after the 2nd dose of ILE on the 3rd hospital day	Catatonia, thrombocytopenia, leukopenia noted after two doses of lipid.

AE: Adverse events; AKI: acute kidney injury; AMS: altered mental status; ARDS: acute respiratory distress syndrome; BB: beta blocker; BM: bone marrow; CCB: calcium channel blocker; CVC: central venous catheter; CVVHF: continuous veno-venous hemofiltration; DIC: disseminated intravascular coagulation; CO: carbon monoxide; DKA: diabetic ketoacidosis; DLCO: carbon monoxide diffusion capacity; DVT: deep vein thrombosis; ECMO: extracorporeal membrane oxygenation; FiO_2: fraction of inspired oxygen; FOBLE: fish oil-based lipid emulsion; GA: gestational age; HPF: high powered field; ICU: intensive care unit; ILE: intravenous lipid emulsion; LCT: long chain triacylglycerols; LFT: liver function tests; LPL: lipoprotein lipase; MCT: medium chain triacylglycerols; MODS: multiorgan dysfunction syndrome; NA: not available; NICU: neonatal intensive care unit; NR: not reported; OD: overdose/poisoning; PAP: pulmonary artery pressure; $P(A–a)O_2$: Alveolar Arterial gradient; PaO_2: arterial partial pressure of oxygen; PAI-1: plasminogen activator inhibitor type I; Pt: patient; PVR: peripheral vascular resistance; R/Q: respiratory quotient; SVC: superior vena cava; TAT: thrombin antiothrombin; TCA: tricyclic antidepressants; TG: triacylglycerols; TPN: total parenteral nutrition; Tx: treatment; V/Q: ventilation perfusion; VCO_2: carbon dioxide production; VO_2: oxygen consumption.

depolarization and nucleus lipid accumulation to explain cell death, which occurred without alteration in reactive oxygen species (ROS) production. This presumed mechanism might enhance patients' susceptibility to infections. The cell death percentage increased from less than 5% immediately after infusion to 15% at 24 h. The decrease in lymphocyte proliferation was greater immediately following infusion than at 18 h afterward.[76]

Liang and colleagues gave a patient 500 mL of an ILE 10% for 2 days (total dose, 1 L) for nutritional support following ingestion of a corrosive agent, which caused an esophageal injury.[22] He experienced an acute catatonia, mutism episode associated with ecchymosis. Severe thrombocytopenia (platelet count of 11,000 cells/μL) and leukopenia (1500/cells/μL) were reported. All symptoms and types of cytopenias resolved within 24 h after discontinuation of the ILE infusion. The hematology team eliminated other possible causes such as thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, and hemolysis. The speculative mechanism was N-methyl-D-aspartate (NMDA) receptor hyperactivity at a high plasma dilution of ILE (1:80 to 1:5). A dose of 50 mL/h for 10 h (500 mL/day) would yield dilution of 1:70.

In a randomized crossover trial of patients receiving LCT or LCT/MCT TPN, Waitzberg and co-workers observed that LCT alone had decreased neutrophil bacterial killing activity compared with LCT/MCT ($p < 0.01$), without any difference in phagocytosis index, chemotaxis, spontaneous migration, or oxidative metabolism.[79] In a separate observational cohort, Fraser and associates found decreased monocyte function (chemotaxis) following administration of Intralipid®.[78]

A patient being treated with ILE for rescue therapy by Geib and colleagues developed sepsis but survived. The association between ILE and sepsis is not described, and it is unclear whether ILE played a causative role.[21] Tomassetti and associates reported no infection susceptibility adverse events in 20 patients who were randomized to receive Intralipid® or Liposyn™ II for TPN following major gastrointestinal surgery.[19]

Ebbert and colleagues collected 103 TPN bottles at the completion of 5–12 h infusions and 5–10 mL samples and cultured them to measure bacterial contamination.[77] Almost 8% of the samples were positive for various bacterial contaminants. None of the patients who received the contents of those bottles experienced bacteremia.

Fat overload syndrome, hypertriglyceridemia, lipemia, hyperamylasemia, pancreatitis, cholestasis

Fat overload syndrome, hypertriglyceridemia, lipemia, hyperamylasemia, pancreatitis, and cholestasis are among the most commonly reported adverse effects associated with ILE rescue and TPN therapy (Table 7). Of the 41 articles that describe these effects, 33 were from TPN [12,14,15,19,20,23,24,27,30,33,41,47,72,73,80–98] and eight were from ILE rescue therapy for overdose.[21,26,28,37,60,99–101] Intralipid® 20% was the most common formulation used in the articles that reported the type of lipid (27/38). In most cases, the laboratory abnormalities were transient and did not appear to play a role in the patient's outcome. Most of the patients who died were neonates or premature infants, or had been on long-term TPN therapy. It is unclear what role, if any, the laboratory abnormalities contributed to mortality when ILE was used in the management of a poisoning. Eight articles addressed fat overload syndrome, a constellation of many of the isolated complications reported and generally accompanied by

Table 7. Fat overload syndrome/hypertriglyceridemia/lipemia/hyperamylasemia/pancreatitis/cholestasis.

