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Early enteral nutrition (within 48 hours) versus delayed enteral nutrition (after 48 hours) with or without supplemental parenteral nutrition in critically ill adults (Review)

Fuentes Padilla P, Martínez G, Vernooij RWM, Urrútia G, Roqué i Figuls M, Bonfill Cosp X

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[Intervention Review]

Early enteral nutrition (within 48 hours) versus delayed enteral nutrition (after 48 hours) with or without supplemental parenteral nutrition in critically ill adults

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ABSTRACT

Background

Early enteral nutrition support (within 48 hours of admission or injury) is frequently recommended for the management of patients in intensive care units (ICU). Early enteral nutrition is recommended in many clinical practice guidelines, although there appears to be a lack of evidence for its use and benefit.

Objectives

To evaluate the efficacy and safety of early enteral nutrition (initiated within 48 hours of initial injury or ICU admission) versus delayed enteral nutrition (initiated later than 48 hours after initial injury or ICU admission), with or without supplemental parenteral nutrition, in critically ill adults.

Search methods

We searched CENTRAL (2019, Issue 4), MEDLINE Ovid (1946 to April 2019), Embase Ovid SP (1974 to April 2019), CINAHL EBSCO (1982 to April 2019), and ISI Web of Science (1945 to April 2019). We also searched Turning Research Into Practice (TRIP), trial registers (ClinicalTrials.gov, ISRCTN registry), and scientific conference reports, including the American Society for Parenteral and Enteral Nutrition and the European Society for Clinical Nutrition and Metabolism. We applied no restrictions by language or publication status.

Selection criteria

We included all randomized controlled trials (RCTs) that compared early versus delayed enteral nutrition, with or without supplemental parenteral nutrition, in adults who were in the ICU for longer than 72 hours. This included individuals admitted for medical, surgical, and trauma diagnoses, and who required any type of enteral nutrition.

Data collection and analysis

Two review authors extracted study data and assessed the risk of bias in the included studies. We expressed results as risk ratios (RR) for dichotomous data, and as mean differences (MD) for continuous data, both with 95% confidence intervals (CI). We assessed the certainty of the evidence using GRADE.

Main results

We included seven RCTs with a total of 345 participants. Outcome data were limited, and we judged many trials to have an unclear risk of bias in several domains.

Early versus delayed enteral nutrition

Six trials (318 participants) assessed early versus delayed enteral nutrition in general, medical, and trauma ICUs in the USA, Australia, Greece, India, and Russia.

Primary outcomes

Five studies (259 participants) measured mortality. It is uncertain whether early enteral nutrition affects the risk of mortality within 30 days (RR 1.00, 95% CI 0.16 to 6.38; 1 study, 38 participants; very low-quality evidence). Four studies (221 participants) reported mortality without describing the timeframe; we did not pool these results. None of the studies reported a clear difference in mortality between groups.

Three studies (156 participants) reported infectious complications. We were unable to pool the results due to unreported data and substantial clinical heterogeneity. The results were inconsistent across studies.

One trial measured feed intolerance or gastrointestinal complications; it is uncertain whether early enteral nutrition affects this outcome (RR 0.84, 95% CI 0.35 to 2.01; 59 participants; very low-quality evidence).

Secondary outcomes

One trial assessed hospital length of stay and reported a longer stay in the early enteral group (median 15 days (interquartile range (IQR) 9.5 to 20) versus 12 days (IQR 7.5 to15); P = 0.05; 59 participants; very low-quality evidence).

Three studies (125 participants) reported the duration of mechanical ventilation. We did not pool the results due to clinical and statistical heterogeneity. The results were inconsistent across studies.

It is uncertain whether early enteral nutrition affects the risk of pneumonia (RR 0.77, 95% CI 0.55 to 1.06; 4 studies, 192 participants; very low-quality evidence).

Early enteral nutrition with supplemental parenteral nutrition versus delayed enteral nutrition with supplemental parenteral nutrition

We identified one trial in a burn ICU in the USA (27 participants).

Primary outcomes

It is uncertain whether early enteral nutrition with supplemental parenteral nutrition affects the risk of mortality (RR 0.74, 95% CI 0.25 to 2.18; very low-quality evidence), or infectious complications (MD 0.00, 95% CI -1.94 to 1.94; very low-quality evidence). There were no data available for feed intolerance or gastrointestinal complications.

Secondary outcomes

It is uncertain whether early enteral nutrition with supplemental parenteral nutrition reduces the duration of mechanical ventilation (MD 9.00, 95% CI -10.99 to 28.99; very low-quality evidence). There were no data available for hospital length of stay or pneumonia.

Authors' conclusions

Due to very low-quality evidence, we are uncertain whether early enteral nutrition, compared with delayed enteral nutrition, affects the risk of mortality within 30 days, feed intolerance or gastrointestinal complications, or pneumonia.

Due to very low-quality evidence, we are uncertain if early enteral nutrition with supplemental parenteral nutrition compared with delayed enteral nutrition with supplemental parenteral nutrition reduces mortality, infectious complications, or duration of mechanical ventilation.

There is currently insufficient evidence; there is a need for large, multicentred studies with rigorous methodology, which measure important clinical outcomes.

PLAIN LANGUAGE SUMMARY

Early versus delayed feeding through a tube for critically ill adults in intensive care, with or without extra nutrition into a vein

Background

Enteral nutrition involves giving liquid nutrition by a tube directly into the stomach or small intestine. Current clinical practice guidelines recommend nutrition support within 48 hours of injury or admission to an intensive care unit (ICU). It is seen as an essential part of the management of critically ill patients and may help to support the function of the gut. If full enteral nutrition is not possible, nutrients can also be given through a catheter into a vein, called supplemental parenteral nutrition (SPN). Evidence from randomized controlled trials (RCTs) is needed to support these guideline recommendations.

Review question

Do adults admitted in an ICU, who receive early enteral nutrition within 48 hours, have better clinical outcomes than those for whom enteral nutrition is delayed (after 48 hours of initial injury or ICU admission), and does additional SPN have added benefits?

Study characteristics

We searched the literature until April 2019 for RCTs that compared early enteral nutrition with delayed enteral nutrition, with or without SPN, in adults in an ICU. RCTs, if designed and conducted properly, represent the highest methodological standard in clinical research. We included seven RCTs with 345 participants. Participants were admitted to the ICU for more than 72 hours with medical, surgical, or trauma diagnoses. Six trials with 318 participants compared early enteral nutrition with delayed enteral nutrition. One trial with 27 participants compared early enteral nutrition with SPN versus delayed enteral nutrition with SPN.

Key results

Overall, results showed no clear differences in the number of deaths within 30 days (one study, 38 participants), intolerance to feeding (one study, 59 participants), or development of pneumonia (four studies, 192 participants), between those who received early enteral nutrition or delayed enteral nutrition. We assessed the evidence as very low-quality, meaning the findings could potentially change with additional studies.

