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Early versus delayed enteral nutrition support for critically ill adults

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To evaluate the efficacy and safety of early (within 48 hours) versus delayed enteral nutrition (after 48 hours) in critically ill adults.

BACKGROUND

Description of the condition

Patients in intensive care units (ICUs) often have different degrees of inflammation that may result in reduced energy and protein intake, increased energy expenditure, and protein catabolism (Bouharras 2015; Jensen 2010). Every critically ill patient, regardless of pre-existing malnutrition, has a highly variable metabolic and immune response to injury or illness, which might be attenuated by an appropriately focused nutrition therapy.

Nutritional support in the ICU is designed to achieve metabolic optimization and attenuation of stress-induced immune responses, rather than simply to provide nutrients to prevent malnutrition (Preiser 2015). Nutritional modulation of the stress response to

critical illness includes early nutrition support, appropriate delivery of macronutrients and micronutrients, and meticulous glycaemic control (Fahy 2009; Fukatsu 2011; McClave 2009). Early nutritional support in the form of enteral nutrition provides important benefits in terms of the interaction between the gut and the systemic immune response in critically ill patients. It helps to maintain gut integrity and the physiologic stress response (Jabbar 2003; Kudsk 2002).

It has been suggested that the cumulative energy debt after the first week of ICU admission is a strong predictor of negative clinical outcomes, such as an increase in days of mechanical ventilation, length of stay in the ICU, and infections. It has also been reported that delayed initiation of nutrition support exposes patients to energy deficits that they might be unable to compensate for during their remaining ICU stay (Villet 2005; Wei 2015). In addition,

protein catabolism and cumulative caloric deficit contribute to lean tissue wasting (Casaer 2013), and are associated with adverse outcomes (Alberda 2009).

Nutrition support is therefore considered to be an essential component in the management of critically ill patients. According to European, Canadian, and American clinical practice guidelines, the enteral route is preferred for delivering early nutrition support (ASPEN 2016; Canadian Guidelines 2015; ESPEN 2006).

Description of the intervention

Critically ill patients are usually not able to maintain adequate nutritional intake to meet their metabolic demands on their own and therefore nutrition support is part of their medical care. This normally includes enteral and parenteral nutrition (ASPEN 2016). Enteral nutrition is the infusion of a standard liquid formulation through the gastrointestinal tract by tube, catheter, or stoma, which delivers nutrients distal to the oral cavity (ASPEN 2015). Routes of enteral nutrition include nasogastric, nasoenteral, or percutaneous tubes into the stomach, duodenum, or jejunum (post-pyloric). Parenteral nutrition is the intravenous administration of nutrients via a central or peripheral venous catheter (ASPEN 2015). If full enteral nutrition support is impossible or when it fails to meet target nutritional goals, the addition of parenteral nutrition (also called supplemental parenteral nutrition (SPN)) is recommended (ASPEN 2016; ESPEN 2009). See the glossary in Appendix 1 (based on ASPEN 2015; ASPEN 2016; Lochs 2006). According to the available clinical practice guidelines on nutritional support in the ICU, early enteral nutrition is recommended for patients who are unable to maintain an adequate oral intake, are haemodynamically stable, and have a functioning gastrointestinal tract (Academy of Nutrition and Dietetics 2012; ASPEN 2016; Canadian Guidelines 2015; ESPEN 2006; SENPE 2011). Although early enteral nutrition is recommended, its timing in critically ill patients varies among the guidelines (24 to 72 hours). However, most studies in the literature define early enteral nutrition as first taking place within 48 hours of initial injury or ICU admission (Casaer 2011; Rice 2012).