References	Study type	Type of population (number)	Indication of ILE	Type of ILE	Total dose/duration of ILE	Timing of adverse events	Adverse events
[80][a]	Randomized controlled trial	42 patients with severe acute pancreatitis randomized to either fish oil-based lipid emulsion (FOBLE) (n = 22) or MCT/LCT (n = 22)	TPN	MCT/LCT/Omega 3 20% (Lipidem) or MCT/LCT 20% (Lipofundin®)	2 g/dL/kg/day (10 mL/kg/day) × 7 days	Post-infusion triglycerides and random cholesterol 6–10 h post-infusion on days 0, 1, 2, 3, 5, and 7.	*Group comparison*: Post-infusion triglycerides and random cholesterol levels were slightly higher in the MCT/LCT group, but not significantly. Also, one patient developed transient hypertriglyceridemia in the MCT/LCT group.
[73]	Randomized controlled trial	Nine neonates on ECMO randomized to receiving TPN either by the ECMO circuit (n = 5) or separate IV access (n = 4)	TPN	LCT 20% (Intralipid®)	3 g/kg (15 mL/kg) max	During the ECMO course	*Group comparison*: No difference in TG between groups receiving ILE via ECMO or peripheral IV access.
[33]	Randomized controlled trial	41 very low birth weight neonates randomized to either 1 g/kg/day on 24 h with subsequent increasing dosage (n = 15), or same intervention on 16 h (n = 14), or 4 g/kg/day on 24 h (n = 12)	TPN	LCT 10% or 20% (Intralipid®)	Max dose 4 g/kg/day (40 mL/kg/day) × 8 days	During the 8 days of the study	Hyperlipidemia: 0% in first group, 7.1% in the second group (1 patient) and 16.7% in the third group (2 patients).
[84]	Randomized controlled crossover trial	18 infants randomized to either Intralipid®) (n = 18) or Liposyn™) (n = 18), alternatively on 2 consecutive days	TPN	LCT? % (Intralipid®) versus LCT? % (Liposyn™)	1 g/kg/day (5 mL/kg/day if 20% ILE)	Baseline and at 2, 4, and 8 h after the start of the infusion	*Pre-/post-comparison*: Increase in triglycerides during infusion was from 58 to 208 mg/dL with Lyposyn™ versus from 53 to 162 mg/dL with Intralipid® (at 8 h compare to baseline). *Group comparison*: Higher triglycerides observed in Lyposyn™ group as compared with Intralipid® ($p < 0.05$, <0.001, and <0.001 at 2, 4, and 8 h of infusion compared to baseline).
[94]	Randomized controlled crossover trial	22 premature infants with physiologic jaundice, first randomized to either low or high heparin dose, then to a 15-h (n = 22) or a 24-h (n = 22) infusion, alternatively on 2 consecutive days	TPN	10% LCT (intralipid®)	2 g/kg/day (20 mL/kg/day) for 2 days	Pre- and post-infusion	*Pre-/post-comparison*: Significant increase in free fatty acids, triglycerides, and cholesterol was from 1.19 to 2.04 μmol/L, 162 to 298 mg/dL and 140 to 169 mg/dL in the 15-h infusion group as compared to 0.92–1.40 μmol/L, 104–192 mg/dL and 132 to 156 mg/dL in the 24-h infusion group. *Group comparison*: Significant higher fatty acids, triglycerides and cholesterol in the 15-h infusion. Also, a greater increase in fatty acids during the high heparin infusion. There was no significant change in unbound bilirubin.
[15]	Randomized controlled crossover trial	32 healthy subjects randomized to either ILE (n = 32) or saline (n = 32), alternatively on two separate occasions	TPN	LCT 10% (Intralipid®)	Unknown amount of infusion given for 180 min.	Pre-infusion and at 180 min	*Pre-/post-comparison*: Significant increase in fatty acids in the ILE group (from 435 to 710 mmol/L, $p < 0.01$) versus no significant increase in the saline group (from 405 to 449 mmol/L). *Group comparison*: Higher levels of fatty acids were observed in the ILE group as compared controls ($p = 0.0001$).

(*continued*)

Table 7. *Continued*

References	Study type	Type of population (number)	Indication of ILE	Type of ILE	Total dose/duration of ILE	Timing of adverse events	Adverse events
[19]	Randomized controlled trial	20 patients post major gastrointestinal surgery randomized to Liposyn™ II (n = 10) or Intralipid® (n = 10)	TPN	LCT 10% Liposyn™ II versus Intralipid®	1.2 g/kg (12 mL/kg)	Baseline and 240 min after start of infusion	*Pre-/post-comparison*: Increase in triglycerides with Liposyn™ II (from 1.1 to 4.9 mM/L) versus with Intralipid® (from 0.9 to 4.6 mM/L). *Group comparison*: No statistical difference in transient rise in triglycerides between the two groups. No cardiovascular, respiratory, or allergic adverse event. No change in hematologic or coagulation parameters.
[95]	Randomized controlled trial	16 patients in pre-cholecystectomy randomized to ILE (n = 8) or saline infusion (n = 8)	TPN	LCT 10%	1000 mL	After 6 h of infusion	Two types of cholesterol crystals were present in 75 and 63% with ILE versus 13 and 0% with saline. *Group comparison*: ILE increased the lithogenicity (supersaturation) of bile (Ps = 0.04 and 0.03)
[97]	Randomized controlled trial	31 patients in post-hepatectomy randomized to olive oil (n = 15) or soybean oil (n = 16)	TPN	Olive oil versus Soybean ILE	0.85 g/kg/day (4.25 mL/kg/day using 20% ILE or 8.5 mL/kg/day using 10% ILE)	At surgery and 7 days after	*Pre-/post-comparison*: Levels of ALT, AST, total bilirubin, and direct bilirubin significantly decreased in both groups between surgery and the 7th post-operative day, while ALP levels remained stable. *Group comparison*: Post-operative liver function were not significantly different between two groups (all Ps > 0.05)
[81]	Observational cohort study (prospective)	26 infants. ≤32 weeks gestational age with indirect hyperbilirubinemia receiving varying ILE dosages (generally in gradually increasing dosages)	TPN	LCT 20% (Intralipid®)	0.5 to 3 g/kg/day (2.5–15 mL/kg/day) × 7 days (between the third and tenth days after birth)	When increasing ILE from 0.5 to 1, 1.5, 2, 2.5 to 3 g/kg/day	*Pre-/post-comparison*: Increase in unbound bilirubin from 0.49 to 0.82, 0.93, 1.01, 1.98 to 2.11 μg/dL. *Group comparison*: Increase in unbound bilirubin was associated with increase in ILE dosage (p = 0.02), even after adjustment for gestational age and glucose infusion (p = 0.003). In infants <28 weeks, increase in unbound bilirubin was significantly associated with an increase in ILE intake, but not in infants >28 weeks.
[87]	Observational cohort study (prospective)	725 critically ill patients receiving artificial nutrition either TPN (n = 303) or EN (n = 422)	TPN	MCT/LCT? %	NR	Various	*Group comparison*: Liver dysfunction in 30% of TPN group as compared to 18% in the EN group. Liver dysfunction was associated with the use of TPN at the univariate (p < 0.001), but also at the multivariate analysis (OR 1.96, 95% CI 1.3 to 2.97, p < 0.001), after adjusting for sepsis, MODS, early use of artificial nutrition, and energy requirements >25 kcal/kg/day
[89]	Observational cohort study(retrospective)	21 low birth weight infants who died and had receiving ILE (n = 9) or human milk with IV carbohydrate solution (n = 12)	TPN	LCT 20% (Intralipid®)	2 g/kg (10 mL/kg) × 8 days (avr)	Various	Lipid accumulation was not found in brain capillaries, but was visible in pulmonary capillaries, macrophages, and alveolar cells in 78, 78, and 78% in the ILE group versus 17, 58, and 50% in controls *Group comparison*: Pulmonary Artery lipid deposits were more frequent in the ILE group. No death was attributed to ILE.

