

## **Parenteral Nutrition in Hospitalized Patients: Comparison of Two Commercially Available Lipid Emulsions**

**Date of Protocol:** 13 March 2014

**Sponsor-Investigator:** Johane P. Allard  
University Health Network, Toronto, ON

**Expected Study Start Date:** 01 June 2013

**Expected Study End Date:** 01 December 2015

**Study Coordinator:** Sultan Alenezi, MScAHN

### **Introduction**

Parenteral nutrition (PN) is an important therapy in patients' recovery. It is indicated when the gastrointestinal tract is not functional or cannot be accessed, or the patients' nutrient needs are greater than those achieved using the gastrointestinal tract (1). Specific indications include complete intestinal obstruction, ileus or severe dysmotility, severe pancreatitis, high-output intestinal fistulae, short bowel syndrome or severe intestinal inflammatory disease (2,3).

It is important to indicate that PN need to be used in the appropriate setting, since it is a costly treatment and is not free of complications. Some of the complications secondary to PN are: catheter infections, hyperglycemia, hepatic dysfunction, hyperlipidemia and refeeding syndrome (2,4,5). Also, PN is associated with gut atrophy, reduced gut absorption, loss of gut barrier, altered gut microflora, increased bacterial adherence, increased microbe translocation, B and T cell dysfunction (3,6)

Bloodstream infections (BSI) rates vary widely among PN patients from 1.3-39% (7,8) even though there is evidence on how to reduce catheter-related infections (9). Still, there are studies that have found high rates of catheter-related infections in patients with parenteral nutrition. There is a cohort study in patients with central venous catheters, with or without PN, this study found that PN was an independent risk factor for BSI (10). Another study in 19 Canadian hospitals found that the rates of BSI among patients with PN were 4 times higher than those not receiving PN (11). The most common organisms in hospitalized patients are coagulase-negative staphylococcus, Staphylococcus aureus, Enterococcus, Candida spp, Klebsiella pneumoniae, and Pseudomonas aeruginosa (8)

Until recently, Intralipid, a soybean oil-based lipid emulsion, has been the only available lipid for intravenous use in Canada. In 2010, ClinOleic, a new, predominantly olive oil based emulsion, has been approved by Health Canada as an alternative lipid.

There is an increasing need for hospitals to do quality-assurance studies for in-patient PN to assess indications, PN prescription, complications, clinical outcomes and costs. The only in-patient population that is well studied is the intensive care unit (ICU) population. Several meta-analyses showed that PN was associated with higher infection rate, longer length of stay and higher mortality when compared with enteral nutrition (12,13). Results from these and other studies were the basis for the Canadian ICU Guidelines (13-17).

The aims of this study (already approved CAPCR 12/5174/AE) ) were to determine if PN prescribed in in-patients follows existing guidelines in terms of timing of nutrition support, prescription and monitoring and, whether it is associated with complications. In addition, clinical outcomes such as length of stay and mortality are assessed.

In addition, we will evaluate, in this cohort of patients, the effect of 2 different lipid emulsions, both approved by Health Canada (Intralipid based on soybean oil and ClinOleic based on olive oil). These lipid emulsions, readily available through our provider, will be prescribed alternatively according to standards of care. We also plan to do additional measurements relevant to nutrition which include: C-reactive protein [CRP], pre-albumin, subjective global assessment, hand grip strength and arm circumference at beginning and 10 days of PN (or at discontinuation if less than 10days). We will also monitor diagnoses of infections during PN, including 1 week after PN discontinuation if patients remain in hospital. We were advised to re-submit as a new study rather than as an amendment.

## **Background**

In a prospective quality control study in Switzerland, 200 patients receiving PN were evaluated to see if PN prescription was justified according to the 2002 ASPEN guidelines. They were recruited during 18 weeks from Medicine, Surgery and Intensive Care Units. In this study, the Nutrition Support Team did not interfere with the PN prescriptions which were made by the medical staff of the different wards. They concluded that PN prescription was justified in all but 14 patients (7%). The energy supply was adequate only in 31.5% of the patients and overfeeding was more frequently observed. Women, thin and elderly patients were at more risk for overfeeding. The same happened with the protein supply, only 21% of the patients received an adequate supply and 65.5% received excess proteins. Also, 23.5% of the patients did not receive supplementation of vitamins and/or trace elements in their PN(18). This study shows the need to establish nutrition support protocols, particularly for PN.