How the intervention might work

Early enteral nutrition has physiological effects that provide both nutritional and non-nutritional benefits to critically ill patients (McClave 2014). Nutritional benefits derive from the delivery of exogenous nutrients, which supply sufficient protein and calories, deliver micronutrients and antioxidants, and maintain lean body mass (Kudsk 2007). However, the effects of the administration of enteral feeding go far beyond the deliverance of macro and micronutrients. When started as soon as safely possible following ICU admission enteral nutrition provides important non-nutritional benefits, which are derived from several physiological

mechanisms that maintain the functional and structural integrity of the intestinal mucosa (Fukatsu 2011). Enteral nutrition directly stimulates intestinal contractility and the release of trophic substances and neuropeptides, which play a role in mucosal defences (Kudsk 2001). Furthermore, enteral nutrition stimulates the release of immunoglobulin A (IgA) by gut-associated lymphoid tissues (GALT), which prevents bacterial adherence to the epithelial cells, and prevents an increase in intestinal permeability (Kudsk 2002; Kudsk 2007). Immune mechanisms caused by enteral nutrition result in the attenuation of oxidative stress and inflammatory responses, while also supporting the humoral immune system (Kudsk 2002). Finally, enteral nutrition modulates the metabolic responses that help reduce insulin resistance (McClave 2009).

The nutritional benefits of early enteral nutrition are partly based on studies that have addressed the concept of the energy deficit that accumulates in critically ill patients, especially in malnourished patients (Alberda 2009; Faisy 2009; Heyland 2011; Heyland 2015). Several studies have shown that a negative energy balance correlates with a significantly longer ICU stay, additional days on mechanical ventilation, and more frequent infections (Mault 2000; Robinson 2004; Villet 2005). This becomes of great importance in patients with respiratory failure who require mechanical ventilation, which is one of the most common reasons for ICU admission. These patients are at high risk of malnutrition due to their underlying disease, their catabolic situation, and the mechanical ventilation itself (Wei 2015). Additionally, other studies on the effect of feeding protocols for the delivery of enteral nutrition and clinical outcomes directly support its early introduction (Heyland 2010; Soguel 2012). For example, one before-and-after study and two randomized controlled trials (RCTs) of feeding protocols have shown that increased delivery of nutrition is associated with reduced infectious complications, hospital stay, and mortality (Barr 2004; Martin 2004; Taylor 1999). Thus, a consistent signal can be observed in studies, which indicate that the use of feeding protocols aimed at delivering early feeding, with progressive increases in the rate of delivery, enhances nutritional benefits by reducing the energy deficit and improving clinical outcomes in patients in the ICU (Barr 2004; Heyland 2004; Singh 2009).

For these reasons, the concept of a “window of opportunity” takes force in critically ill patients. It occurs early after ICU admission and during this time the achievement of enteral access and initiation of nutrition changes clinical outcomes and length of hospital stay (McClave 2009).

According to current clinical practice guidelines, the use of early enteral nutrition is recommended for ICU patients (Academy of Nutrition and Dietetics 2012; ASPEN 2016; Canadian Guidelines 2015; ESPEN 2006; SENPE 2011).

Why it is important to do this review

The importance of this systematic review is based on the following premises: a) according to current clinical practice guide-

lines, the use of early enteral nutrition is recommended for ICU patients, but the recommendations regarding its timing in critically ill patients differ between guidelines ([Academy of Nutrition and Dietetics 2012](#); [ASPEN 2016](#); [Canadian Guidelines 2015](#); [ESPEN 2006](#); [SENPE 2011](#)); b) although guidelines recommend the use of early enteral nutrition, recently published contradictory evidence exists. Several observational studies have suggested an association between early enteral nutrition and lower mortality ([Artinian 2006](#); [Khalid 2010](#)). However, ICU stay was shorter and the incidence of ventilator-associated pneumonia was lower in the delayed enteral nutrition group. Moreover, other researchers have found more gastrointestinal complications and a longer ICU stay in patients with high illness severity treated with early enteral nutrition ([Huang 2012](#)). On the other hand, some previously published meta-analyses in this field (with different methodologies and definitions of early enteral nutrition) have drawn contradictory conclusions about the advantages of the use of early enteral nutrition in terms of mortality and hospital length of stay ([Doig 2009](#); [Heyland 2015](#); [Marik 2001](#)); and c) the recommendations regarding the timing of SPN in critically ill patients differ between guidelines ([ASPEN 2016](#); [ESPEN 2009](#)), and the evidence about the benefits of early SPN has been questioned ([Bost 2014](#); [Casaer 2011](#)). Finally, d) the risk of treatment-related complications (e.g. feed intolerance, gastrointestinal issues, pneumonia, or other infections) may be of concern when considering an early start for nutrition support.