(*continued*)

Table 7. *Continued*

References	Study type	Type of population (number)	Indication of ILE	Type of ILE	Total dose/duration of ILE	Timing of adverse events	Adverse events
[96][a]	Observational nested case–control study (retrospective)	523 preterm infants who received various duration of TPN were compared based on the presence (n = 46) or absence (n = 477) of TPN-associated cholestasis	TPN	NR	NR	Various	TPN-associated cholestasis: 8.8% of the cohort. *Group comparison*: TPN-associated cholestasis was associated with longer duration of TPN, higher calorie intake, but also with lower gestational age, lower birth weight, later enteric feeding and complications of prematurity.
[98]	Observational case-–control study (retrospective)	24 neonates who died and had received various duration of TPN were compared based on the severity of liver histopathological abnormalities: normal-to-mild (n = 16) and moderate-to-severe (n = 8)	TPN	NR	NR	Various	In this cohort with liver histopathological findings: 83% periportal inflammation, 79% cholestasis, 79% bile duct proliferation, 71% fibrosis, 29% steatosis, 17% necrosis, and 13% cirrhosis. *Group comparison*: More severe liver abnormalities were associated with a longer duration of TPN (p = 0.0008), but also with smaller gestational age, bronchopulmonary dysplasia, and direct hyperbilirubinemia.
[86]	Observational cohort (pre-/post-intervention)	21 patients mechanically ventilated in ICU after a major trauma	TPN	LCT 20* Elolipid	0.075–0.15 g/kg (0.375–0.75 mL/kg)	Starting on day 2 and then day 3, 5, and 7	*Pre-/post-comparison*: Significant transient rises in median triglycerides during the infusion period (from 107 to 191, to 271, and to 271 mg/dL).
[88]	Observational cohort (pre-/post-intervention)	20 normal subjects	TPN	LCT 20% (Intralipid®)	500 mL	Baseline and after 4 h of ILE infusion	*Pre-/post-comparison*: Transient hyperlipidemia observed (Increase in triglycerides from 68 to 339 mg/100 mL).
[14]	Observational cohort (prospective pre-/post-intervention)	12 patients (7 critically ill patients and 5 healthy volunteers)	TPN	LCT 20% (Intralipid®)	500 mL	Pre-infusion, 2 and 4 h after start of infusion	*Pre-/post-comparison*: During infusion, plasma triglycerides increased in the volunteer group (from 1 to 7.3 and 8.5 mmol/L (P <0.01) and in the patients (from 1.4 to 5.0 and 6.3 mmol/L, p < 0.01).
[47]	Observational cohort (prospective pre-/post-intervention)	Eight premature infants	TPN	LCT 10% (Intralipid®)	1 g/kg (10 mL/kg)	Baseline and at 15 min, 30 min, 60 min, 2 h and 4 h post-infusion	*Pre-/post-comparison*: Increase in triglycerides (10 fold) at 15 min post-infusion.
[41]	Observational cohort (prospective pre-/post-intervention)	Three normal fasting patients	TPN	LCT 20% (Intralipid®)	200 mL over 30 min	Before, during and 2 h after infusion	*Pre-/post-comparison*: Increase in triglycerides (up to 3–4 fold) during infusion returning to baseline 2 h after.
[60]	Descriptive cohort (prospective)	48 patients with drug toxicity (online lipid registry): 10 with LA, 38 other OD)	Rescue	Multiple preparations	Variable	NR	One patient exhibited hyperamylasemia 1/48 (2.1%) without clinical signs of pancreatitis. Amylase level NR.
[21]	Descriptive cohort (retrospective)	Nine patients with cardiovascular drug toxicity	Rescue	LCT 20% (Intralipid®)	Bolus ± Infusion	NR	Three patients out of nine developed lipemia (33.3%), reported to have potential to cause laboratory interference. Lipid levels NR.
[83][a]	Descriptive cohort(prospective)	105 neonates in ICU	TPN	LCT 20% (Intralipid®)	NR	NR	Lipidemia: 18.1% and abnormal LFT/ Hepatitis: 19.0%
[148]	Descriptive cohort (retrospective)	78 patients	TPN	Unknown	Unknown	NR	35 (44.9%) developed elevated liver enzymes, not significantly associated with mortality.

(*continued*)

Table 7. *Continued*

References	Study type	Type of population (number)	Indication of ILE	Type of ILE	Total dose/duration of ILE	Timing of adverse events	Adverse events
[91]	Descriptive cohort (retrospective)	120 infants and children	TPN	LCT 20% (Clinoleic)	1.9 g/kg (9.5 mL/kg) × 7 days	NR	9 (7.9%) developed subacute onset of biochemical hepatotoxicity (GGT rise in 7 days).
[93]	Descriptive cohort	267 neonates	TPN	NR	1–3 g/kg/day, % ILE NR (5–15 mL/kg/day using 20% ILE; 10–30 mL/kg/day using 10% ILE)	NR	23 (8.6%) developed cholestatic jaundice and found that patients with less than 32 weeks' gestation were more likely to develop cholestasis.
[26]	Case report	One with amitriptyline OD	Rescue	LCT 20% (Intralipid®)	250 mL bolus, then 100 mL/h for 24 h, then 18 mL/h for 17 days	NR	Severe lipemia observed after ILE administration, acute renal failure observed.
[99][a]	Case report	One with Bupropion OD	Rescue	LCT 20% (Intralipid®)	4000 mL	NR	Survival, asymptomatic pancreatitis, laboratory interference
[100]	Case report	One with Cocaine OD	Rescue	LCT 20% (Intralipid®)	500 mL total	NR	Survival, transient hypertriglyceridemia and hyperamylasemia- resolved in 6 h.
[37]	Consecutive Case series	Nine patients with lipophilic drug toxicity	Rescue	LCT 20%	Various	NR	Three developed clinical signs and symptoms of pancreatitis. For one patient, the lipase level is NR. One patient had Lipase peak at 2951 IU/L, and one at 185 IU/L.
[101]	Case report	One with Bupivacaine OD	Rescue	LCT 20% (Intralipid®)	500 mL	NR	Hyperamylasemia of unknown clinical significance after successful resuscitation following bupivacaine toxicity.
[28][a]	Case report	One with Diltiazem OD refractory to standard therapy	Rescue	LCT 20% (Intralipid®)	1 mg/kg (5 mL/kg) bolus then 0.5 mg/kg/min (2.5 mL/kg/min) drip	NR	Dramatic improvement with ILE but developed lipemia, pancreatitis, transaminitis, and renal failure.
[20]	Case series	Four infants	TPN	LCT 20% (Intralipid®)	0.08–0.15 g/kg/h (0.4–0.75 mL/kg/h) for 11–18 days	NR	Autopsies showed evidence of fat emboli and lipid laden macrophages. All had received prolonged ILE.
[27][a]	Case report	One patient	TPN	LCT 20% (Intralipid®)	100 mL of 20%	NR	Accidental OD in premature infant resulting in transient hypertriglyceridemia, and elevation in blood urea nitrogen.
[82]	Case report	1 (43 yo alcoholic patient)	TPN	LCT 20% (Intralipid®)	200 mL	On the fourth day of ILE right at the end of infusion of 200 mL	Relapse of chronic pancreatitis
[12]	Case report	1 (70 yo)	TPN	LCT 10–20% (Intralipid®)	2580 mL/24 h	4 days after TPN	Plasma cholesterol 6.1 mmol/L and triacylglyerol 9.0 mmol/L.
[30]	Case report	1 (32 week old infant)	TPN	LCT 20% (Intralipid®)	250 mL of 20% – 24 g Lipid/kg body weight	Fifth of life, at the end of ILE infusion	Massive OD of TPN: Patient developed hypertriglyceridemia, respiratory distress, metabolic acidosis, lethargy, apnea – Treated with exchange transfusion, full recovery.

