

**Nutrition Support in Mechanically Ventilated, Critically Ill Adult Patients – study
protocol for systematic reviews and meta-analyses**

Address for correspondence:

Dr. Daren Heyland
Kingston General Hospital
Kingston, Ont. Canada K7L 2V7
Phone: 613 549 6666 ext 3339
Fax: 613 548-2577
Email: dkh2@post.queensu.ca

Dr. Carina Benstöm
Medical Faculty RWTH Aachen
University Hospital
D – 52074 Aachen
Phone: +49 241 80 38038
Email: cbenstoem@ukaachen.de

Key Words: Nutrition Support, Intensive Care Units, Systematic Review

Structured Abstract

Objective:

To develop and maintain evidence-based systematic reviews for nutrition support (i.e. enteral and parenteral nutrition) in mechanically ventilated critically ill adults.

Methods:

The following interventions will be systematically reviewed for inclusion: enteral nutrition (EN) vs. parenteral nutrition (PN); early vs. late EN; dose of EN; composition of EN (immune-enhancing additives, carbohydrate, lipids, protein/peptides, pH & fibre); strategies to optimize delivery of EN and minimize risks (i.e. feeding protocols, rate of advancement, checking residuals, use of bedside algorithms, motility agents, small bowel vs. gastric feedings, elevation of head of the bed, closed delivery systems, pre/pro/synbiotics, bolus administration, gastrostomy vs. nasogastric feedings, fasting); enteral nutrition in combination with supplemental PN; use of PN vs. standard care in patients with an intact GI tract; dose of PN and composition of PN (protein, carbohydrates, intravenous lipids, additives, vitamins, trace elements, immune enhancing substances) and the use of intensive insulin therapy.

Outcomes:

The outcomes considered are mortality (ICU, hospital, and long term), length of stay (ICU and hospital), duration of mechanical ventilation, functional measures, quality of life, and specific complications.

Evidence:

We will systematically search Medline, CINAHL (Cumulative Index to Nursing and Allied Health Literature), Embase, the Cochrane Database of Systematic Reviews (CDSR) and the Cochrane Central Register of Controlled Trials (CENTRAL) to identify randomized controlled trials (RCT) or systematic reviews of randomized trials that evaluated any form of nutrition support in critically ill adults. We will also search reference lists of included studies and personal files, considering all articles published or unpublished available by August 2018. Each included study will be critically appraised in duplicate using a standard scoring system.

Values:

For each intervention, we will consider the validity of the randomized trials and/or meta-analyses, the effect size and its associated confidence intervals, the homogeneity of trial results, safety, feasibility, and the economic consequences. The context for discussion will be mechanically ventilated patients in Canadian ICUs.

Benefits, Harms, and Costs:

The major potential benefit from publishing these findings will be improved clinical outcomes of critically ill patients (reduced mortality and ICU stay). Potential harms of implementing these findings include increased complications and costs related to the suggested interventions.

Introduction

In critically ill patients malnutrition is associated with impaired immune function, impaired ventilatory drive and weakened respiratory muscles leading to prolonged ventilatory dependence and increased infectious morbidity and mortality (1). Malnutrition is prevalent in ICU patients, has been reported as being as high as 40 %, and is associated with poor patient outcomes (2).

The benefits of nutrition support in the critically ill include improved wound healing, a decreased catabolic response to injury, improved gastrointestinal structure and function, and improved clinical outcomes including a reduction in complication rates and length of stay with accompanying cost savings (3). However, nutrition support is not without adverse effects or risks. Early enteral nutrition can be associated with high gastric residual volumes, bacterial colonization of the stomach, and an increased risk of aspiration pneumonia (4,5). Parenteral nutrition has been associated with gut mucosal atrophy, overfeeding, hyperglycemia, an increased risk of infectious complications and increased mortality in critically ill patients (6). Both forms of nutrition support can increase health care costs and workloads of care providers.

Despite the widespread use of nutrition support, many areas in clinical practice remain controversial. Variation in nutrition support practices in ICUs throughout the world are widely reported. The use of nutrition support in ICUs has been shown to vary from 14 to 67 % of all patients in the ICU (7,8,9,10,11). Recent surveys report the use of PN ranging from 12% to 71 % and the use of enteral nutrition ranging between 33 to 92% of patients receiving nutrition support in the ICU (7-11). These survey data highlight the tremendous opportunity to improve the practice of nutrition in ICU settings. As a first step, clinical practice guidelines aim to set the standard of what 'ought' to be done in the clinical setting.