In the light of the aforementioned issues, a systematic review with meta-analysis is needed to re-evaluate the potential benefits and adverse effects of early enteral nutrition in critically ill adult patients.

OBJECTIVES

To evaluate the efficacy and safety of early (within 48 hours) versus delayed enteral nutrition (after 48 hours) in critically ill adults.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all RCTs that compare early (within 48 hours) versus delayed enteral nutrition (after 48 hours) in adult ICU patients. We will exclude prospective cohort studies, pseudo-randomized or quasi-randomized trials. We will not exclude any study on the basis of language of publication or publication status (we will seek translation services within the Cochrane network).

Types of participants

We will include studies in adults (aged 18 years or older) receiving enteral nutrition while they are admitted in ICUs. We will include all critical care setting patient populations, including those admitted for medical, surgical, and trauma diagnoses, requiring any type of enteral nutrition access procedure. We will exclude trials that mostly include patients who have had surgical procedures that would not normally require admission to an ICU, elective cardiac surgery patients admitted for postoperative monitoring, or patients with an ICU length of stay of less than 72 hours.

Types of interventions

The experimental intervention will be enteral nutrition starting within 48 hours of initial injury or ICU admission, with or without SPN, independent of the amount of calories or protein intake. We will accept any route for feeding tube or compound of enteral formula for inclusion in this review.

The control intervention will be enteral nutrition administered later than 48 hours after injury or ICU admission in critically ill patients, with or without SPN.

Whenever SPN has been used in the experimental arm of a study, for inclusion in this review the control arm has to include SPN as well. Therefore, we include two comparisons in this review to be analysed separately:

1. Early versus delayed enteral nutrition.
2. Early enteral nutrition with SPN versus delayed enteral nutrition with SPN.

Types of outcome measures

We will evaluate the differences in effects between the intervention group and the control group on the following outcomes:

Primary outcomes

1. Mortality (at the end of follow-up).
2. Infectious complications, independent of specific site (as defined in each of the included studies, with follow-up from the day of enrolment in the study until enteral nutrition or SPN is discontinued).
3. Feed intolerance or gastrointestinal complications: vomiting, diarrhoea, high gastric residual volume, or gastrointestinal bleeding. We will accept the authors' definitions of outcome events (follow-up from the day of starting enteral nutrition until discontinued).

Secondary outcomes

1. ICU mortality.
2. Length of ICU stay.
3. Length of hospital stay (LOS).

4. Duration of mechanical ventilation in days (follow-up from the day of starting mechanical ventilation (invasive or non-invasive) until discontinued).

5. Weaning failure (the re-initiation of mechanical ventilation after discontinuation, or the requirement for protracted mechanical ventilation).

6. Pneumonia (as defined in each of the included studies (follow-up from time of enrolment in the study until enteral nutrition is discontinued, participant death, or discharge from the ICU)).

Search methods for identification of studies

Electronic searches

In order to identify relevant RCTs, we will search the Cochrane Central Register of Controlled Trials (CENTRAL, most recent issue), MEDLINE via Ovid SP (1946 to date), Embase via Ovid SP (1966 to date), and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCO host (1982 to date), as well as ISI Web of Science (1973 to date). We will not apply any language restrictions to the search and we will ask for translation services within the local Cochrane centres. We will develop a specific strategy for each database by transforming the strategy developed for MEDLINE. The preliminary search strategy is shown in [Appendix 2](#).

Searching other resources

We will review the reference lists of all included RCTs for additional studies that may meet our criteria. In addition, we will search Turning Research Into Practice (TRIP) (www.tripdatabase.com) and trial registers (www.clinicaltrials.gov; www.controlled-trials.com). We will review the titles and abstracts, if available, of the scientific conferences (from start to present) of both the American Society for Parenteral and Enteral Nutrition (ASPEN) and the European Society for Clinical Nutrition and Metabolism (ESPEN).