In one Canadian study (19), the authors conducted a cross-sectional national survey of dietitians working in ICUs and identified interventions to target for quality improvement initiatives. In this study, 24% of the sites that responded reported the presence of a nutrition support team. The enteral route was the main route of administering nutrition support and of the 702 patients studied, 7.1% received parenteral nutrition only. Underfeeding seemed

to be a significant problem in the group of patients that stayed in the ICU for more than 3 days since 16% of these patients did not receive any nutrition support. Furthermore, of those that received nutrition support the average of calories and proteins received was 56% to 62% of their estimated needs over the first 12 days in the ICU. Another study conducted in Canadian ICUs evaluated whether an auditing practice and providing feedback is an effective strategy to improve adherence to nutrition guidelines. Twenty-six ICUs participated in an audit in 2007 and were given a feedback of their performance compared with the Canadian Critical Care Nutrition guidelines. The authors observed improvement in some nutrition practices in many ICUs after the reaudit in 2008 (20).

There is another study from Spain that shows the development and implementation of an audit tool for quality control of PN(21). In 1995, this quality control program was implemented by the Pharmacy Service and became a tool that measured compliance with accepted standards in the literature. The authors show the results of 5 audits during the past 10 years. This study was made in hospitalized patients with PN with the exception of ICU patients, pediatric patients and patients with chronic renal dysfunction. The authors concluded that in the last audit 9 out of 22 criteria reached the predefined standards, but also found some they needed to improve such as the indication of PN, assessment at the beginning of nutrition support and infectious complications.

The last study found(22), describes the approach taken by one hospital in California to improve safety and quality of PN. Process improvement strategies included revisions to the PN order form, education of clinicians, increased collaboration between pharmacists and registered dietitians and initiation of PN rounds. These process strategies positively impacted quality and costs. There was improvement in compliance with safe practice standards, percentage of patients with appropriate indication for PN, glycemic management, laboratory monitoring. The average number of patients receiving PN decreased from approximately 15 to less than 5 per day, this decreased the costs significantly.

In Canada, there are guidelines for nutrition support in mechanically ventilated critically ill adults. These guidelines were made by searching in four bibliographic databases randomized clinical trials or meta-analysis of randomized controlled trials that included any form of enteral or parenteral nutrition and the outcomes were: mortality, length of stay, quality of life, complications and cost. The search was done between the years 1980 to 2002. With respect to PN, the authors concluded that it should not be indicated until all strategies to maximize enteral nutrition delivery have been attempted. Also, when PN is indicated, glutamine should be used as a parenteral supplement if it is available. They also concluded that in patients who are not malnourished, are tolerating some enteral nutrition or when PN is indicated for short-term use (<10 days), hypocaloric PN and also withholding lipids should be considered in these specific setting. In surgical critically ill patients with

nutrition support, intensive insulin therapy to achieve blood glucose levels between 4.4 and 6.1 mmol/L should be considered(16)

The literature has mentioned that there is an overprescription of PN in patients with functional gastrointestinal tracts. It is important to mention that PN is associated with adverse events when compared to enteral nutrition. One review analyzed randomized clinical trials and concluded that there are more infections and longer lengths of stay in ICU patients receiving PN than those receiving enteral nutrition. Major complications such as: pneumothorax and air embolus are greater in parenterally fed patients. Also, the cost of PN is higher (6). Kudsk and colleagues reported pneumonia, abscesses, line infection or all three in 40% of parenterally fed patients versus 16% of enterally fed patients (23).

It is also known that PN is an expensive treatment and its cost differs among countries. In Europe, the daily cost of one compounded PN bag for neonates is around 55 Euros. An average cost per bag for infants <2 year was around 84 Euros. A major proportion of the cost is due to staff time(24). In the United States, when comparing compounded PN versus multi-chamber PN based on the underlying bloodstream infection risk the daily mean PN acquisition cost for patients receiving multi-chamber PN was US \$164 compared with US \$239 for patients receiving compounded PN(25). In Toronto General Hospital, the cost of a bag of parenteral nutrition is around \$140 CAD per day.