Over the past two decades, several guidelines have been developed to help ICU practitioners make decisions and implement strategies regarding their patients' nutrition care in the ICU (12-16). However, there remain differences between these guidelines, which leaves practitioners unclear of what best practice is and reveals the need for research to continue in the area of critical care nutrition (17,18). One thing

that should be 'in common' with all these guidelines is the body of evidence that contributes to the CPGs.

That body of evidence continues to evolve over time and guideline developers are slow to update their guidelines based on the evolving evidence. We aim to continually review of new evidence in the area of critical care nutrition to facilitate more up-to-date and scientifically sound nutrition guidelines in the adult critical care setting. This protocol describes the methods used to develop our systematic reviews and the summaries of evidence that emerged.

Methods

This study protocol details the methodology applied for the systematic reviews in 2018 and beyond.

Search methods for identification of studies

To locate relevant articles to be included,, five electronic databases (Medline, CINAHL, Embase, CDSR, and CENTRAL) were searched. Detailed search strategies will be developed, the search terms will include: nutritional support or dietary supplementation or enteral nutrition or parenteral nutrition or peripheral parenteral nutrition or total parenteral nutrition or nutritional support team or nutritional requirements or nutritional assessment or parenteral nutrition solutions and critical care or critical illness or intensive care units. The searches will span from 1980 until August 2018. In addition, personal files, relevant review articles and reference lists of matching studies will be searched for additional studies. There were no language restrictions on included studies. Unpublished manuscripts will be included in the review process; however, data reported as abstracts only will be excluded.

Study selection criteria

Studies were selected for inclusion in the review process if they met the following criteria:

Study design: randomized clinical trials or meta-analysis of randomized controlled trials. When treatment allocation was not truly random, such as assigning a treatment intervention based on day of admission or month of service (pseudo-randomized trials), these trials were excluded).

Population: mechanically ventilated, critically ill adult patients (elective surgery patients were excluded). For the purpose of this review process, we defined a critically ill patient as a patient cared for in an intensive care unit (ICU) environment who had urgent or life threatening complications (high baseline mortality rate) to distinguish them from patients with elective surgery who also are cared for in some ICU's but have a low baseline mortality rate (< 5 %).

Intervention: any form of enteral nutrition (EN) or parenteral nutrition (PN) or IV nutrients

Outcome: mortality (ICU, hospital, long term), length of stay, length of mechanical ventilation, quality of life, physical outcomes, complications and cost. Studies with only surrogate outcomes will be excluded.

Selection of studies

Two review authors [CB, ML] will independently screen titles and abstracts for inclusion of all the potential studies we identify as a result of the search and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. If there are any disagreements, a third author will be asked to arbitrate (DH). We will retrieve the full-text study reports/publication and two review authors [or more; initials here] will independently screen the full-text and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third person [DH]. We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table.

Based on the above search and study selection criteria, the included articles cover the range of topics listed on <https://www.criticalcarenutrition.com>. Practical aspects of tube placement and management for EN and catheter placement for PN are beyond the scope of these systematic reviews.

Data extraction and management

The panel agreed to review all randomized controlled trials and the most recent meta-analyses for all topics. Each randomized trial will be critically appraised

independently by each member of a pair of reviewers according to an explicit procedure. Appraisers will be given instructions on how to appraise studies. For each trial the following descriptors will be abstracted: intervention, study population, nature of allocation, co-interventions, exclusions after randomization, double-blinding, event rates, relative risk, and other outcomes. Authors of primary studies will be contacted for supplementary information or clarification, if necessary.

Assessment of risk of bias in included studies

Clinical trials will be assigned “level 1” if randomization was concealed, outcome adjudication was blinded, and an intention to treat analysis was performed. Trials will be assigned “level 2” if any one of the above characteristics was unfulfilled.

Measures of treatment effect

We will undertake meta-analyses only where this is meaningful i.e. if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense. The common risk ratios and their confidence intervals were estimated using the random effects model of DerSimonian and Laird (19) as implemented in RevMan 4.1 (20). We considered $P < 0.20$ to be supportive of a trend and $P < 0.05$ to be statistically significant. We will analyse dichotomous data as odds ratios or risk ratios with 95% confidence intervals and continuous data as mean difference or standardised mean difference (for outcomes applying different scales) with 95% confidence intervals. We will enter data presented as a scale with a consistent direction of effect. We will narratively describe skewed data reported as medians and interquartile ranges.

For each meta-analysis included in the review process, the following descriptors will be abstracted: intervention, number of trials, population selection criteria, search strategy, independent validity assessment, method of pooling results, assessment of homogeneity, pooled event rates, and other outcomes. Patients’ perspectives will most probably not be elicited due to the inability of most critically ill patients to engage in discussions about their nutrition.