Data collection and analysis

Selection of studies

We will combine the results of the searches above and exclude duplicate records. Two review authors (PF and GM) will independently screen titles and abstracts for eligibility by referring to the inclusion criteria. Each of these authors will separately record the reason for trial exclusion ([Appendix 3](#)). For all titles or abstracts considered by either review author as relevant or to potentially

meet the criteria, we will retrieve the full article for further evaluation. Two authors (PF and GM) will assess these articles for eligibility. We will initially resolve disagreements on trial selection between authors by discussion. If we are unable to reach consensus, a third author (RV) will be consulted. If there is insufficient published information to make a decision about inclusion, we will contact the first author of the relevant trial. If multiple reports describe the same trial, we will include all reports to allow the complete extraction of the trial details, but we will only include the results of the study with the longest follow-up. We will record the selection process in sufficient detail to complete a PRISMA flow diagram ([Moher 2009](#)), and a 'Characteristics of excluded studies' table.

Data extraction and management

Two review authors (PF and GM) will independently extract and validate data, and assess the quality of each trial, using data extraction forms that we will design for this purpose ([Appendix 4](#)). We will collect data on the outcomes relevant to the review mentioned in [Types of outcome measures](#). We will resolve any discrepancies in the extracted data by discussion. If the two authors still disagree, a third author (RV) will be contacted to reach a consensus. Should additional information be needed, one review author (PF) will contact the first author of the relevant trial.

Assessment of risk of bias in included studies

Two authors (PF and GM) will independently assess the risk of bias of the included studies using the Cochrane 'Risk of bias' tool ([Higgins 2011](#)). We will resolve any disagreement by discussion or by consulting a third review author (RV). When the risk of bias for a study is unclear, we will contact the study authors.

We will report each of the domains as low risk, high risk, or unclear risk. We will categorize the level of risk of bias as follows:

1. Low risk: when there is available information that clearly demonstrates that efforts were made to ensure minimal bias in that domain and the described methods are robust enough to have a high likelihood of being effective.
2. Unclear risk: when the information available is insufficient to be confident that the method used to minimize bias was robust enough to be effective.
3. High risk: when the study does not report any method to minimize bias in that domain.

For each included primary study, we will assess the following domains of bias:

Random sequence generation

We will consider that there is a low risk of bias for allocation sequence generation when it is generated by a computer or a random number table algorithm, coin tossing, shuffling cards, envelopes,

throwing dice, drawing lots, or minimization (it may be implemented without a random element and this is considered to be equivalent to being random).

Allocation concealment

We will consider that there is a low risk of bias for allocation concealment when the participant recruiters and investigators enrolling participants are unable to anticipate the treatment assignment. Adequate methods include a central allocation system (including telephone, web-based, and pharmacy-controlled randomization), sequentially numbered drug containers of identical appearance, or sequentially numbered opaque or sealed envelopes.

Blinding of participants and personnel

We will describe the methods used, if any, by each included study to blind study participants and personnel from knowing which intervention a participant received. We will judge studies as low risk of bias if they were blinded, or if we judge that the lack of blinding could not have affected the results, which could be plausible in the context of our systematic review when, for example, the patients are comatose.

Blinding of outcome assessment

We will separately assess blinding for different outcomes or classes of outcomes. We will judge studies to be at low risk of bias if they were blinded, or if we judge that the lack of blinding could not have affected the results.

Incomplete outcome data

We will consider that there is a low risk of bias for incomplete outcome data if any of the following criteria are fulfilled: no missing outcome data; the reasons for missing outcome data are unlikely to be related to true outcome (for survival data, censoring is unlikely to introduce bias); missing outcome data are balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with the observed event risk is not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, the plausible effect size (mean difference or standardized mean difference) among missing outcomes is not enough to have a clinically relevant impact on the observed effect size or missing data have been imputed using appropriate methods.

Selective outcome reporting

We will consider that there is a low risk of selective reporting bias if any one of the following criteria are fulfilled: the study protocol is available and all of the studies pre-specified (primary

and secondary) outcomes that are of interest for the systematic review have been reported in the pre-specified way; or when the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

Other bias

We will describe any important concerns we have about other possible sources of bias (baseline imbalance, sponsorship bias, confirmation bias, bias of the presentation data, etc.) for each included study. We will consider that there is a low risk of bias if the trial appears to be free of other components that could put it at risk of bias. We will consider that there is an unclear risk if the trial may or may not be free of other components that could put it at risk of bias. We will consider that there is a high risk of bias if there are other factors in the trial that could put it at risk of bias, e.g. academic fraud, industry involvement, or extreme baseline imbalance.