Intralipid is a soybean oil (SO) intravenous fat emulsion, available since 1961, rich in omega-6 polyunsaturated fatty acids (PUFA) and may enhance the generation of arachidonic acid-derived eicosanoids that could exaggerate the inflammatory response during stress and trauma (26). This pro-inflammatory effect may be detrimental. For example, in a prospective, randomized, controlled study comparing the vascular, metabolic, immune and inflammatory effects of 24h- infusion of parenteral nutrition (PN) with SO-based lipid emulsion (Intralipid), olive oil-based lipid emulsion (ClinOleic), lipid free and normal saline in 12 healthy subjects, the authors found that Intralipid increased blood pressure and altered endothelial function (27). A recent ASPEN position paper (28) reviewed the literature on lipid emulsions. While the current available, standard SO-based lipid emulsion like Intralipids meet the needs of most PN patients, alternative oil-based fat emulsions, like olive oil (OO) are used extensively in Europe and have been shown to be less proinflammatory and immunosuppressive due to different metabolic pathways. Patients receiving these alternative lipid emulsions may have better clinical outcomes but further research is needed to identify which type of lipid emulsion or which combination of oils may be most clinically useful for specific patient populations. SO lipid emulsions have plant sterols known as phytosterols, these are thought to alter hepatic function and have been associated with cholestasis in children on long-term PN (29,30). Also, most SO lipid emulsions have small amounts of  $\alpha$ -tocopherol, a known antioxidant. Studies have shown that vitamin E has a role in the prevention of hepatic injury in animal models(31), but there is still deficit in human data.

ClinOleic is a lipid emulsion composed of OO (80%) and SO (20%) (27,32). It is a third-generation of lipids and was introduced in Europe in the 1990s (28). It has more monounsaturated fatty acids (MUFA) than PUFA, in a proportion of 65% MUFA and 20% PUFA (32). Even though it has a lower proportion of PUFA, no significant changes in plasma fatty acid profile and no deficiency of essential fatty acids have been reported (33). However, this was observed in a mouse model (34). ClinOleic is also rich in  $\alpha$ -tocopherol, and MUFAs are resistant to lipid peroxidation so this intravenous lipid emulsion is potentially beneficial in subjects with risk of oxidative stress (32). There is a lack of studies that critically evaluate indications and outcomes regarding parenteral nutrition in different hospital units and in a wider variety of pathologies. There are very few studies published that compare two types of intravenous lipid emulsions and all have limited number of patients. There is a need to elucidate if the new lipid generations are a better option than the classic SO-based lipid emulsions and which patient populations will benefit most from them. This and our personal need for evaluating the indications and outcomes of patients with parenteral nutrition motivated us to do this study in our own center.

## **Part A:**

### **Primary Objective**

- To evaluate parenteral nutrition prescriptions in hospitalized patients
- **Secondary Objectives**
- Describe patient population according to the pathology that caused the hospitalization
- Record the indication that determined the need for PN and whether they are medical, surgical or ICU patients
- Assess updated Charlson co-morbidity index (CCI)
- Record the number of days with intakes less than 50% of requirements or NPO before PN was prescribed
- Perform a nutritional assessment which includes: weight at admission (if recorded in chart) and at time of starting PN, height, body mass index (BMI), Subjective Global Assessment (SGA), albumin and estimate of nutritional requirements.
- Record the initial PN prescription in terms of energy and proteins
- Record how many days it took to reach the nutritional requirements estimated by the dietitian
- Compare energy received as a goal with calculated energy requirements using published equations
- Record the number of times PN was interrupted
- Record the total number of PN days the patient received
- Determine the type of line (central or peripheral) and number of days with peripheral and/or central lines.

- Determine the type of vascular access (if central line)
- Record laboratory results once a week to assess potential metabolic complications associated with PN
- Record catheter related infections, whether suspected or confirmed
- Record any other complications deemed related to PN
- Record number of antibiotic-days to treat catheter-associated infections
- Record the reason why PN was discontinued
- Record total length of stay
- Record in-hospital mortality and cause of mortality during PN as well as during entire hospital stay

## **Part B: Intralipid vs ClinOleic**

### **Primary Objective**

To evaluate metabolic, nutritional, infectious and inflammatory parameters in patients receiving SO-based lipid emulsion compared to those of patients receiving OO -based lipid emulsion.