In the one small trial that also gave SPN, the number of deaths, people with infectious complications, and the duration of mechanical ventilation were not clearly different between those who received early enteral nutrition or delayed enteral nutrition (very low-quality evidence).

Future trials should continue to look into the impact of early enteral nutrition, with or without SPN, on important clinical outcomes in adults hospitalized in ICUs.

Quality of the evidence

We assessed the quality of the evidence as very low, meaning we were uncertain about the findings, as included studies were small, and provided an unclear description of the methods that they used. Participants in the studies had different causes for their critical illness. The outcomes were not always measured in the same way or at the same time in the different trials; some trials did not report on them.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Early enteral nutrition compared to delayed enteral nutrition for critically ill adults

Early enteral nutrition compared to delayed enteral nutrition

Patient or population: critically ill adults
Setting: ICUs in university teaching hospitals, tertiary care hospitals, and general hospitals from the USA (2), Australia (1), Greece (1), India (1), and Russia (1)
Intervention: early enteral nutrition (initiated within 48 hours of initial injury or ICU admission)
Comparison: delayed enteral nutrition (initiated later than 48 hours after initial injury or ICU admission)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with delayed enteral nutrition	Risk with early enteral nutrition				
Mortality (measured at 30 days)	Study population 105 per 1000	105 per 1000 (17 to 672)	RR 1.0 (0.16 to 6.38)	38 (1 RCT)	⊕⊝⊝⊝ very low[a]	Mortality at 90 days or 180 days was not reported.
Infectious complications (independent of specific site, as defined by the trial authors) (follow-up from the day of enrolment in the study until enteral nutrition or SPN was discontinued)	See comment		-	156 (3 RCTs)	⊕⊝⊝⊝ very low[b]	We did not pool the trial data due to unreported data and due to infectious complications varied across the trials.
Feed intolerance or gastrointestinal complications (as defined by the trial authors, vomiting, diarrhoea, high gastric residual volume, or gastrointestinal bleeding) (follow-up from the day the enteral nutrition was started until it was discontinued)	Study population 280 per 1000	235 per 1000 (98 to 563)	RR 0.84 (0.35 to 2.01)	59 (1 RCT)	⊕⊝⊝⊝ very low[c]	
Hospital length of stay (measured in days)	See comment		-	59 (1 RCT)	⊕⊝⊝⊝ Very low[d]	One trial reported longer hospital stay in the early nutrition group (median

						15 days (IQR 9.5 to 20) versus 12 days (IQR 7.5 to15), P = 0.05.
Duration of mechanical ventilation (measured in days) (follow-up from the day mechanical ventilation was started until it was discontinued (invasive or non-invasive))	See comment		-	125 (3 RCTs)	⊕⊖⊖⊖ Very low[e]	We did not pool the data due to high heterogeneity.
Pneumonia (as defined by the authors) (follow-up from time of enrolment in the study until enteral nutrition was discontinued, participant died, or was discharged from the ICU)	Study population		RR 0.77 (0.55 to 1.06)	192 (4 RCTs)	⊕⊖⊖⊖ Very low[f]	A 5th trial reported total number of events; we did not include it in the meta-analysis.
	484 per 1000	373 per 1000 (266 to 513)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **IQR:** interquartile range; **MD:** mean difference; **RR:** risk ratio; **SD:** standard deviation

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by 1 for risk of bias; unclear allocation concealment and selective reporting. Downgraded by 1 for imprecision; wide confidence interval, small sample size, only one study. Downgraded by 1 for indirectness; study focused on blunt trauma patients.

[b]Downgraded by 1 for risk of bias; unclear allocation concealment and selective reporting, and high risk of bias in allocation concealment in one included study. Downgraded by 1 for imprecision; small sample sizes and number of studies. Downgraded by 1 for indirectness; different population and different type of events were included as infectious complications in each trial.

[c] Downgraded by 1 for risk of bias; unclear random sequence generation, allocation concealment, and selective reporting. Downgraded by 1 for imprecision; wide confidence interval, small sample size, only one study. Downgraded by 1 for indirectness; study focused on people with traumatic brain injury.

[d]Downgraded by 1 for risk of bias; high risk of bias for allocation concealment, and unclear selective reporting. Downgraded by 1 for imprecision; wide confidence interval, small sample size, only one study; total sample size was lower than the calculated optimal information size. Downgraded by 1 for indirectness; study focused on people with organophosphate poisoning.

[e]Downgraded by 1 for risk of bias; unclear or high risk of bias for allocation concealment and selective reporting. Downgraded by 1 for imprecision; wide confidence interval, small sample sizes and number of studies. Downgraded by 1 for inconsistency; high heterogeneity in point estimates (I^2 = 86%). Downgraded by 1 for indirectness; different populations included (blunt trauma, organophosphate poisoning, and medical and surgical ICU patients).

[f]Downgraded by 1 for risk of bias; unclear random sequence generation and allocation concealment, and high risk of bias in allocation concealment and selective reporting. Downgraded by 1 for imprecision; wide confidence interval, small sample sizes and number of studies. Downgraded by 1 for indirectness; different populations included multiple trauma, traumatic brain injury, organophosphate poisoning, and medical and surgical ICU patients.

Summary of findings 2. Early enteral nutrition with supplemental parenteral nutrition (SPN) compared to delayed enteral nutrition with SPN for critically ill adults

Early enteral nutrition with supplemental parenteral nutrition (SPN) compared to delayed enteral nutrition with SPN

Patient or population: critically ill adults
Setting: burn ICU in the USA
Intervention: early enteral nutrition with SPN (within 48 hours of initial injury or ICU admission)
Comparison: delayed enteral nutrition with SPN (later than 48 hours after initial injury or ICU admission)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with delayed enteral nutrition with SPN	Risk with early enteral nutrition with SPN				
Mortality (timing of outcome measurement unclear)	Study population 385 per 1000	285 per 1000 (96 to 838)	RR 0.74 (0.25 to 2.18)	27 (1 RCT)	⊕⊖⊖⊖ very low[a]	We planned to analyse mortality at 30, 90, and 180 days, however, the study did not report when they measured mortality.
Infectious complications (independent of specific site, as defined by the trial authors) (follow-up from the day of enrolment in the study until enteral nutrition or SPN was discontinued)	The mean number of infectious complications in the delayed enteral nutrition group was 3	The mean number of infectious complications in the early enteral nutrition group was 0 (1.94 lower to 1.94 higher)	-	27 (1 RCT)	⊕⊖⊖⊖ very low[a]	
Feed intolerance or gastrointestinal complications	See comment		-	-	-	No studies reported this outcome.