We will consider a study as having a low risk of bias if all domains except blinding of participants or personnel are assessed as low risk. Given the difficulties of blinding the intervention, and the fact that the most outcomes in the review are objective, we consider that any risk of bias in this dimension will not have an impact on the results and thus should not be considered in the assessment of overall risk of bias for the studies. We will consider a trial as having a high risk of bias if we assess one or more domains as high risk. We will consider a trial to have an unclear risk of bias if one or more domains are unclear.

We will complete for each trial included in the review a 'Risk of bias' table. This table will form part of the data extraction form ([Appendix 4](#)). We will summarize our 'Risk of bias' assessments in risk of bias graphs and figures and across domains in the 'Summary of findings' table.

Measures of treatment effect

For dichotomous variables, we will calculate risk ratios (RR) with 95% confidence intervals (CIs). In the case of continuous variables, we will calculate the mean differences (MD) or standardized mean difference (SMD) with 95% CI. We will calculate the SMD when different instruments or scales are used to measure the outcome across trials.

Unit of analysis issues

We will use individual study participants in each trial arm as the unit of analysis. We anticipate that all included trials will have a parallel-group design and therefore no adjustment is expected to be necessary for cross-over or clustering.

Dealing with missing data

We will try to contact the trial investigators whenever data are missing, unclear, or when we believe we have detected a potential error in the published data. If this is unsuccessful, we will impute the missing data for the primary outcomes, assuming the worst case scenario, and we will conduct sensitivity analyses to assess how sensitive the results are to changes in the assumptions that are made. In addition, we will deal with the aspect of missing data in our 'Risk of bias' assessment, considering attrition higher than 10% to 15% as a likely source of bias.

Assessment of heterogeneity

We will assess clinical and methodological heterogeneity by performing an informal inspection of study characteristics using clinical judgement. We will use the I^2 statistic to quantify the level of inconsistency between the included studies (Higgins 2011). We will consider heterogeneity to be relevant when the I^2 value is more than 50%. Additionally, we will create a forest plot to illustrate any heterogeneity visually. When relevant statistical heterogeneity is found, we will explore the potential sources by examining the individual trials and the subgroup characteristics.

Assessment of reporting biases

We will visually analyse funnel plots for the meta-analyses of the primary outcomes, if we manage to identify sufficient trials (approximately 10) to contribute to the analyses of the primary outcomes (Higgins 2011). If there is a sufficient number of included trials (10 or more), we will generate funnel plots of the treatment effect size against the precision of the trial ($1/\text{standard error}$) to assess for publication bias. Should asymmetry exist, we will use the 'trim and fill' method described in Sutton 2000 to calculate an adjusted overall confidence interval. Since there can also be other reasons for an asymmetric funnel plot, we will look for evidence of poor methodological quality, true heterogeneity, or chance as possible causes (Egger 1997).

Data synthesis

We will perform all statistical analyses using Review Manager 5.3 software (RevMan 5.3). We will conduct meta-analyses where there are sufficient data from the included studies to estimate an overall treatment effect of comparable interventions, comparators, and outcomes. We will pool the treatment effect measures across studies with the inverse-variance method, applying a random-effects model in all cases. We assume that there will be heterogeneity due to the diversity of the patients. If no pooling of data can be conducted, we will present a narrative summary of results. In the extreme situation of no events occurring in all arms of all studies or events below 1%, we will use Peto's method to meta-analyse a specific outcome (Bradburn 2007).

Subgroup analysis and investigation of heterogeneity

We will perform subgroup analysis to identify the source of heterogeneity and, therefore, stratify the studies into homogenous groups. If sufficient data from studies exist, we will carry out the following subgroup analyses:

Subgroups of participants

1. Participant subsets (medical, surgical, traumatic, and burn).
2. Participants nutritionally at-risk or malnourished on ICU admission (as defined in each of the included studies).
3. Participants with obesity (as defined in each of the included studies).
4. Participants post cardiac arrest (post cardiopulmonary resuscitation (CPR), following successful resuscitation).
5. Participants with a high severity of illness score (defined by validated severity scales specific to critically ill patients, such as the Acute Physiology and Chronic Health Evaluation (APACHE), Simplified Acute Physiology Score (SOFA), Sequential Organ Failure Assessment (SAPS)).