- Primary Outcome: length of stay
- Secondary Outcomes: mortality, nutritional parameters (anthropometry, handgrip-strength, mid-arm circumference, , pre-albumin), inflammation (high sensitivity C-reactive protein; hs-CRP), documented infections, ICU stay, antibiotic-days, liver enzymes, essential fatty acid status

### **Study design**

This is a prospective study that will evaluate the indications of parenteral nutrition in an inpatient setting. As part of their PN prescription, patients will receive either standard lipid (Intralipid) or OO-based lipid emulsion (ClinOleic), alternately depending on their time point of PN start, i.e. one person will receive Intralipid, the next one ClinOleic, etc. We will collect information from patients that have started with parenteral nutrition during their hospitalization and that are hospitalized in medical, surgical or ICU wards. We will also collect retrospective data of 100 patients to compare if the actions of the nutrition team and results change with respect to the prospective data.

Inclusion Criteria:

- Patients 18 years or older

- Patients that are expected to require PN for 5 days or more during their hospitalization
- Patients hospitalized in medical, surgical or ICU wards
- Signed informed consent either from the patient, their legally authorized representative or a direct family member

Exclusion Criteria:

- Patients without PN during their hospitalization

**Part A:** Patients will be approached when they start with PN during their hospitalization and will be followed until their last day of PN or, if occurred before PN ends, death. **Part B:** For the proposed study, we will start PN as usual, according to the patients needs. We will randomly assign patients to receive either Intralipid or ClinOleic as the lipid emulsion in the PN. The amount of calories from the lipid emulsion will be equivalent.

Patients will be followed for one week after their last day on PN and, in addition, major outcomes such as mortality and length of stay will be assessed during the entire hospitalization.

Information regarding the patients nutrition will be obtained from the hospital chart and by direct communication with the PN team (dietitian, nurse, pharmacist) after signed informed consent.

We will analyze the nutritional indications and laboratory results of patients hospitalized in different units who are starting with PN alone or in combination with enteral or oral feeding twice a week. We will use a registry to enter the data.

**Measurements:** **Part A** 1) Patient demography: age, sex; 2) Type of patient: medical, surgical and/or ICU patients; 3) Type of any surgery the patient has during hospitalization; 4) Primary indications related to parenteral nutrition, comorbidities, updated CCI (31,32); 5) Nutritional assessment: weight, height, BMI, SGA, estimated energy and protein requirements; 6) comparison of energy received as a goal vs calculated energy requirements using published equations; 7) Energy, dextrose, aminoacids and lipids received by PN. Total energy and proteins received including enteral nutrition and oral intake. Energy provided by Propofol, if received. In case of enteral nutrition, name and amount of product used; 8) Type of line used (peripheral or central); 9) Vascular access; 10) Reason for ending PN; 11) Number of times and reasons for interruption of PN; 12) Weekly PN related laboratory results; 13) Complications secondary to PN; 14) Outcome of patient

**Part B:** We will include the same measurements as in part A, but will add some additional nutritional parameters which will be done at baseline (Day 0) and after 10 days (Day 10)

with PN. Baseline or day 0 assessments to be done prior to or within 24 hours of PN initiation. Day 10 measurements to be done on day 10 of PN administration. If the PN ends before day 10, we will consider a cutoff at day 7 of PN. This means that if the PN ends before day 7, we will not repeat the measurements or blood work. If PN ends between days 7-9 we will repeat the measurements instead of doing them on day 10 for this special cases.

The parameters to measure will be: hand grip strength (kg), mid arm circumference (cm), SGA and weight as measures of nutritional status. We will also add hs-CRP, pre-albumin, and fatty acid profile in red blood cells (RBC) and plasma to the laboratory results at both time points. Clinical outcomes (documented infections, antibiotic-days or other adverse events) will be monitored for one week post-PN. In addition, mortality and length of stay will be documented for the entire hospitalization.