(as defined by the authors)						
Hospital length of stay (measured in days)	See comment		-	-	-	No studies reported this outcome.
Duration of mechanical ventilation (measured in days) (follow-up from the day mechanical ventilation was started until it was discontinued (invasive or non-invasive))	The mean duration of mechanical ventilation in the delayed enteral nutrition group was 23 days	The mean duration of mechanical ventilation in the early enteral nutrition group was 9 days higher (10.99 lower to 28.99 higher)	-	27 (1 RCT)	⊕⊖⊖⊖ very low[a]	
Pneumonia (as defined by the authors) (follow-up from time of enrolment in the study until enteral nutrition was discontinued, participant died, or was discharged from the ICU)	See comment		-	-	-	No studies reported this outcome.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

MD: mean difference; **RR:** risk ratio.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by 2 for imprecision; wide confidence interval, small sample size, only one study. Downgraded by 1 for indirectness; study focused on burned patients.

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 may or may not be beneficial, and which might be modulated by nutrition.

Nutritional support in the ICU is designed to achieve metabolic optimisation, 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 helps to maintain gut integrity and the physiologic stress response, promoting an interaction between the gut and the systemic immune response in critically ill patients (Jabbar 2003; Kudsk 2002).

It has been suggested that the cumulative energy debt after the first week of ICU admission could be a 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, for which they might be unable to compensate 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).

Therefore, nutrition support is 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 2019).

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 may include enteral nutrition, parenteral nutrition, or a combination of both (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 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 2019; SENPE 2011). Although early enteral nutrition is recommended, its timing in critically ill patients varies from 24 to 72 hours among the guidelines. However, most studies in the literature define early enteral nutrition as being initiated 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). The non-nutritional benefits 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 reduces 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 perceived 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; Rubinson 2004; Villet 2005). This becomes of great importance for 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). 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). There is a consistent trend in the studies, which indicates that the use of feeding protocols in ICUs focused on early feeding and progressive increases in the rate of delivery of enteral nutrition, enhances nutritional benefits by reducing the energy deficit and improving clinical outcomes (Barr 2004; Heyland 2004; Singh 2009).

On the other hand, the importance of full feeding over permissive underfeeding in patients admitted to the ICU is a strategy that has not demonstrated significant benefits (EDEN 2012). In a recent RCT in mechanically ventilated patients in an ICU, using early

enteral nutrition in both arms, the comparison of full feeding support versus permissive underfeeding did not show a significant improvement in the rate of survival at 90 days (ANZICS 2018).

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

According to current clinical practice guidelines, early enteral nutrition is recommended for ICU patients (Academy of Nutrition and Dietetics 2012; ASPEN 2016; Canadian Guidelines 2015; ESPEN 2019; SENPE 2011).

Why it is important to do this review

The importance of this systematic review is based on the following premises:

1. according to current clinical practice guidelines, 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 2019; SENPE 2011);
2. 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);
3. 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); and
4. 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 light of the aforementioned issues, a systematic review 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 enteral nutrition (initiated within 48 hours of initial injury or intensive care unit (ICU) admission) versus delayed enteral nutrition (initiated later than 48 hours after initial injury or ICU admission), with or without supplemental parenteral nutrition, in critically ill adults.

METHODS

Criteria for considering studies for this review

Types of studies

We included all RCTs that compared early (within 48 hours) versus delayed enteral nutrition (later than 48 hours) with or without supplemental parenteral nutrition (SPN), in critically ill adult participants.

We excluded cross-over studies, prospective cohort studies, pseudo-randomized, and quasi-randomized trials. We did not include studies that compared the effects of enteral versus parenteral methods of nutrition; this comparison is reviewed elsewhere (Lewis 2018).

We did not exclude any study based on the language of publication or publication status (we sought translation services within the Cochrane Network).

Types of participants

We included studies in adults (aged 18 years or older) receiving enteral nutrition while they were in intensive care units (ICU). We included all critical care setting patient populations, including those admitted for medical, surgical, and trauma diagnoses, who required any type of enteral nutrition access procedure.

We excluded trials that primarily included participants who had surgical procedures that would not normally require admission to an ICU: elective cardiac surgery patients admitted for postoperative monitoring, or participants with an ICU length of stay of fewer than 72 hours.

Types of interventions

The experimental intervention was enteral nutrition, starting within 48 hours of initial injury or ICU admission, with or without SPN, independent of the number of calories or amount of protein intake. We accepted any route for the feeding tube, and any compound of enteral formula.

The control intervention was enteral nutrition started later than 48 hours after initial injury or ICU admission, with or without SPN, in critically ill adults.

Whenever SPN was used in the experimental arm of a study, the control arm had to include SPN as well. Therefore, we included two comparisons in this review, which we 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 evaluated the differences in effects between the intervention group and the control group on the following outcomes:

Primary outcomes

1. Mortality (measured in hospital, within 30 days, within 90 days, and within 180 days)
2. Infectious complications, independent of specific site (as defined by the study authors, with follow-up from the day

of enrolment in the study until enteral nutrition or SPN was discontinued). We collected information on tallies of infectious complications, as well as on the risk of infectious complications.

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

Secondary outcomes

1. ICU mortality
2. Length of ICU stay in days
3. Hospital length of stay in days
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 discontinuing it, or the requirement for protracted mechanical ventilation)
6. Pneumonia (as defined by the study authors, with follow-up from time of enrolment in the study until enteral nutrition was discontinued, participant died, or was discharged from the ICU). We collected information on tallies of pneumonia, as well as on the risk of pneumonia.

Search methods for identification of studies

Electronic searches

We identified RCTs through literature searching, using the systematic and sensitive search strategies as outlined in Chapter 6.4 of the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011). We did not apply restrictions to language or publication status.

We searched the following databases or clinical search engines for relevant trials:

1. Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 4); in the Cochrane Library (searched 15 April 2019);
2. MEDLINE Ovid (1946 to 12 April 2019);
3. Embase Ovid (1974 to 12 April 2019);
4. CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature; 1982 to 12 April 2019);
5. ISI Web of Science (1945 to April 2019).

We developed a subject-specific search strategy in MEDLINE and used that as the basis for the search strategies in the other databases listed. Where appropriate, we expanded the search strategy with search terms for identifying RCTs. All search strategies can be found in Appendix 2.

We searched the following trial registries for ongoing and unpublished trials:

1. US National Institutes of Health Ongoing Trials Register Clinical Trials.gov (www.clinicaltrials.gov; searched 12 April 2019);
2. ISRCTN registry (www.isrctn.com; searched 12 April 2019)

We also searched in the Turning Research Into Practice (TRIP) database for additional trials.

We developed the search strategy in consultation with the Cochrane Information Specialist for Cochrane Emergency and Critical Care.

Searching other resources

We scanned the reference lists and citations of included trials and any relevant systematic reviews identified, for references to additional trials. We reviewed the titles and abstracts, if available, of the scientific conferences (from start to April 2019) of both the American Society for Parenteral and Enteral Nutrition (ASPEN) and the European Society for Clinical Nutrition and Metabolism (ESPEN). When necessary, we contacted trial authors for additional information.