Subgroups of the intervention

1. Very early enteral nutrition (VEEN), started within 24 hours of admission to the ICU, versus early enteral nutrition (started between 24 and 48 hours after admission).
2. VEEN started within 24 hours of admission to the ICU with SPN versus early enteral nutrition (started between 24 and 48 hours after admission) with SPN.

Sensitivity analysis

If we identify sufficient trials, we will perform sensitivity analyses to separately evaluate trials at high and low risk of bias, as determined with the Cochrane tool for assessing risk of bias (Higgins 2011).

Summary of findings table and GRADE

We will use the principles of the GRADE system to assess the quality of the body of evidence associated with specific outcomes (as listed below) (Guyatt 2008), and we will draw up 'Summary of findings' tables using the GRADEpro software (GRADEpro 2014). We will create two 'Summary of findings' tables, one for the comparison of early versus delayed enteral nutrition and the other for the comparison early enteral nutrition with SPN versus delayed enteral nutrition with SPN. We will present the following outcomes in the 'Summary of findings' tables:

1. Mortality (at the end of follow-up).
2. Infectious complications, independent of specific site (as defined in each of the included studies, with follow-up from the day of enrolment in the study until enteral nutrition or SPN is discontinued).

3. Feed intolerance or gastrointestinal complications: vomiting, diarrhoea, high gastric residual volume, or gastrointestinal bleeding. We will accept the authors' definitions of outcome events (follow-up from the day of starting enteral nutrition until discontinued).

4. Length of hospital stay (LOS).

5. Duration of mechanical ventilation in days (follow-up from the day of starting mechanical ventilation (invasive or non-invasive) until discontinued).

6. Pneumonia (as defined in each of the included studies (follow-up from time of enrolment in the study until enteral nutrition is discontinued, participant death, or discharge from the ICU)).

The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality of a body of evidence is based on within-study risk of bias (methodological quality), directness of the evidence, heterogeneity of the data, precision of effect estimates, and risk of publication bias (Chapter 12, *Cochrane Handbook for Systematic Reviews of Interventions*) (Higgins 2011). Two review authors (PF and GM) will independently assess the quality of the eligible trials for all the

outcomes. We will refer discrepancies in our assessments of the quality of evidence to a third author (RV) for a final decision.

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Paulina Fuentes Padilla is a doctoral candidate for a PhD in Methodology of Biomedical Research and Public Health at the Department of Paediatrics, Obstetrics, Gynaecology and Preventive Medicine of Universitat Autònoma de Barcelona, Barcelona, Spain.

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* Indicates the major publication for the study

APPENDICES

Appendix I. Glossary

Energy: Required to sustain the body's various functions by oxidation (primarily from carbohydrates, fats, and amino acids), yielding the chemical energy needed to sustain metabolism, nerve transmission, respiration, circulation, and physical work. This term should be used in preference to calorie. Calorie should only be used in the quantification of energy.

Enteral access device: Tube placed directly into the gastrointestinal tract for the delivery of nutrients, drugs, or both.

Enteral nutrition: Feeding provided through the gastrointestinal tract via a tube, catheter, or stoma that delivers nutrients distal to the oral cavity. Enteral nutrition is to be used in preference to 'enteral feeding'.

Food fortification: Normal food enriched with specific nutrients, in particular with energy and/or proteins, minerals, vitamins, and trace elements.

Macronutrient: Nutrients that are required in relatively large amounts compared to other nutrients, which can be metabolized to produce energy (carbohydrates, proteins, fats).

Malnutrition: An acute, subacute, or chronic state of nutrition, in which a combination of varying degrees of overnutrition or undernutrition with or without inflammatory activity have led to a change in body composition and diminished function.

Micronutrient: Nutrients present and required in the body in minute quantities as compared to macronutrients (e.g. vitamins, trace elements).

Nutrient: Proteins, carbohydrates, lipids, vitamins, minerals, or water.

Nutrition assessment: A comprehensive approach to defining the nutritional state, which uses a combination of the following: medical, nutritional, and medication histories; physical examination; anthropometric measurements; and laboratory data.