There are numerous studies that try to elucidate which equation is the best to estimate the energy requirements of hospitalized and healthy people, but none have shown to be comparable to indirect calorimetry, which is considered the gold-standard. The ASPEN guidelines refer to the non-obese critically ill patient and suggest using 25 kcal/kg actual body weight per day, published equations, or to measure energy requirements using indirect calorimetry (35). Moreover, the ESPEN guidelines also suggest prescribing 25 kcal/kg in the ICU population increasing to target over the next 2-3 days (36). In the case of obese critically ill patients, ASPEN guidelines suggest a hypocaloric feeding and they mention that the goal of the enteral nutrition regimen should not exceed 60-70% of target energy requirements, 11-14 kcal/kg actual body weight per day or 22-25 kcal/kg ideal body weight (35). Recently published studies have found that the Penn State equation can be used in patients with mechanical ventilation and that the Penn State modified can be used in older obese patients with mechanical ventilation (37-40).

For non-Icu population, ASPEN and ESPEN guidelines agree in using weight based formulas to calculate energy requirements. The estimated energy requirements should be between 20-40 kcal/kg, depending on the pathology (41-45). At the same time, both guidelines suggest using ideal body weight (IBW) in case of obesity and ESPEN adds ascites as another condition were IBW should be used (35,42,45). For the calculation of IBW we will use Hamwi's equation (46). We will use Penn State formula for ICU ventilated patients and weight based formulas for all other patient populations. Ideal body weight will be used in patients with ascites, obesity or in cases of edema were body weight with edema is much more than usual body weight or body weight at admission. Actual body weight will be used for undernourished or normal weight population.

### **Blood sample collection and processing:**

Blood will be collected in the morning during the routine blood draw on the wards. Samples for plasma and RBC fatty acids will be collected in EDTA containing tubes, and

samples for pre-albumin and hs-CRP in tubes without anticoagulant. The tubes will be centrifuged ( $910 \times g$ , 10 min), and serum and plasma will be aliquoted and stored at  $-80^{\circ}\text{C}$  until analysis.

From the plasma tube, all remaining plasma and the buffy coat, which shows on top of the erythrocyte sediment as a white ring will be discarded. The remaining packed RBC will be aliquoted and frozen at  $-80^{\circ}\text{C}$  until analysis.

Pre-albumin and hs-CRP will be measured by routine methods at an accredited laboratory (Hospitals In-Common Laboratory Inc., Toronto).

Red blood cell and plasma fatty acid profile will be assessed using gas chromatography. Briefly, total lipids will be extracted from RBC or plasma into chloroform/methanol (47), containing butylated hydroxytoluene as antioxidant. Extracted lipids will be saponified and transmethylated using boron-trifluoride (48). Fatty acid methyl esters were then separated using an Agilent 6890 gas chromatograph equipped with a flame ionization detector (49). Peaks will be identified from C14:0 to C22:6n-3. The relative amount of the essential fatty acids, alpha-linoleic acid and linolenic acid will be reported as % of total lipids.

## **Statistical analysis**

**Part A:** Descriptive statistics will be performed. Results will be expressed as absolute numbers and percentages, mean  $\pm$  standard deviation (SD) or median (minimum; maximum) depending on the variable types and distributions, separately for the prospective and the retrospective dataset. For the prospective study, multivariate logistic regression will be performed to identify risk factors associated with specific PN prescription: for example, inadequate administration of PN. In addition, data from the prospective study and the retrospective chart review will be compared by unpaired t-test, Mann-Whitney-test or chi-square test as appropriate. A p value  $<0.05$  will be considered statistically significant. **Part B:** For the Intralipid and the ClinOleic analysis, all variables will be tested for normal distribution (Shapiro Wilks test). *Primary outcome* is length of stay (in days). The Intralipid and ClinOleic groups will initially be compared with unpaired t-test or Mann-Whitney test as appropriate. *Secondary outcomes:* other clinical outcomes (days in ICU, antibiotic-days, infections, mortality) will also be analyzed the same way initially. For secondary outcomes that may change over time, i.e. hs-CRP, pre-albumin and other laboratory results, BMI, arm circumference, hand grip strength, changes will be compared between groups using unpaired t-test or Mann-Whitney test as appropriate. To account for possible covariate effects (eg. age, baseline BMI, Charlson comorbidity index), regression methods such as generalized linear models will be employed. All tests will be based on two-sided alternatives and a test will be considered statistically significant using  $\alpha=0.05$ . SAS Enterprise Guide 4.1 software (SAS Institute Inc., Cary, NC, USA) will be used.