(*continued*)

Table 7. *Continued*

References	Study type	Type of population (number)	Indication of ILE	Type of ILE	Total dose/duration of ILE	Timing of adverse events	Adverse events
[90]	Case report	One patient	TPN	LCT/MCT 20% SMOFlipid (soy oil, medium-chain triglyceride, olive and fish oil-based lipid emulsion)	20 g, 3.6 g/kg/h (18 mL/kg/h)	One hour after infusion of excessive dose	Tachypneic, dyspneic, perioral cyanosis, tachycardia, hypertension, and hyperthermia observed. Survived.
[92]	Case report	1 (22 yo with Crohn's disease)	TPN	LCT 20% (Intralipid®) then re-challenge with 10%	500 mL/day	36 h after re challenge with ILE pancreatitis recurred.	Developed pancreatitis while on TPN with lipid, re-challenge with 20% after resolution resulted in recurrence. Re-challenge with 10% was tolerated.
[23]	Case report	One patient	TPN	LCT 20% (Intralipid®)	87 mL	NR	Dosing error in a premature infant resulting in hyponatremia, elevated liver enzymes and intraventricular hemorrhage, unable to measure blood gas and TG.
[24]	Case report	One patient	TPN	LCT 10% (Intralipid®)	500 mL/day for 3 weeks	6 h after administration	ILE given over 2 h instead of 8, 6 h after the patient experienced abdominal pain. Laboratory investigation revealed lipemia, hemolysis, and elevated liver function tests.
[72]	Case report	One pediatric patients	TPN	LCT 20% (Intralipid®)	5.1 mg/kg/day (25.5 mL/kg/day) for 1 day	24 h after infusion ILE	TG rose to 1575 mg/dL, death within 48 h

[a]A study available in abstract only.

Table 8. Organ dysfunction adverse effects reported in animal studies.

References	Study design	Type of ILE	Indication	Total dose	Outcome
AE group Cardiac effects					
[107]	Experimental Rabbit model	LCT 20% (Intralipid®)	Bolus Rescue	3 mL/kg	In asphyxia induced cardiac arrest rabbits who received ILE had lower rate of ROSC (1/11) than did rabbits receiving normal saline (7/12). All animals had received epinephrine in this study.
Hematologic effects					
[108]	Experimental Rabbit model	LCT 10% (Intralipid® and Lipofundin®)	TPN	1 g/kg/h (10 mL/kg/h)	Infusion of Lipofundin® resulted in thrombocytopenia more so than Intralipid®. 35/40 animals died of DIC when co-administered endotoxin
[109]	Experimental Rabbit model	LCT 10% (Intralipid®)	TPN	7 mL/kg × 2 h	ILE infusion resulted in increased production of tissue factor from phagocytes. When phagocytes were exposed to endotoxin this finding was enhanced
[110]	Experimental Canine model	LCT 15% (FE-S15)	TPN	4–9 g/kg/day (26.7–60 mL/kg/day) for 28 days	Significant decrease in Hgb/Hct after 21 days of ILE infusion in the 9 g/kg/day group
Fat Overload (Hypertriglyceridemia, Pancreatitis, and Lipemia)					
[111]	Experimental Murine model	LCT 20% (Intralipid®)	Bolus Rescue	20–80 mL/kg	Hypertriglyceridemia, hyperamylasemia, hyperphosphatemia, elevated aminotransferases in all ILE treated animals. Hepatic and pulmonary histologic abnormalities noted. LD50 w/in 48 h is 68 ± 10 mL/kg in rats, human equivalent is 10.5 mL/kg. No cause of death noted for three animals deaths at 48 h after ILE.
[112]	Experimental Canine model	LCT 10% (Intralipid®)	TPN	Variable	Administration of ILE at a rate of 0.8 g/kg/h resulted in accumulation of triglycerides in circulation
[113]	Experimental Murine model[a]	LCT 20% (Intralipid®)	TPN	Pancreatic duct 100 mL versus 5 mL IV	Pancreatitis seen if ILE injected directly into pancreatic duct. Not observed when intravenously
[149]	Experimental Rabbit model	LCT 20% (Intralipid®)	Bolus Rescue	6, 12, and 18 mL/kg	ILE rescue bolus after Haloperidol overdose. Reported increased transaminase levels in the 18 mL/kg group as compared with control. Also reported dose dependent lung infiltration due to fat emboli.

ARDS: Acute respiratory distress syndrome; DIC: disseminated intravascular coagulation; GBS: Group B Streptococcus; ILE: intravenous lipid emulsion; IV: intravenous; LCT: long chain triacylglycerols; LD50: median lethal dosage; LPS: lipopolysaccharide; NEFA: non-esterified fatty acids; MCT: medium chain triacylglycerols; NA: not available; NR: not reported; RBC: red blood cell; ROSC: return of spontaneous circulation; Rxn: reaction; SVC: superior vena cava; TG: triacylglycerols; TNF: tumor necrosis factor; TPN: total parenteral nutrition; V/Q: ventilation perfusion.
[a]A study available in abstract only.

intravascular lipid deposition in organs such as the liver, kidney, or brain (found at autopsy).[12,72,89,90,102–104]

Animal studies

The animal studies reported in the literature were arranged into the following categories: organ failure (including cardiac, hematological, fat overload syndrome, hypertriglyceridemia/pancreatitis/lipemia); pulmonary (including acute respiratory distress syndrome [ARDS], hypoxia, and ventilation/perfusion (V/Q) mismatch); and infection susceptibility (including sepsis and systemic inflammatory response syndrome [SIRS]).