Data collection and analysis

Selection of studies

We combined the results of the above searches and excluded duplicate records. Two review authors (PF and GM) independently screened titles and abstracts for eligibility, by referring to the inclusion criteria. Each of the review authors separately recorded the reason for trial exclusion (Appendix 3). For all titles or abstracts considered by either review author as relevant, or as potentially meeting the criteria, we retrieved the full-text article for further evaluation. Two review authors (PF and GM) independently assessed these articles for eligibility. We initially resolved disagreements on trial selection between review authors by discussion. If we were unable to reach consensus, we consulted a third author (RV). If there was insufficient published information to make a decision about inclusion, we contacted the first author of the relevant trial. If multiple reports described the same trial, we included all reports, to enable us to extract all trial details, but we only included the results of the study report with the longest follow-up. Details of the study selection process are presented in the PRISMA flow diagram and a 'Characteristics of excluded studies' table (Moher 2009).

Data extraction and management

Two review authors (PF and GM) independently extracted and validated data, and assessed the risk of bias of each trial, using data extraction forms that we designed for this purpose (Appendix 4). We collected data on the outcomes relevant to the review, mentioned in Types of outcome measures. We resolved any discrepancies in the extracted data by discussion. If the two authors still disagreed, we contacted a third author (RV) to help reach a consensus. When we needed additional information, one review author (PF) contacted the first author of the relevant trial.

Assessment of risk of bias in included studies

Two authors (PF and GM) independently assessed the risk of bias of the included studies using the Cochrane 'Risk of bias' tool (Higgins 2011). We resolved any disagreement by discussion, or by consulting a third review author (RV). When the risk of bias for a study was unclear, we contacted the study authors.

We assessed the risk of bias for each of the domains as low, high, or unclear. We categorised the level of risk of bias as:

1. Low risk: when there was available information that clearly demonstrated that efforts were made to ensure minimal bias in

that domain, and the described methods were robust enough to have a high likelihood of being effective;

2. Unclear risk: when the information available was insufficient to be confident that the method used to minimize bias was robust enough to be effective;
3. High risk: when the study did not report any method to minimise bias in that domain.

For each included primary study, we assessed the domains of bias as described in Appendix 5.

We completed a 'Risk of bias' table for each included trial in the review. This table was included as part of the data extraction form (Appendix 4). We summarized our 'Risk of bias' assessments in graphs and figures, and across domains in the 'Summary of findings' table.

Measures of treatment effect

For dichotomous variables, we calculated risk ratios (RR) with 95% confidence intervals (CIs). For continuous variables, we calculated the mean difference (MD) or standardized mean difference (SMD) with 95% CI. We calculated the SMD when different instruments or scales were used to measure the outcome across trials. For count variables collecting the number of events, we had intended to calculate rate ratios with 95% CI to combine trials that measure the same outcome (infectious complications and pneumonia), but the included studies provided insufficient data.

Unit of analysis issues

We used individual study participants in each trial arm as the unit of analysis. We did not include any cluster trials, therefore, no adjustment was necessary for clustering. If cluster trials are included in the future, we will use the analytical methods described by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

We tried to contact the trial investigators whenever data were missing, unclear, or when we believed we had detected a potential error in the published data. If this was unsuccessful, we had planned to impute the missing data for the primary outcomes, assuming the worst-case scenario, and we had planned to conduct sensitivity analyses to assess how sensitive the results were to changes in the assumptions made. In addition, we had planned to 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 assessed clinical and methodological heterogeneity by performing an informal inspection of study characteristics using clinical judgement. We used the I^2 statistic to quantify the level of inconsistency between the included studies (Higgins 2011). We considered heterogeneity to be substantial when the I^2 value was more than 50%. We created a forest plot to illustrate any heterogeneity visually. When we found substantial statistical heterogeneity, we explored the potential sources by examining the individual trials and the subgroup characteristics.

Assessment of reporting biases

We had planned to visually analyse funnel plots for the meta-analyses of the primary outcomes if we managed to identify sufficient trials (approximately 10) to contribute to the analyses of the primary outcomes (Higgins 2011). If asymmetry existed, we planned to 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 planned to look for evidence of poor methodological quality, true heterogeneity, or chance as possible causes (Egger 1997).

Data synthesis

We performed all statistical analyses using Review Manager 5 (Review Manager 2014). We conducted meta-analyses when there were sufficient data from the included studies to estimate an overall treatment effect of comparable interventions, comparators, and outcomes. We pooled the treatment effect measures across studies with the generic inverse variance method in all cases, based on the DerSimonian and Laird method (DerSimonian 1986). We assumed that there would be clinical heterogeneity due to the diversity of the patients, therefore, we used random-effects models throughout. If we were unable to pool the data, we presented a narrative summary of results. In the extreme situation of no events occurring in any arm of the studies, or events below 1%, we planned to use Peto's method to meta-analyse a specific outcome (Bradburn 2007).

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analysis to identify the source of heterogeneity, and therefore, stratify the studies into homogenous groups. If sufficient data from studies were available, we planned to 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

We planned to perform sensitivity analyses, excluding all the studies that we judged at high or unclear risk of selection and performance risk of bias, as determined using the Cochrane 'Risk of

bias' tool (Higgins 2011). We aimed to perform sensitivity analyses on the primary outcomes.

Summary of findings' table and GRADE

We used the principles of the GRADE system to assess the certainty of the body of evidence associated with the outcomes listed below (Guyatt 2008). We developed 'Summary of findings' tables using GRADEpro GDT software (GRADEpro GDT). We created two 'Summary of findings' tables, one for the comparison of early versus delayed enteral nutrition (Summary of findings for the main comparison), and the other for the comparison early enteral nutrition with SPN versus delayed enteral nutrition with SPN (Summary of findings 2). We presented the following outcomes in the 'Summary of findings' tables.

1. Mortality (measured in hospital within 30 days, within 90 days, and within 180 days);
2. Infectious complications, independent of specific site (as defined by the study authors, with follow-up from the day of enrolment in the study until enteral nutrition or SPN was discontinued).
3. Feed intolerance or gastrointestinal complications: vomiting, diarrhoea, high gastric residual volume, or gastrointestinal bleeding. We accepted the trial authors' definitions of outcome events; follow-up was from the day of starting enteral nutrition until it was discontinued;
4. Hospital length of stay in days;
5. Duration of mechanical ventilation in days (follow-up from the day of starting mechanical ventilation (invasive or non-invasive) until it was discontinued);
6. Pneumonia as defined by the study authors (follow-up from time of enrolment in the study until enteral nutrition was discontinued, the participant died, or was discharged from the ICU).