Nutrition screening: A process to identify an individual who may be malnourished or at risk of malnutrition to determine if a comprehensive nutrition assessment is indicated.

Nutrition support or nutrition support therapy: A component of medical treatment that includes the provision of enteral or parenteral nutrition (or both).

Oral nutritional supplements (ONS): Supplementary oral intake of dietary food for special medical purposes in addition to normal food. ONS are usually liquid but they are also available in other forms like powder, dessert-style, or bars.

Parenteral nutrition: The intravenous administration of nutrients. Parenteral nutrition is to be used in preference to 'parenteral feeding'. It could be:

1. central: parenteral nutrition delivered into a large-diameter vein, usually the superior vena cava adjacent to the right atrium;
2. peripheral: parenteral nutrition delivered into a small-diameter peripheral vein, usually of the hand or forearm.

Supplemental parenteral nutrition (SPN): parenteral nutrition combined with enteral nutrition when enteral nutrition alone fails to meet target nutritional goals.

Appendix 2. MEDLINE (OVID SP) search strategy

1 (exp Enteral Nutrition/ or enteral nutrition*.mp. or enteral feed*.mp. or tube feed*.mp.)

2 (early or late or delay* or tim*).mp.

3 1 and 2

4 ((critical* adj3 ill*) or (intensive adj2 care) or ICU or burn* or (head adj3 injur*)).mp. or exp Critical Illness/ or exp Intensive Care/ or exp Intensive Care Units/

5 3 and 4

6 ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (animals not (humans and animals)).sh.

7 5 and 6

Appendix 3. Study selection form

Review title or ID	
Study ID (<i>surname of first author and year first full report of study was published</i>)	
Report ID	
Report ID of other reports of this study including errata or retractions	
Notes:	

General information	
Date form completed (<i>dd/mm/yyyy</i>)	
Name/ID of person extracting data	
Reference citation	
Study author contact details	
Publication type (<i>e.g. full report, abstract, letter</i>)	
Journal/conference proceedings	
Single centre/multicentre	
Notes:	

Study eligibility					
Study characteristics	Eligibility criteria	Eligibility criteria met?			Location in text or source (<i>pg & ¶/fig/table/other</i>)
		Yes	No	Unclear	
Type of study	Randomized controlled trial				
Participants	Adults (aged 18 years or older) admitted to ICU				
Types of intervention	Enteral nutrition starting within 48 hours after initial injury or ICU admission, with or without SPN				
Types of comparison	Enteral nutrition administered later than 48 hours after injury or ICU admission, with or without SPN				
Types of outcome measures	1. Mortality: at the end of follow-up, ICU mortality				
	2. Infectious complications, independent of specific site (as defined in each of the included studies)				
	3. Feed intolerance or gastrointestinal complications: vomiting, diarrhoea, high gastric residual volume, or gastrointestinal bleeding				
	4. Length of ICU stay				

(Continued)

	5. Length of hospital stay (LOS)				
	6. Duration of mechanical ventilation in days (follow-up from the day of starting mechanical ventilation (invasive or non-invasive) until discontinued)				
	7. Weaning failure (the re-initiation of mechanical ventilation after discontinuation, or the requirement for protracted mechanical ventilation)				
	8. Pneumonia (follow-up from time of enrolment in the study until enteral nutrition is discontinued, participant death, or discharge from ICU)				
INCLUDE		EXCLUDE			
Reason for exclusion					
Notes:					

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

Appendix 4. Data extraction form

Characteristics of included studies

Methods	Descriptions as stated in report/paper			Location in text or source (pg & ¶/fig/table/other)
Aim of study				
Study design				
Methods of recruitment				
Inclusion/exclusion criteria for participation in study				
Unit of allocation				
Study start date				
Study end date				
Randomization method				
Sequence generation				
Allocation concealment method				
Blinded	Yes	No		
Blinding method				
Duration of participation (from recruitment to last follow-up)				
Total number of intervention groups				
Ethical approval needed/obtained for study	Yes	No	Unclear	
Notes:				