## **Feasibility and Sample Size**

**Part A:** Based on previous studies, there are about 200 in-patients per year receiving PN. All patients will be assessed as per standard medical guidelines for PN and it is expected that 90% will agree to participate in the project. We calculate that we will have enrolled about 50 patients for Part A, before we start with part B. We will later include 150 more patients from Part B to have a total of 200 patients. We will compare the data obtained with 100 retrospective patients to see if the actions of the nutrition team changed since we started the project.

**Part B:** When we receive the ClinOleic in the hospital, patients will receive either SO-based lipid emulsion (Intralipid= 150 patients) or OO-based lipid emulsion (ClinOleic=150 patients) on an alternate basis (one-to-one) for the duration of the PN.

The total number of patients including part A and part B is estimated to be 350 patients. It is expected to take about one and a half years to recruit this number of patients.

For the Intralipid and ClinOleic analysis, we based our sample size on a study that evaluated the use of either SO or SO + fish oil (FO) in 206 patients with gastrointestinal or colonic cancer during 7 days after surgery and found that the patients that were given the FO treatment had significantly shorter length of stay than the SO group (Mean (SD) 15(5) versus 17(8)  $p= 0.041$ ). Also, they had fewer infectious complications (50). Another study compared soybean oil and soybean oil+FO in 57 elderly patients with colorectal cancer. In the treatment group, there were fewer infectious complications and incidences of systemic inflammatory response syndrome (SIRS), and shorter lengths of hospital stay were observed(51).

Based on this, we estimate that a sample size of 150 in each group with a power of 0.8 and alpha of 0.05 will be sufficient to show a similar difference in length of stay between the two groups (soybean or ClinOleic) using the online sample size calculation provided by G.W. Snedecor & W.G. Cochran <http://www.biomath.info/power/ttest.htm>.

## **Significance**

There are currently no data prospectively collected in Canada that evaluate the indications and outcomes of hospitalized patients with PN in different hospital units. There is a need for prospective interventional studies to compare clinical outcomes between the traditional soybean oil-based lipid emulsion and the olive oil-based lipid emulsion. The results of this project will help establish standards of practice and this will greatly benefit the inpatient population requiring PN.

## References

1. Russell MK, Andrews MR, Brewer CK *et al.* Standards for specialized nutrition support: adult hospitalized patients. *Nutr Clin Pract* 2002;17:384-391.
2. Stratton RJ, Smith TR. Role of enteral and parenteral nutrition in the patient with gastrointestinal and liver disease. *Best Pract Res Clin Gastroenterol* 2006;20:441-466.
3. Marik PE. Maximizing efficacy from parenteral nutrition in critical care: appropriate patient populations, supplemental parenteral nutrition, glucose control, parenteral glutamine, and alternative fat sources. *Curr Gastroenterol Rep* 2007;9:345-353.
4. Cheung NW, Napier B, Zaccaria C *et al.* Hyperglycemia is associated with adverse outcomes in patients receiving total parenteral nutrition. *Diabetes Care* 2005;28:2367-2371.
5. Guglielmi FW, Boggio-Bertinet D, Federico A *et al.* Total parenteral nutrition-related gastroenterological complications. *Dig Liver Dis* 2006;38:623-642.
6. Zaloga GP. Parenteral nutrition in adult inpatients with functioning gastrointestinal tracts: assessment of outcomes. *Lancet* 2006;367:1101-1111.
7. Dissanaik S, Shelton M, Warner K *et al.* The risk for bloodstream infections is associated with increased parenteral caloric intake in patients receiving parenteral nutrition. *Crit Care* 2007;11:R114.
8. Opilla M. Epidemiology of bloodstream infection associated with parenteral nutrition. *Am J Infect Control* 2008;36:S173 e175-178.
9. Pittiruti M, Hamilton H, Biffi R *et al.* ESPEN Guidelines on Parenteral Nutrition: central venous catheters (access, care, diagnosis and therapy of complications). *Clin Nutr* 2009;28:365-377.
10. Beghetto MG, Victorino J, Teixeira L *et al.* Parenteral nutrition as a risk factor for central venous catheter-related infection. *JPEN J Parenter Enteral Nutr* 2005;29:367-373.
11. Holton D, Paton S, Conly J *et al.* Central venous catheter-associated bloodstream infections occurring in Canadian intensive care units: A six-month cohort study. *Can J Infect Dis Med Microbiol* 2006;17:169-176.
12. Gramlich L, Kichian K, Pinilla J *et al.* Does enteral nutrition compared to parenteral nutrition result in better outcomes in critically ill adult patients? A systematic review of the literature. *Nutrition* 2004;20:843-848.