The GRADE approach appraises the certainty 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 certainty 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) independently assessed the certainty of the evidence for all the outcomes. We referred discrepancies in our assessments of the certainty of evidence to a third author (RV) for a final decision.

RESULTS

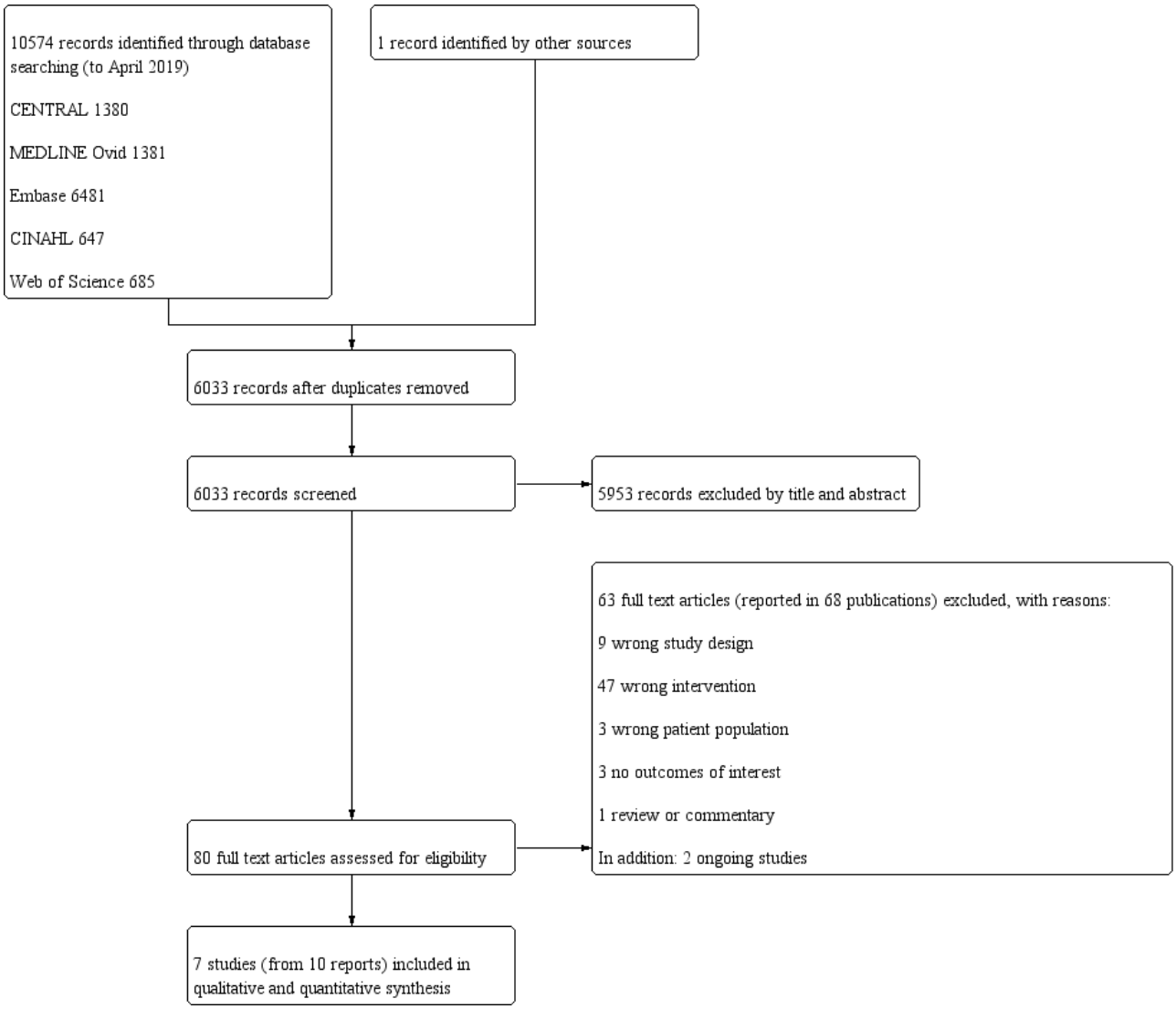
Description of studies

See Characteristics of included studies and Characteristics of excluded studies.

Results of the search

In April 2019, we identified 10,574 potentially relevant records through searching CENTRAL (N = 1380), MEDLINE (N = 1381), Embase (N = 6481), CINAHL (N = 647), and ISI Web of Science (N = 685). We identified one additional reference by screening the included studies in another systematic review (Koretz 2014). We excluded 4542 duplicate references. We screened 6033 records and excluded 5953 references, based on their titles and abstracts. We assessed 80 full-text articles for eligibility. Of these, we excluded 63 studies (reported in 68 publications) as they did not meet our inclusion criteria. We recorded the reasons for exclusion in the 'Characteristics of excluded studies' table. We ultimately included seven RCTs, reported in 10 publications. We identified two ongoing trials (see Figure 1 (PRISMA Study flow diagram)).

Figure 1. Study flow diagram



Included studies

We included seven trials in this systematic review (Chourdakis 2012; Eyer 1993; Hill 2002; Leiderman 2002; Moses 2009; Nguyen 2008; Peck 2004). For further details on the included trials, see Characteristics of included studies.

Participants

The seven included trials enrolled a total of 345 participants, ranging from 27 (Peck 2004) to 88 participants (Leiderman 2002). The mean age of the participants in six trials ranged between 29 and 56.3 years (Chourdakis 2012; Eyer 1993; Hill 2002; Moses 2009; Nguyen 2008; Peck 2004); one trial did not report the mean age (Leiderman 2002). Four of the seven included trials were conducted in participants with trauma (Chourdakis 2012; Eyer 1993; Hill 2002; Leiderman 2002).

Setting

The trials included participants from the USA (Eyer 1993; Hill 2002; Peck 2004), Australia (Nguyen 2008), Greece (Chourdakis 2012), India (Moses 2009), and Russia (Leiderman 2002). Of the seven included trials, four were conducted in general intensive care units (ICU (Chourdakis 2012; Hill 2002; Leiderman 2002; Nguyen 2008), one trial was conducted in a medical ICU (Moses 2009), one in a trauma ICU (Eyer 1993), and one was conducted in a burn ICU (Peck 2004).

Intervention

Enteral nutrition was delivered via nasogastric tube in five of the included trials (Chourdakis 2012; Leiderman 2002; Moses 2009; Nguyen 2008; Peck 2004). One trial used a duodenal feeding tube (Eyer 1993); in one trial the type of enteral route was not defined (Hill 2002). Early enteral nutrition (EN) was used in two included trials (Chourdakis 2012; Moses 2009), and VEEN (within 24 hours of admission) was used in five of the seven included trials (Eyer 1993; Hill 2002; Leiderman 2002; Nguyen 2008; Peck 2004). We identified one trial that used supplemental parenteral nutrition (SPN) in both the intervention and control group (Peck 2004). We summarised the interventions reported in the 'Characteristics of included studies' table.