Organ dysfunction adverse events

Cardiac effects

One study addressed the cardiac and circulatory effects of ILE (Table 8).[107] In a study of cardiac arrest resulting from hypoxia (not poisoning), rabbits given ILE instead of normal saline resuscitation had a much lower rate of return of spontaneous circulation (1/11 versus 7/12).[107]

Hematologic effects

Three studies reported hematological effects related to ILE given as part of TPN.[108–110] A canine model demonstrated hemoglobin and hematocrit decrease after 21 days of soybean-oil fat emulsion administration.[110] A rabbit model demonstrated that thrombocytopenia occurred more often with cottonseed oil than Intralipid® soybean oil.[108] A separate rabbit model found increased production of tissue factor from phagocytes with Intralipid® infusion.[109]

Fat overload (hypertriglyceridemia, pancreatitis, and lipidemia)

Three studies demonstrate a predictable rise in serum triglycerides but minimal organ damage in the pancreas and biliary system after short-term ILE.[111–113] In a dog model,

Table 9. Pulmonary adverse events reported in animal studies.

References	Study design	Type of ILE	Indication	Total dose	Outcome
AE group ARDS/Acute lung injury/Hypoxia					
[117]	Experimental Canine model	Oleic acid alone versus LCT 20% (Intralipid®)	TPN	0.03 g/kg Oleic Acid versus 0.5 mL/kg of 20% ILE	Oleic acid alone increased shunt fraction and decreased lobar perfusion. ILE had no side effects
[115][a]	Experimental Porcine model	LCT 20% (Intralipid®)	TPN	N/A	ILE infusion results in more hypoxemia. Endotoxin + ILE resulted in a rapid (within 15 min) and sustained decrease in PaO_2 (85.2 versus 76.4 Torr at 0 and 180 min, respectively, $p < 0.01$), whereas no change (8l.4 versus 84.4 Torr, p = NS) was observed in Endotoxin alone. Suspected to be prostaglandin mediated.
[150][a]	Experimental Murine model	LCT (20% Clinoliec versus 20% Lipoven)	TPN	Unclear	Measurement of inflammatory markers in an *E. Coli* LPS model of Acute Lung Injury following TPN administration. No significant difference in survival between groups. Lipoven group had a more pronounced inflammatory response as measured by higher concentrations of TNF alpha and Macrophage inflammatory protein
[106]	Experimental Murine model	LCT 20% (Intralipid®)	TPN	40 mL/kg/day × 1/3/7 days	SVC thrombosis, pancytopenia, granulomatous lung Inflammatory reaction on autopsy
[118]	Experimental Murine model	Soybean oil emulsion	TPN	2.8 g (14 mL of 20% ILE)	Unstable lipid emulsions cause increased lung oxidative stress
[120][a]	Experimental Canine model	20% Fat Emulsion Solution	TPN	3.6 mL/kg	No significant hemodynamic or respiratory change over 2 h infusion
[116]	Prospective Randomized Murine model	LCT 20% (Intralipid®)	TPN	6 g/kg/day (30 mL/kg/day) for 7 days	ILE infusion in rats with normal lungs produced structural changes in pulmonary vasculature similar to those seen in conditions producing pulmonary hypertension. Intralipid® administration did not cause additional remodeling to the pulmonary vasculature of rats with baseline pulmonary vasculature remodeling.
[149]	Experimental Rabbit model	LCT 20% (Intralipid®)	Bolus Rescue	6, 12, and 18 mL/kg	ILE rescue bolus after Haloperidol overdose. Reported increased transaminase levels in the 18 mL/kg group as compared with control. Also reported dose dependent lung infiltration due to fat emboli.
[119]	Prospective Randomized Porcine model	LCT 20% (Intralipid®)	TPN	0.25 g/kg/h (1.25 mL/kg/h) or 0.8 g/kg/h (4 g/kg/day)	Endotoxin challenge in control, propofol infusion, and Intralipid® infusion groups. All groups noted hypoxia and Increased pulmonary resistance. Increased Thromboxane A2 production in high dose Intralipid® group
V/Q mismatch					
[122][a]	Experimental Porcine model	LCT 20% (Intralipid®)	TPN	1 g/kg/h (5 mL/kg/h) × 2 h	Intralipid® infusions resulted in hypoxia improved by thromboxane A2 receptor antagonist
[121]	Experimental Rabbit model	LCT 10% (Intralipid®)	TPN	4 mL/kg × 1 h	Rabbits with ARDS induced by oleic acid were treated with ILE. Hypoxia after lipid infusion did not correlate with TG increase. Hypoxia blunted by indomethacin. Suggested V/Q mismatch is due to prostaglandin production

ARDS: Acute respiratory distress syndrome; DIC: disseminated intravascular coagulation; GBS: Group B Streptococcus; ILE: intravenous lipid emulsion; IV: intravenous; LCT: long chain triacylglycerols; LD50: median lethal dosage; LPS: lipopolysaccharide; NEFA: non-esterified fatty acids; MCT: medium chain triacylglycerols; NA: not available; NR: not reported; RBC: red blood cell; ROSC: return of spontaneous circulation; Rxn: reaction; SVC: superior vena cava; TG: triacylglycerols; TNF: tumor necrosis factor; TPN: total parenteral nutrition; V/Q: ventilation perfusion.

[a]A study available in abstract only.

Table 10. Immunologic effects reported in animal studies.