13. Heyland DK. Nutritional support in the critically ill patients. A critical review of the evidence. *Crit Care Clin* 1998;14:423-440.
14. Heyland DK, MacDonald S, Keefe L *et al*. Total parenteral nutrition in the critically ill patient: a meta-analysis. *JAMA* 1998;280:2013-2019.
15. Heyland DK, Cook DJ, Schoenfeld PS *et al*. The effect of acidified enteral feeds on gastric colonization in critically ill patients: results of a multicenter randomized trial. Canadian Critical Care Trials Group. *Crit Care Med* 1999;27:2399-2406.
16. Heyland DK, Dhaliwal R, Drover JW *et al*. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. *JPEN J Parenter Enteral Nutr* 2003;27:355-373.
17. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. *JPEN J Parenter Enteral Nutr* 2002;26:1SA-138SA.
18. Nardo P, Dupertuis YM, Jetzer J *et al*. Clinical relevance of parenteral nutrition prescription and administration in 200 hospitalized patients: a quality control study. *Clin Nutr* 2008;27:858-864.
19. Heyland DK, Schroter-Noppe D, Drover JW *et al*. Nutrition support in the critical care setting: current practice in canadian ICUs--opportunities for improvement? *JPEN J Parenter Enteral Nutr* 2003;27:74-83.
20. Sinuff T, Cahill NE, Dhaliwal R *et al*. The value of audit and feedback reports in improving nutrition therapy in the intensive care unit: a multicenter observational study. *JPEN J Parenter Enteral Nutr* 2010;34:660-668.
21. Garcia-Rodicio S, Abajo C, Godoy M *et al*. Development and implementation of an audit tool for quality control of parenteral nutrition. *Nutr Clin Pract* 2009;24:500-507.
22. Boitano M, Bojak S, McCloskey S *et al*. Improving the safety and effectiveness of parenteral nutrition: results of a quality improvement collaboration. *Nutr Clin Pract* 2010;25:663-671.
23. Kudsk KA, Croce MA, Fabian TC *et al*. Enteral versus parenteral feeding. Effects on septic morbidity after blunt and penetrating abdominal trauma. *Ann Surg* 1992;215:503-511; discussion 511-503.
24. Walter E, Liu FX, Maton P *et al*. Cost analysis of neonatal and pediatric parenteral nutrition in Europe: a multi-country study. *Eur J Clin Nutr* 2012;66:639-644.