Participants	Description
Population description	
Number	
Setting	
Total N° randomized	
Number allocated to each intervention group (no. of individuals)	
Baseline imbalances	
Withdrawals and exclusions (<i>if not provided below by outcome</i>)	
Age (mean, median, range, etc.)	
Male sex (N°/%)	
Disease status/type, etc.	
Score severity of illness at ICU admission (APACHE II, SAPS, SOFA, etc.)	
Co-morbidities	
Sepsis (N°/%)	
Weight (kg)	
BMI (kg/m ²)	
Nutritional evaluation (NRS-2002; MUST; MNA; SGA or other)	
Interventions	
N° of arms	
Intervention type	
Intervention timing	
Route of EN administration	
Mean REE (kcal/day)	

(Continued)

Mean energy delivered/day (kcal/day or cal/kg)	
Mean enterally delivered energy/day (kcal/day or cal/kg)	
Mean parenterally delivered energy/day (kcal/day or cal/kg)	
Daily mean blood glucose (mg/dL)	
Mean protein delivered/day (g/day or g/kg)	
Mean daily energy balance (kcal)	
Cumulative energy balance (kcal)	
Duration	
Assessed	
Length of follow-up	

(BMI: Body Mass Index; NRS-2002: Nutritional Risk Screening; MUST: Malnutrition Universal Screening Tool; SGA: Subjective Global Assessment; APACHE: Acute Physiology and Chronic Health Evaluation; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment; REE: Resting Energy Expenditure; kcal: kilocalories)

Outcomes	Information available in paper
Outcome 1 Mortality at the end of follow-up	Yes/No
Outcome 2 Infectious complications, independent of specific site	Yes/No
Outcome 3 Feed intolerance or gastrointestinal complications: vomiting, diarrhoea, high gastric residual volume, or gastrointestinal bleeding	Yes/No
Outcome 4 ICU mortality	Yes/No
Outcome 5 Length of ICU stay	Yes/No
Outcome 6 Length of hospital stay (LOS)	Yes/No

(Continued)

Outcome 7 Duration of mechanical ventilation in days	Yes/No
Outcome 8 Weaning failure	
Outcome 9 Pneumonia	Yes/No
Other outcome	

For continuous data			
Outcomes	Intervention group	Control group	Details if outcome only described in text
	N/Mean (SD)	N/Mean (SD)	
Outcome 5: Length of ICU stay (days)			
Outcome 6: Length of hospital stay (days)			
Outcome 7: Duration of mechanical ventilation in days			
Other outcome			
Other information which you feel is relevant to the results			

For dichotomous data			
Outcomes	Intervention group	Control group	Details if outcome only described in text
	N/Mean (SD)	N/Mean (SD)	
Outcome 1: Mortality at the end of follow-up			
Outcome 2: Infectious complications, independent of specific site			

(Continued)

Outcome 3: Feed intolerance or gastrointestinal complications: vomiting, diarrhoea, high gastric residual volume, or gastrointestinal bleeding			
Outcome 4: ICU mortality			
Outcome 8: Weaning failure			
Outcome 9: Pneumonia			
Other outcome			
Other information which you feel is relevant to the results			

Results	
No. of participants allocated to each treatment arm	
No. who received each treatment arm	
No. who did not receive intended treatment and why	
Number followed up	
Number lost to follow-up and why	
Number included in the final analysis	
Analysis	
Method	
Sample size details	
Reported effect size	
Authors conclusions	
Funding source	
Reviewer comments	

Methodological quality assessment

Domain	State here reasons for grading	Judgement
Random sequence generation <i>Was the allocation sequence adequately generated?</i>		Low High Unclear
Allocation concealment <i>Was allocation adequately concealed?</i>		Low High Unclear
Blinding of participants and personnel <i>Was knowledge of the allocated intervention adequately prevented during the study?</i>		Low High Unclear
Blinding of outcome assessment <i>Was knowledge of the allocated intervention adequately prevented during the study?</i>		Low High Unclear
Incomplete outcome data <i>Were incomplete outcome data adequately addressed? State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), and reasons</i>		Low High Unclear
Selective outcome reporting <i>Are reports of the study free of suggestion of selective outcome reporting?</i>		Low High Unclear
Other bias <i>Role of possible conflicts of interest for study authors</i>		Low High Unclear

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