References	Study design	Type of lipid	Indication	Total dose	Outcome
AE group Infection risk					
[124]	Prospective Randomized Murine model	LCT 10% or 20% (Intralipid®)	TPN	6.48 mL versus 10.8 mL	0.6 mL/h group had decreased *S. aureus* clearance, and decreased granulocyte function
[125]	Experimental Rabbit model	LCT 20% (Intralipid®) versus MCT/LCT 20% (Lipofundin®)	TPN	3 g/kg (15 mL/kg)	Mild impairment of reticuloendothelial function
[127][a]	Experimental Murine model	LCT 20% (Intralipid®)	TPN	N/A	Impaired radiolabeled RBC clearance by reticuloendothelial system, and decreased neutrophil activity
[128]	Experimental Murine model	LCT assumed 20% (Intralipid®)	TPN	10 g/kg (50 mL/kg)	9/10 deaths from GBS bacteremia in Intralipid® emulsion group. 3/10 death in control group. Hypothesized to be due to impaired neutrophil chemotaxis
[130]	Experimental Murine model	20% (Nutrilipid)	TPN	4 g/kg/day (20 mL/kg/day) for 4 days	Lipid emulsion decreased hepatic phagocytosis, increased pulmonary localization of *E. coli*.
[123]	Experimental Murine model	LCT 10% (Intralipid®)	TPN	5 mL/kg	No Lymphocyte suppression – primary end point
[106]	Experimental Murine model	LCT 20% (Intralipid®)	TPN	40 mL/kg × 24 h	SVC Thrombosis, Pancytopenia, Granulomatous Lung Inflammatory rxn
[126]	Experimental Murine model	LCT 20% (Intralipid®)	TPN	70 mg/kg/day (0.35 mL/kg/day) given IV versus PO	Increased enteral translocation and decreased lymphocyte activity in ENTERALY fed group versus Control or IV group
[129]	Experimental Murine model	LCT 20% (Intralipid®) versus MCT/LCT 20% (Lipofundin®) versus LCT 20% (ClinOleic)	TPN	13.24 g/kg (66 mL/kg) total	Decreased bacterial clearance in LCT, and MCT + LCT group compared to controls and Oleic Acid group
[131]	Experimental Bovine model	LCT 20% Multiple types: tallo, Linseed oil, fish oil emulsions	TPN	0.54 g/kg (2.7 mL/kg) over 4 h for 4 days	Leukocytes demonstrated decreased ability to respond to mitogens after Tallow derived LCT emulsions as compared with linseed oil and fish oil derived LCT emulsions
[105]	Experimental Murine model	LCT 20% (Liposyn™ III)	TPN	2.5 mL	Increased endoplasmic reticulum stress. Marker for Insulin resistance

ARDS: Acute respiratory distress syndrome; DIC: disseminated intravascular coagulation; GBS: Group B Streptococcus; ILE: intravenous lipid emulsion; IV: intravenous; LCT: long chain triacylglycerols; LD50: median lethal dosage; LPS: lipopolysaccharide; NEFA: non-esterified fatty acids; MCT: medium chain triacylglycerols; NA: not available; NR: not reported; RBC: red blood cell; ROSC: return of spontaneous circulation; Rxn: reaction; SVC: superior vena cava; TG: triacylglycerols; TNF: tumor necrosis factor; TPN: total parenteral nutrition; V/Q: ventilation perfusion.
[a]A study available in abstract only.

triglycerides rose after the administration of 10% lipid emulsion and normalized quickly at a dose of 0.4 mg/kg/h (0.004 mL/kg/h), reflecting rapid clearance from the circulation. This was not observed at the higher dose of 0.8 mg/kg/h (0.008 mL/kg/h), which was associated with prolonged abnormalities in serum triglycerides and fatty acids.[114] In a murine model of high-dose, rapidly administered ILE 20% (ranging from 20 to 80 mL/kg over 30 min), all subjects had elevations in triglycerides, serum amylase, and aspartate aminotransferase; however, histological examination of the pancreas and liver at autopsy was normal.[111] A lower-dose model in rats demonstrated a similar safety profile of ILE with respect to pancreatitis, demonstrating no such effect.[113]

Pulmonary adverse events

ARDS and hypoxia

Seven studies reported pulmonary adverse effects in animal models, all related to TPN administration (Table 9).[115–120] A porcine model demonstrated elevated thromboxane B2 levels after ILE, which might be causative in pulmonary hypertension and correlate with the degree of hypoxemia.[119] Another porcine model demonstrated an association between ILE and hypoxemia. [115] In a murine model, Intralipid® infusion in rats with normal lungs produced structural changes in pulmonary vasculature, similar to those seen in conditions that produce pulmonary hypertension.[116] Intralipid® administration did not cause additional remodeling in the

pulmonary vasculature of guinea pigs. Infusion of unstable lipid emulsion might cause oxidative stress in the lungs. [118] Two canines models demonstrated no acute deleterious effects from 20% fat emulsion on pulmonary gas exchange, blood flow distribution, or edema.[117,120] After prolonged infusion (3–7 days), superior vena cava thrombosis and pancytopenia occurred in a murine model, in addition to a granulomatous reaction in alveolar macrophages.[106]

Lung ventilation–perfusion (V/Q) mismatch

Two studies reported V/Q mismatch related to lipid administration as a component of TPN. A porcine model and a rabbit model both demonstrated a decrease in pO_2 and paO_2, respectively, following lipid infusions.[121,122] Both were thought to be related to prostaglandin mediation.

Immunologic effects

Infection susceptibility

Ten studies in primarily murine and rabbit models examined the effects of short-term TPN (24 h to 4 days) on cell-mediated immune function and survival in response to a bacteremia challenge (Table 10).[106,123–131] Intralipid® 10–20% was the primary source of ILE used; however, total doses, rates of infusion, and duration of treatment varied significantly between the studies. These studies did demonstrate mild to moderate impairments of reticuloendothelial cell-mediated function as well as somewhat higher rates of bacteremia in the TPN groups.[124,125,127,128,130] Similar effects on insulin resistance, measured by endoplasmic reticulum stress, occurred with the administration of glucose and ILE to rats.[105]

Special populations

The administration of lipid emulsion to children warrants special mention. Several reports of children receiving TPN were found, in whom fat overload syndrome developed (headaches, fever, jaundice, hepatosplenomegaly, respiratory distress, and spontaneous hemorrhage), particularly neonates. One report described a 3-year-old child who experienced pulmonary insufficiency, fever, lethargy, and tachycardia after the administration of an excess of ILE (170 mL or 15 mL/kg total) for bupivacaine toxicity.[44] Another report described an acute overdose of ILE in a 5-day-old infant after 32 weeks of gestation, who received 250 mL of 20% ILE and experienced respiratory distress, metabolic acidosis, lethargy, and apnea; treatment was successful with double-volume exchange transfusion.[30] Hojsak and colleagues reported their management of a 2-year-old child with short gut, who was given a novel lipid formulation, SMOFlipids (20% soy, MCT, olive oil, and fish oil), in whom fat overload developed after ultra-rapid infusion (100 mL over 30 min [total 20 g, 1.75 g/kg/day, 3.6 g/kg/h]).[90]

Discussion

The first "safe" ILE was developed over 50 years ago as a nutritional therapy, then later as a carrier for lipid-soluble drugs.[1] Subsequently, ILE has been employed as a treatment in toxicology, often as a last resort for the most critically ill poisoned patients. However, this therapy is not without adverse effects. Although lipid emulsions vary in composition, the majority of case reports found in this review used 10 or 20% soybean oil emulsion, such as Liposyn™ III, Intralipid®, and Nutrilipid®. It is unclear if all ILEs are associated with the same adverse effects. Newer lipid emulsions, which do not contain high omega-6 fatty acid oils, could have other adverse effects that are not well represented in the literature.