25. Turpin RS, Canada T, Liu FX *et al.* Nutrition therapy cost analysis in the US: pre-mixed multi-chamber bag vs compounded parenteral nutrition. *Appl Health Econ Health Policy* 2011;9:281-292.
26. Yaqoob P. Monounsaturated fatty acids in parenteral nutrition; evaluation of risks and benefits. *Br J Nutr* 2005;94:867-868.
27. Siqueira J, Smiley D, Newton C *et al.* Substitution of standard soybean oil with olive oil-based lipid emulsion in parenteral nutrition: comparison of vascular, metabolic, and inflammatory effects. *J Clin Endocrinol Metab* 2011;96:3207-3216.
28. Vanek VW, Seidner DL, Allen P *et al.* A.S.P.E.N. position paper: Clinical role for alternative intravenous fat emulsions. *Nutr Clin Pract* 2012;27:150-192.
29. Pianese P, Salvia G, Campanozzi A *et al.* Sterol profiling in red blood cell membranes and plasma of newborns receiving total parenteral nutrition. *J Pediatr Gastroenterol Nutr* 2008;47:645-651.
30. Clayton PT, Bowron A, Mills KA *et al.* Phytosterolemia in children with parenteral nutrition-associated cholestatic liver disease. *Gastroenterology* 1993;105:1806-1813.
31. Soden JS, Devereaux MW, Haas JE *et al.* Subcutaneous vitamin E ameliorates liver injury in an in vivo model of steatocholestasis. *Hepatology* 2007;46:485-495.
32. Thomas-Gibson S, Jawhari A, Atlan P *et al.* Safe and efficacious prolonged use of an olive oil-based lipid emulsion (ClinOleic) in chronic intestinal failure. *Clin Nutr* 2004;23:697-703.
33. Reimund JM, Rahmi G, Escalin G *et al.* Efficacy and safety of an olive oil-based intravenous fat emulsion in adult patients on home parenteral nutrition. *Aliment Pharmacol Ther* 2005;21:445-454.
34. Meisel JA, Le HD, de Meijer VE *et al.* Comparison of 5 intravenous lipid emulsions and their effects on hepatic steatosis in a murine model. *J Pediatr Surg* 2011;46:666-673.
35. McClave SA, Martindale RG, Vanek VW *et al.* Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr* 2009;33:277-316.
36. Singer P, Berger MM, Van den Berghe G *et al.* ESPEN Guidelines on Parenteral Nutrition: intensive care. *Clin Nutr* 2009;28:387-400.

37. Frankenfield DC, Ashcraft CM. Estimating energy needs in nutrition support patients. *JPEN J Parenter Enteral Nutr* 2011;35:563-570.
38. Frankenfield DC, Coleman A, Alam S *et al.* Analysis of estimation methods for resting metabolic rate in critically ill adults. *JPEN J Parenter Enteral Nutr* 2009;33:27-36.
39. Cooney RN, Frankenfield DC. Determining energy needs in critically ill patients: equations or indirect calorimeters. *Curr Opin Crit Care* 2012;18:174-177.
40. Frankenfield D. Validation of an equation for resting metabolic rate in older obese, critically ill patients. *JPEN J Parenter Enteral Nutr* 2011;35:264-269.
41. Van Gossum A, Cabre E, Hebuterne X *et al.* ESPEN Guidelines on Parenteral Nutrition: gastroenterology. *Clin Nutr* 2009;28:415-427.
42. Plauth M, Cabre E, Campillo B *et al.* ESPEN Guidelines on Parenteral Nutrition: hepatology. *Clin Nutr* 2009;28:436-444.
43. Gianotti L, Meier R, Lobo DN *et al.* ESPEN Guidelines on Parenteral Nutrition: pancreas. *Clin Nutr* 2009;28:428-435.
44. Cano NJ, Aparicio M, Brunori G *et al.* ESPEN Guidelines on Parenteral Nutrition: adult renal failure. *Clin Nutr* 2009;28:401-414.
45. Braga M, Ljungqvist O, Soeters P *et al.* ESPEN Guidelines on Parenteral Nutrition: surgery. *Clin Nutr* 2009;28:378-386.
46. Anderegg BA, Worrall C, Barbour E *et al.* Comparison of resting energy expenditure prediction methods with measured resting energy expenditure in obese, hospitalized adults. *JPEN J Parenter Enteral Nutr* 2009;33:168-175.
47. Folch J, Lees M, Sloane Stanley GH. A simple method for the isolation and purification of total lipides from animal tissues. *J Biol Chem* 1957;226:497-509.
48. Arendt BM, Mohammed SS, Aghdassi E *et al.* Hepatic fatty acid composition differs between chronic hepatitis c patients with and without steatosis. *Journal of Nutrition* 2009;139:691-695.
49. Ma DW, Ngo V, Huot PS *et al.* N-3 polyunsaturated fatty acids endogenously synthesized in fat-1 mice are enriched in the mammary gland. *Lipids* 2006;41:35-39.
50. Jiang ZM, Wilmore DW, Wang XR *et al.* Randomized clinical trial of intravenous soybean oil alone versus soybean oil plus fish oil emulsion after gastrointestinal cancer surgery. *Br J Surg* 2010;97:804-809.

51. Zhu MW, Tang DN, Hou J *et al.* Impact of fish oil enriched total parenteral nutrition on elderly patients after colorectal cancer surgery. *Chin Med J (Engl)* 2012;125:178-181.