Outcomes

Of the seven included trials, two (28.6%) included clinical outcomes as primary outcomes (Leiderman 2002; Moses 2009). Across the seven trials, all the outcomes included in this review for the comparison 'early versus delayed EN' were reported. For the comparison 'early EN with SPN versus delayed EN with SPN' the outcomes reported were: mortality, infectious complications, length of ICU stay, and duration of mechanical ventilation.

Publication type

Of the seven included trials, five (71.4%) were published as full-text papers (Chourdakis 2012; Eyer 1993; Moses 2009; Nguyen 2008; Peck 2004). Two included trials were presented in a conference abstract form, without subsequent full publication (Hill 2002; Leiderman 2002). All of the seven included trials were published in English. We contacted all seven trial authors for missing information; two (28.6%) replied, and provided supplementary data (Eyer 1993; Peck 2004).

Funding sources

Four (57.1%) of the included trials did not report the source of funding (Chourdakis 2012; Hill 2002; Leiderman 2002; Moses 2009). Two trials were partially supported by national health grants (Nguyen 2008; Peck 2004). One trial received funding from a pharmaceutical company (Eyer 1993).

Excluded studies

We excluded 63 studies after full-text assessment. Nine studies were not RCTs (Bakiner 2013; Grahm 1989; Ibrahim 2002; Liu 2018; Ohbe 2019; Perez-Guisado 2013; Su 2018; Wereszczynska-Siemiatkowska 2013; Woo 2010)), 47 studies had an intervention that did not meet our inclusion criteria (ACTRN12615000876594; Bakker 2014; Beale 2008; Braunschweig 2015; Cao 2014; Casaer 2011a; Casaer 2011b; Casaer 2013; ChiCTR-INR-17010741; Chuntrasakul 1996; Couto 2014; Davies 2012; De Castro 2012; Dennis 2005; Desachy 2008; Dou 2011; Dvorak 2004; Engel 1997; Grau-Carmona 2011; Hasse 1995; Heslin 1997; ISRCTN12233792; ISRCTN63461816; Jana 2014; JPRN-UMIN000003569; JPRN-UMIN000009552; Kemen 1995; Kompan 1999; Kompan 2004; Maude 2011; Minard 2000; NCT00883948; NCT01432769; NCT02837861; Ostadrahimi 2016; Petrova 2017; Pilika 2015; Pupelis 2001; Singh 1998; Sun 2013; Vicic 2013; Wang 1997; Wang 2007; Yi 2015; Yuan 2019; Zhong 2014; Zou 2014); three studies did not include ICU participants (Chatterjee 2012; Wang 2015; Zhang 2018); three studies did not measure clinical outcomes (Jazayeri 2016; Jazayeri 2018; Yan 2019); and one study was a review (Weijs 2018). The reasons for excluding studies are given in the 'Characteristics of excluded studies' table.

Awaiting classification

We did not have any studies awaiting classification.

Ongoing studies

We identified two ongoing studies (ChiCTR-IOR-17011914; ChiCTR-INR-17012709).

Risk of bias in included studies

We assessed the risk of bias in the seven included trials based on the information we collected from the published reports and information provided by the study authors. We present summaries of risk of bias judgements in Figure 2. We judged that many trials to have an unclear risk of bias in several domains (see the 'Risk of bias' graph in Figure 3) because they did not describe the methodology. We obtained additional information from the authors for two trials (Eyer 1993; Peck 2004).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

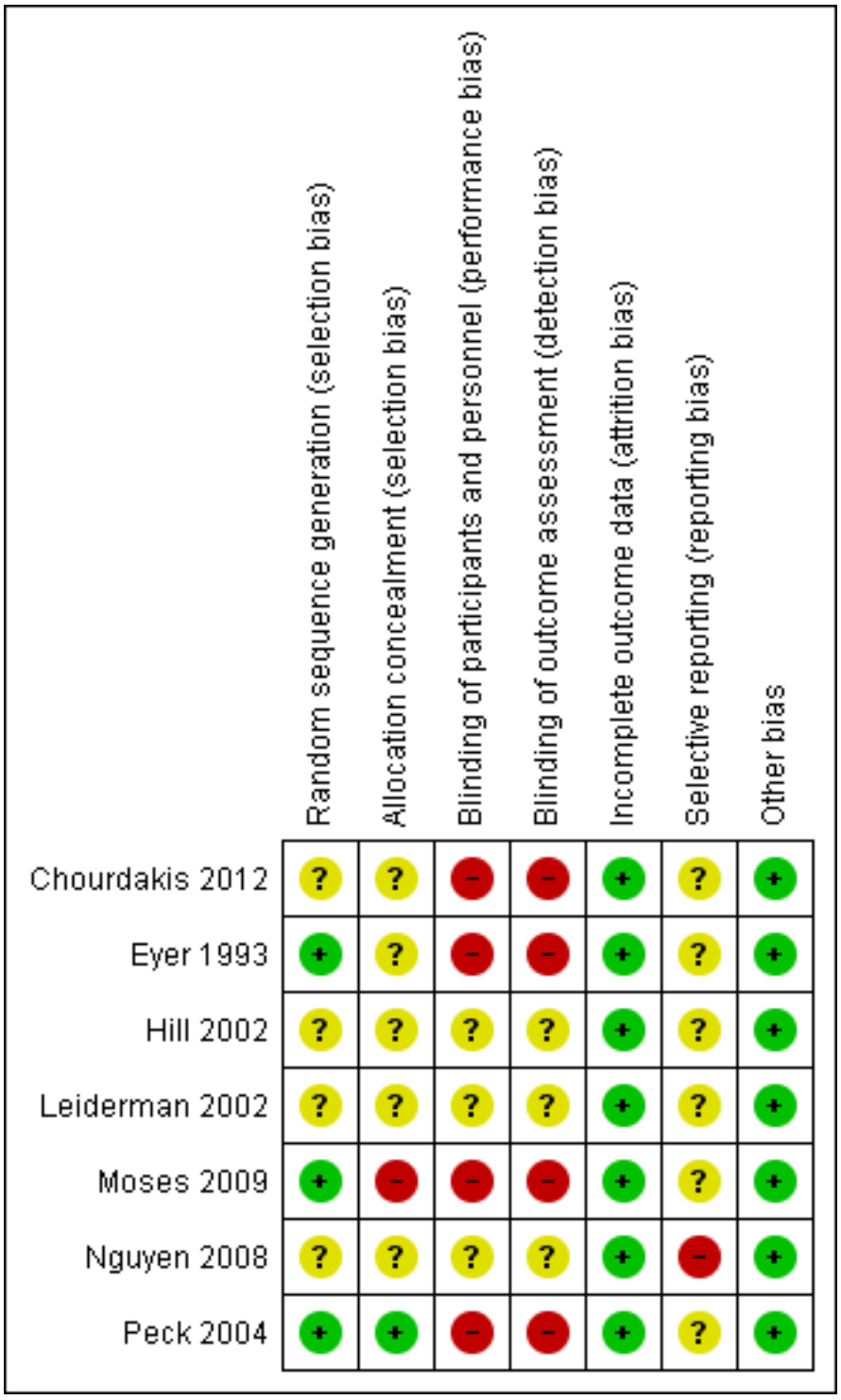
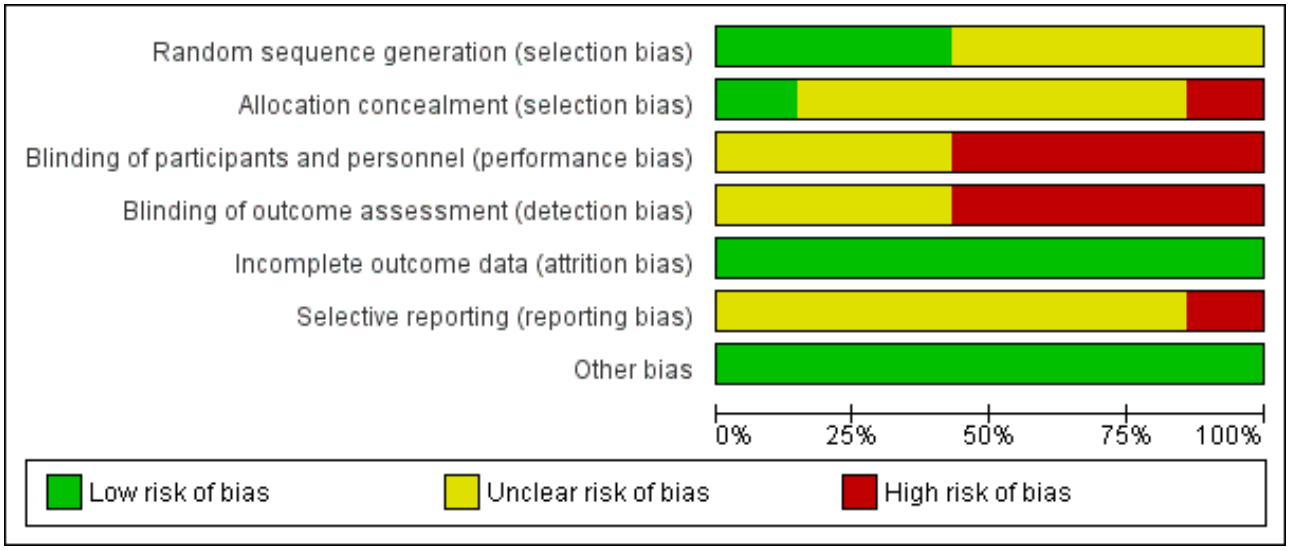