Much of the published evidence about the adverse effects of ILE comes from the early years of its use in nutrition therapy, when adverse effects were not uncommon. Adverse effects are rare when the current nutritional guidelines for ILE use are followed. The guidelines include a general limit of 2 g/kg body weight/day (10 mL/kg/day of 20% ILE) and a maximum of 3g/kg (15 mL/kg/day of 20% ILE) without special precautions in adults. The rate of infusion typically should not exceed 0.11 g/kg/h (0.55 mL/kg/h of 20% ILE) with a maximum of 0.125 g/kg/h (0.625 mL/kg/h of 20% ILE).[58] For neonates and infants, the dose should not exceed 4 g/kg/day (20 mL/kg/day of 20% ILE) and the rate not more than 0.17 g/kg/h (0.85 mL/kg/h of 20% ILE). Relatively few adverse effects associated with the treatment of various drug toxicities are reported in the clinical toxicology literature. However, given that the doses and infusion rates used in the toxicology setting often exceed those used for nutritional therapy, the dearth of reported adverse effects may represent a reporting bias or inadequate follow-up.[1]

Adverse effects of ILE fall into two major categories based on the duration of therapy. Immediate or short-term effects occur quickly, often within minutes to a few days (48 h), while delayed effects typically require much longer exposure to ILE therapy, as occurs with outpatient parenteral nutrition therapy. With the exception of hypersensitivity/allergic reactions, immediate or short-term effects tend to be associated with the dose and/or infusion rate of the ILE.

Some adverse effects of lipid emulsion appear to arise primarily in the setting of TPN and have not been reported with the use of high-dose, short-term ILE. These include cholestasis, catheter-related complications (infection, phlebitis, and thrombosis), predisposition to sepsis and immune deficiency, and catatonia.[22,63,64,132] Although there are at least four reports in the nutrition literature, no reports of these sequelae attributed to ILE therapy for poisoning were found. Comparing different lipid emulsions for TPN in surgical patients, a systematic review and meta-analysis of randomized controlled trials found no difference in adverse effects or hospital length of stay among SMOFlipid® 20% and Lipoven 20%, ClinOleic 20%, or MCT/LCT 20%.[133]

Adverse effects of ILE which have occurred either in the treatment of poisoning, or in the TPN setting at faster infusion rates similar to those administered in poisoning, include hypoxia, ARDS, priapism, fat overload syndrome, and fat emboli. The spectrum of respiratory complications, ranging from simple hypoxia to ventilator-dependent respiratory failure, has been repeatedly described in both settings. The potential for lipid administration to interfere with gas

exchange and create a ventilation–perfusion mismatch is supported by a controlled study in ICU patients, which demonstrated a detrimental effect on bronchial inflammatory markers in patients with ARDS receiving ILE.[134] Critically ill-poisoned patients, especially those suffering cardiac arrest, often develop ARDS as an evolution of illness. It is impossible to determine which of these reported effects is directly due to ILE without a more controlled study design.

AKI as a result of ILE administration is controversial, and the clinical relevance is unknown.[135] In a critically ill poisoned patient, AKI can develop for a number of reasons, including decreased renal perfusion in the setting of a shock state. When the origin of AKI is likely multifactorial, it is impossible to determine what role, if any, ILE played in its development. In addition, a transient rise in creatinine often does not translate into a true negative outcome, such as the need for CRRT. In the observational study by Tabel et al., treated with TPN tended to be younger, smaller, sicker, and at higher risk of complications.[29] Because the infants only had laboratory comparisons at 3 and 30 days, it was impossible to determine if the AKI began prior to the 14th day. However, it seems more likely than not that the modest changes in biomarkers of renal function developed gradually throughout the 30-day study period.

Differentiating adverse effects of TPN from those specific to lipid emulsion is challenging. Phlebitis is a problem with TPN due to its very high osmolarity (>1100 mOsm).[136] ILE has a lower risk from the osmolarity standpoint, as its osmolarity is about 300 mOsm, compared with a maximum of 900 mOsm for peripheral parenteral nutrition and >1500 mOsm for most TPN products. An *ex vivo* study using six simulated real-life ECMO circuits utilized a 3 mL/min infusion of Intralipid® 20% with a constant flow rate of 200 mL/min and heparin doses to maintain a clotting time greater than 200 seconds.[137] Agglutinations and layering occurred in all six circuits, and clotting occurred in five of them, especially at areas of stasis (ports), within 30 min after ILE infusion. In addition, increased circuit pressure caused the tubing to crack. The authors recommended that ILE be administered via its own line during ECMO treatment of a neonate. This article was actually excluded by the search criteria, but it is mentioned here because the model circuit mimicked real-life conditions.

The fat overload syndrome is a constellation of many of the isolated complications; the sudden onset of hypoxia, respiratory insufficiency, fever, lethargy, hepatosplenomegaly, jaundice, coagulopathy, and neurologic compromise, including altered mental status and seizures. Fat embolic complications, both pulmonary and cerebral, are more commonly reported in association with TPN than with rescue therapy for poisoning (perhaps because rescue therapy is in its relative infancy). Complications which appear to be unique to high-dose, rapidly administered ILE continue to emerge. They have been reported in the context of inadvertent TPN error leading to rapid infusion of a high dose, defined as exceeding the estimated maximum oxidation rate of 1.2–1.7 mg/kg/min (for ILE 20%, this is 0.35–0.51 mL/kg/h or 8.6–12.24 mL/kg/day). The physiologic consequences of such doses can be expected to be similar to those of rescue therapy. However, the paucity of human toxicological literature and the lack of necropsy and lung examination in the animal studies on the use of ILE in poisoning make it impossible to evaluate the true risk of fat emboli with ILE administration.

The risk of infection in patients receiving ILE is difficult to anticipate. Neutrophil and lymphocyte counts decrease almost immediately after an ILE bolus, but it is unclear how this effect translates to meaningful outcomes when treating poisoned patients.[76] Measurement of counts could also be affected by dilution after bolus administration. Most of the human research on immunologic function as it relates to ILE comes from studies that evaluated long-term effects, that is, from 4 to 14 days of therapy.[138] For most cases of poisoning, treatment lasted less than 4 days, although at least one poisoned patient received ILE for 19 days.[26] Overall, immune function seems to be most affected by the duration of ILE therapy, but the applicability of this observation to toxicological use is uncertain because the length of therapy is not standard.