Two review authors [CB, ML] will independently extract outcome data from included studies. We will resolve disagreements by consensus or by involving a third person [DH]. One review author [ML] will transfer data into the Review Manager (RevMan

2014) file. We will double-check that data is entered correctly by comparing the data presented in the systematic review with the data extraction form. A second review author [CB] will spot-check study characteristics for accuracy against the trial report.

References

1. Dark DS, Pingleton SK. Nutrition and nutritional support in critically ill patients. *J Intensive Care Med* 1993;8;16-33.
2. Giner M, Laviano A, Meguid MM, et al. In 1995 a Correlation between malnutrition and poor outcomes in critically ill patients still exists. *Nutrition* 1996 12;23-29.
3. Heyland DK. Nutritional support in the critically ill patient, a critical review of the evidence. *Crit Care Clin.* 1998 Jul;14(3):423-40.
4. Heyland DK, Cook DJ, Schoenfeld PS, et al. The effect of acidified enteral feeds on gastric colonization in the critically ill patient: Results of a multicenter randomized trial. *Crit Care Med.* 2001 Oct;29(10):1955-61.
5. Mentec H, Dupont H, Bocchetti M, et al. Upper digestive intolerance during enteral nutrition in critically ill patients: frequency, risk factors, and complications. *Crit Care Med.* 2001 Oct;29(10):1955-61..
6. Heyland DK, MacDonald S, Keefe L, et al. Total parenteral nutrition in the critically ill patient; A meta-analysis. *JAMA.* 1998 Dec 16;280(23):2013-9.
7. Payne-James J, De Gara CJ, Grimble GK, et al. Artificial Nutrition support in hospitals in the United Kingdom-1991:second national survey. *Clinical Nutrition* 1992;11:187-192
8. Hill SA, Nielsen MS, Lennard-Jones JE. Nutrition Support in intensive care units in England and Wales: a survey. *European Journal of Clinical Nutrition* 1995;49;371-378
9. De Jonghe B, Appere-De-Vechi C, Fournier M, et al. A prospective survey of nutritional support practices in intensive care units patients: what is prescribed ? what is delivered ? *Crit Care Med* 2001;29;1:8-12
10. Preiser JC, Berre J, Carpentier Y, et al. Management of nutrition in European intensive care units: results of a questionnaire. *Int Care Med* 1999;25;95-101
11. Heyland DK, Schroter-Noppe D, Drover J, et al. Nutrition support practice in Canada: Results of a national survey. *JPEN* 2003 (in press).

12. McClave SA, Taylor BE, Martindale RG, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr.* 2016;40(2):159-211.
13. Fernandez-Ortega JF, Herrero Meseguer JI, Martinez Garcia P; Spanish Society of Intensive Care Medicine and Coronary Units–Spanish Society of Parenteral and Enteral Nutrition (SEMICYUC-SENPE). Guidelines for specialized nutritional and metabolic support in the critically-ill patient: update. Consensus of the Spanish Society of Intensive Care Medicine and Coronary Units–Spanish Society of Parenteral and Enteral Nutrition (SEMICYUC-SENPE): indications, timing and routes of nutrient delivery. *Med Intensiva.* 2011;35(suppl 1):7-11.
14. Dhaliwal R, Cahill N, Lemieux M, Heyland DK. The Canadian Critical Care Nutrition guidelines in 2013: an update on current recommendations and implementation strategies. *Nutr Clin Pract.* 2014;29(1):29-43.
15. Academy of Nutrition and Dietetics. Critical illness evidence-based nutrition practice guidelines. <https://www.andeal.org/topic.cfm?cat=4800>. Accessed December 11, 2018.
16. Kreyman KG, Berger MM, Deutz NE, et al. ESPEN guidelines on enteral nutrition: intensive care. *Clin Nutr.* 2006;25(2):210-223.
17. Patel JJ, Lemieux M, McClave SA, Martindale RG, Hurt RT, Heyland DK. Critical Care Nutrition Support Best Practices: Key Differences Between Canadian and American Guidelines. *Nutr Clin Pract.* 2017 Oct;32(5):633-644.
18. Dhaliwal R, Madden SM, Cahill N, et al. Guidelines, guidelines, guidelines: what are we to do with all of these North American guidelines? *JPEN J Parenter Enteral Nutr.* 2010;34(6):625-643.
19. DerSimonian R, Laird N. Meta-Analysis in Clinical Trials. *Controlled Clinical Trials* 7:177-188, 1986.
20. RevMan 4.1 User's Guide. The Cochrane Collaboration, 2000.