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies



Allocation

We rated the generation of the allocation sequence as having a low risk of bias in three trials (Eyer 1993; Moses 2009; Peck 2004), in all of them, the random sequence generation was well described. The remaining four trials were described as randomized, although we recorded these as having unclear risk of bias because the methodology used for sequence generation was not explained in these trials (Chourdakis 2012; Hill 2002; Leiderman 2002; Nguyen 2008).

We rated allocation concealment at low risk of bias in one trial, as it used a computer random number generator (Peck 2004). We classified one trial at high risk of bias because it stated that sealed envelopes were not used (Moses 2009). The remaining five trials did not describe the methodology used for allocation concealment, so we assessed them at unclear risk of bias (Chourdakis 2012; Eyer 1993; Hill 2002; Leiderman 2002; Nguyen 2008).

Blinding

Four trials did not blind the participants, personnel, or outcome assessor, and we assessed them at high risk of bias (Chourdakis 2012; Eyer 1993; Moses 2009; Peck 2004). We judged the remaining three trials as having unclear risk of bias as they did not describe the methodology used to blind participants, personnel, or outcome assessors (Hill 2002; Leiderman 2002; Nguyen 2008).

Due to the nature of the intervention, and the fact that most participants were sedated or comatose, blinding participants was considered unlikely to influence results. Blinding outcome assessors could potentially bias the results, although the direction of this effect remains unclear.

Incomplete outcome data

We identified no attrition bias in the included studies. Three trials used intention-to-treat analyses (Chourdakis 2012; Eyer 1993; Peck 2004). Three analysed all randomized participants (Hill 2002; Leiderman 2002; Nguyen 2008). In the last trial, the number of dropouts was not high enough to have a clinically relevant impact on the intervention effect estimate (Moses 2009). We judged the seven included trials to have low risk of bias.

Selective reporting

We did not identify protocols for any of the included trials, and therefore, we were unable to adequately judge the risk of bias for this domain. However, we assessed one trial at high risk of bias because it did not report results for all of the outcomes that were outlined in the methods section of the article (Nguyen 2008).

Other potential sources of bias

All trials included less than 100 participants. One trial reported the use of a power calculation to determine the number of people that had to be recruited, although it failed to recruit the minimum number of participants needed in each group to detect significant differences (Moses 2009).

Effects of interventions

See: **Summary of findings for the main comparison** Early enteral nutrition compared to delayed enteral nutrition for critically ill adults; **Summary of findings 2** Early enteral nutrition with supplemental parenteral nutrition (SPN) compared to delayed enteral nutrition with SPN for critically ill adults

This review included seven RCTs, with a total of 345 participants.

Comparison 1. Early enteral nutrition versus delayed enteral nutrition

We identified six trials that compared early versus delayed enteral nutrition, enrolling 318 participants, or 92.2% of participants in this review (Chourdakis 2012; Eyer 1993; Hill 2002; Leiderman 2002; Moses 2009; Nguyen 2008).

Primary outcomes

1. Mortality (measured in hospital within 30 days, within 90 days, and within 180 days)

Five trials, enrolling 259 participants (75% of the total participants in this review) reported on mortality (Eyer 1993; Hill 2002; Leiderman 2002; Moses 2009; Nguyen 2008). In total, 42 participants died in the hospital.

Mortality within 30 days

One study (38 participants) measured mortality within 30 days (Eyer 1993). They reported two deaths in each group (RR 1.00, 95% CI 0.16 to 6.38; Analysis 1.1). We rated the certainty of evidence as very low due to risk of bias, imprecision, and indirectness (Summary of findings for the main comparison).

Mortality within 90 days

We did not identify any studies reporting data on mortality within 90 days.

Mortality within 180 days

We did not identify any studies reporting data on mortality within 180 days.

The other four trials (221 participants) reported the numbers but not the timeframe for mortality (Hill 2002; Leiderman 2002; Moses 2009; Nguyen 2008). Therefore, we refrained from pooling the results.