Patients at the extremes of age present challenges with drug therapy, as do pregnant women. Prescribing information for ILE from the US Food and Drug Administration includes a warning of death reported in preterm infants following ILE administration, with pulmonary intravascular fat accumulation noted at autopsy.[58] One report indicated development of hypertriglyceridemia without hypoxia in low-birth-weight infants receiving 10% or 20% ILE at a maximum of 4 g/kg/day (20 mL/kg/day using 20% ILE) for 8 days [33]; however, most reports involving neonates describe adverse pulmonary events.[30,39,42,43,46–49] Preterm infants appear to be particularly susceptible to hypoxia associated with ILE-induced hypertriglyceridemia during their first week of life.[42] The cause of ILE-associated hypoxia might be a dose- and time-dependent increase in pulmonary vascular resistance in response to increased prostaglandin synthesis from higher free fatty acid concentrations following ILE infusion, rather than hypertriglyceridemia itself.[43] Alterations in pulmonary vascular resistance occur with short-term ILE doses of 1.5–3 g/kg/day (7.5–15 mL/kg/day of 20% ILE). Doses as low as 1 g/kg/day (5 mL/kg/day using 20% ILE) in premature infants reduced arterial oxygen tension in a high percentage of patients.[47] Alveolar oxygen tension is reduced in full-term infants receiving ILE 2 g/kg/day (10 mL/kg/day of 20% ILE).[48] Reduced transcutaneous PO_2 also appears to be prominent following ILE doses as small as 0.5 g/kg/day (2.5 mL/kg/day of 20% ILE) given over 10 h (0.05 g/kg/h; 0.25 mL/kg/h with 20% ILE) in infants with underlying pulmonary disease.[39]

Disturbances of fat metabolism in elderly patients, including reduced skeletal muscle fat oxidation, may occur due to lower oxidative enzyme concentrations, inhibited fatty acid transport into the mitochondria, or reduced activation of fatty acid transport.[139] Lipid oxidation during TPN, however, appears to be higher in elderly patients compared with middle-aged people.[140] Capacity for fat oxidation and plasma removal of ILE appears to be as good in elderly men as in young men.[141] This suggests that elderly patients are no more likely to develop hypertriglyceridemia or other problems related to ILE clearance than younger patients. One case report of ILE use for local anesthetic poisoning in a 91-year-old man indicated successful reversal of central nervous

system and cardiac toxicity without any indication of adverse events with the ILE.[142] None of the adverse events in this literature review showed an increased incidence among elderly patients.

All ILE products are listed as pregnancy category C, except 10% Soyacal, which is category B. Concerns about the use of ILE during pregnancy come primarily from adverse events associated with a cottonseed oil emulsion that was removed from the market in 1965, but there are still at least two remaining concerns.[143] ILE is used routinely at recommended doses and infusion rates for pregnant women requiring TPN. However, high ILE infusion rates (actual rates are not reported) may induce uterine contractions.[144] In addition, a study evaluating the effect of TPN on the placenta reported one case out of the 20 evaluated with placental fat deposits evident before fetal death occurred at 22 weeks' gestation.[145] Successful rescue ILE occurred in an 18-year-old primigravida patient at 38 weeks gestation with no reported adverse effect.[146] Pregnant women are at increased risk of local anesthetic toxicity; thus there is potentially an increased need for ILE in pregnancy.[147]

Limitations

The search criteria and citation screening were designed to be as inclusive as possible in order to estimate the clinical adverse effects associated with ILE given in doses typically used to treat acute poisonings, but the studies included in this systematic review were consistently of low or very low quality according to GRADE criteria. Furthermore, included studies could have suffered from reporting bias, in that not all adverse effects reported were related to the use of ILE and those that do occur were not always reported. Neonates and small children seem to be at higher risk of adverse events as reported in the TPN literature, however as the care of neonates has significantly changed in the last three decades since these reports were published, it is unclear if the adverse events reported are only associated with the administration of ILE. The patient populations were also quite heterogeneous in terms of age and medical comorbidities, which limits generalizability of the incidence and nature of adverse events associated with the administration of ILE in the management of poisonings. For example, gut malabsorption would be of little consequence to the use of ILE for TPN, but it could be a major issue when treating patients who have been poisoned. Nonetheless, cohort and observational studies on adverse events in the TPN setting that are applicable to clinical toxicology may answer the many questions which have arisen on the risks of this therapy at various dosages and infusion rates.[76,138]

Conclusion

This systematic review reported adverse effects from ILE administration, as reported from clinical settings and animal studies, with a focus on those most generalizable to clinical toxicology. Because few publications describe adverse events following antidotal use of ILE, the true incidence remains unknown. Extrapolation from TPN cases suggests that adverse effects might occur with the use of ILE for poisoning. The potential for significant adverse effects seems to be associated with higher doses and rapid infusion rates. Therefore, the suggestions in many case reports and review articles that large doses of ILE are safe for the purpose of reversal of drug toxicity and may not pose a risk of immediate adverse events seems to be inaccurate or at the very least unproven. Further studies in both the TPN setting and the poisoned patient will hopefully shed additional light on the risks of this therapy.

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Appendix

Medline (Ovid) search strategy for adverse effects

1. exp Fat Emulsions, Intravenous/
2. lipid rescue.ti,ab,kw.
3. (lipid adj3 emulsi*).mp.
4. (fat adj3 emulsi*).mp.
5. ((lipid or fat*) adj5 bolus).mp.
6. (lipid adj3 (resuscitat* or therap* or infus*)).mp.
7. (ILE adj5 (lipid* or emulsi* or fat*)).mp.
8. (IFE adj5 (lipid* or emulsi* or fat*)).mp.
9. (lipid adj3 sink*).mp.
10. (lipid adj3 sequest*).mp.
11. intravenous* lipid*.ti,ab,kw.
12. intralipid*.mp.
13. exp Parenteral Nutrition/
14. (parenteral* adj3 nutrition*).ti,ab,kw.
15. (parenteral* adj3 (feed* or fed)).ti,ab,kw.
16. TPN.ti,ab.
17. or/1-16
18. ae.fs.
19. to.fs.
20. po.fs.
21. co.fs.
22. (safe or safety).ti,ab.
23. side effect$.ti,ab.
24. ((adverse or undesirable or harm$or serious or toxic) adj3 (effect$ or reaction$ or event$ or outcome$)).ti,ab.
25. exp Product Surveillance, Postmarketing/
26. exp Adverse Drug Reaction Reporting Systems/
27. exp Clinical Trials, Phase IV as Topic/
28. exp Poisoning/
29. exp Substance-Related Disorders/
30. exp Drug Toxicity/
31. exp Abnormalities, Drug-Induced/
32. exp Drug Monitoring/
33. exp Drug Hypersensitivity/
34. (toxicity or complication$ or noxious or tolerability).ti,ab.
35. exp Postoperative Complications/
36. exp Intraoperative Complications/
37. or/18-36
38. 17 and 3