Hill 2002 reported no deaths in the early and two deaths in the delayed EN group (RR 0.22, 95% CI 0.01 to 4.29; 46 participants). Leiderman 2002 reported five deaths in the early and 13 deaths in the delayed EN group (RR 0.51, 95% CI 0.20 to 1.30; 88 participants). Moses 2009 reported three deaths in the early and three deaths in the delayed EN group (RR 1.03, 95% CI 0.23 to 4.71; 59 participants). Nguyen 2008 reported six deaths in the early and six deaths in the delayed EN group (RR 1.00, 95% CI 0.43 to 2.35; 28 participants) (Analysis 1.1).

2. Infectious complications

Three trials (156 participants) reported on infectious complications (45.2% of total participants in this review) (Chourdakis 2012; Eyer 1993; Moses 2009). We were unable to pool the results due to a lack of reporting of data required for analysis and because infectious complications varied across the trials.

Two trials reported the total of events of infectious complications in both study arms (Chourdakis 2012; Eyer 1993). Chourdakis 2012 reported that there was no difference between groups for each infectious complication (including ventilator-associated pneumonia (VAP), non-VAP, central nervous system (CNS) infections, bacteraemia, and urinary system infections); they did not report a P value. Eyer 1993 suggested that there was no difference between groups in the event rate of infectious complications evaluated (including pneumonia, bacteraemia, urinary system infections, abdominal abscess, wound infection, catheter sepsis, sinusitis and other), although the total number of infections was higher in the early enteral group (the authors reported $P < 0.05$; see Table 1).

The third trial reported the total number of events of infectious complications and the number of participants who developed infections (Moses 2009). The infections included VAP, catheter-related bloodstream infections and urinary tract infections; the difference in risk of infections between groups was inconclusive (RR 0.97, 95% CI 0.57 to 1.62; 59 participants; Analysis 1.2).

We rated the certainty of evidence as very low due to risk of bias, imprecision, and indirectness (Summary of findings for the main comparison).

3. Feed intolerance or gastrointestinal complications

One trial reported on feed intolerance or gastrointestinal complications (Chourdakis 2012). The risk of feed intolerance or gastrointestinal complications between early and late enteral nutrition was inconclusive (RR 0.84, 95% CI 0.35 to 2.01; 59 participants; Analysis 1.3). We rated the certainty of evidence as very low due to risk of bias, imprecision, and indirectness (Summary of findings for the main comparison).

Secondary outcomes

1. ICU mortality

Two trials, enrolling 87 participants (25.2% of the total participants in this review) reported ICU mortality (Chourdakis 2012; Nguyen 2008). In total, 13 participants died in the ICU. The risk of ICU mortality was inconclusive between early and late enteral nutrition (RR 1.03, 95% CI 0.39 to 2.71; 87 participants; $I^2 = 0\%$; Analysis 1.4). We rated the certainty of evidence as very low due to the risk of bias, imprecision, and indirectness.

2. Length of ICU stay in days

Four trials, enrolling 184 participants (53.3% of total participants in this review) reported on the length of ICU stay (Chourdakis 2012; Eyer 1993; Moses 2009; Nguyen 2008).

Moses 2009 reported the medians and interquartile range (IQR) for the length of ICU stay in both groups and observed no significant differences ($P = 0.27$). Because the trial authors did not report variance on the mean (e.g. standard deviation (SD)), and the likelihood of skewed results, we chose not to include data from this study in a meta-analysis.

In the remaining three trials, we pooled estimates of relative effects via a random-effects model, resulting in substantial statistical heterogeneity (MD -2.26, 95% CI -6.12 to 1.60; 125 participants; $I^2 = 58\%$; Analysis 1.7). We noted heterogeneity in the type of participants in the included studies. Chourdakis 2012 and Eyer 1993 included trauma participants, in contrast to Nguyen 2008, which included both medical and surgical participants. Therefore, we decided to refrain from reporting the pooled results.

We rated the certainty of evidence as very low due to the risk of bias, inconsistency, imprecision, and indirectness.

3. Hospital length of stay in days

The single study that examined hospital length of stay enrolled 59 participants and reported medians and IQR for both groups (Moses 2009). The hospital length of stay was longer in the early EN group, with medians of 15 days (IQR 9.5 to 20) versus 12 days (IQR 7.5 to15) in the delayed EN group ($P = 0.05$). We did not subject these data to further analysis. We rated the certainty of evidence as very low due to the risk of bias, imprecision, and indirectness (Summary of findings for the main comparison).

4. Duration of mechanical ventilation (MV) in days

Three trials, enrolling 125 participants (36.2% of total participants in this review), reported on the duration of MV (Eyer 1993; Moses 2009; Nguyen 2008).

Moses 2009 reported medians and IQR in both groups. They found inconclusive results for duration of MV (median 12 days in the early EN group (IQR 5.5 to 14) versus 10 days (IQR 4 to 12) in the delayed EN group; 59 participants; P = 0.17). They did not report a SD and the data for the outcome were likely skewed, therefore, we chose not to include this study in the pooled analysis.

In the remaining two trials, pooled estimates of relative effects resulted in considerable statistical heterogeneity (MD -1.31, 95% CI -7.78 to 5.15; 66 participants; I^2 = 76%; Analysis 1.10). We noted heterogeneity in the type of participants in the included studies, trauma participants in Eyer 1993 and both medical and surgical participants in the study of Nguyen 2008. Therefore, we decided to refrain from reporting the pooled results.

The authors of the trial on trauma participants reported no significant difference between the groups for the duration of MV (MD 2.10, 95% CI -2.66 to 6.86; 38 participants; P = 0.39). However, in the study with both medical and surgical participants, the authors reported a shorter duration of MV in early EN compared with delayed EN (MD -4.50, 95% CI -8.62 to -0.38; 28 participants; P = 0.03; Analysis 1.11).

We rated the certainty of evidence as very low due to the risk of bias, inconsistency, imprecision, and indirectness (Summary of findings for the main comparison).

5. Weaning failure

One trial reported on weaning failure (Moses 2009). The risk of weaning failure between early and late enteral nutrition was inconclusive (RR 1.03, 95% CI 0.07 to 15.77; 59 participants; Analysis 1.12). We rated the certainty of evidence as very low due to the risk of bias, imprecision, and indirectness.

6. Pneumonia

Five trials, enrolling 230 participants (66.7% of total participants in this review) assessed the outcome of pneumonia (Chourdakis 2012; Eyer 1993; Hill 2002; Moses 2009; Nguyen 2008). See Table 2 for the definitions of pneumonia (VAP and non-VAP) included in the trials.

Eyer 1993 reported the data as events of pneumonia. This study reported no significant differences between groups (38 participants; no P value was reported). We did not subject these data to further analysis.

The risk of pneumonia was inconclusive between early and delayed enteral nutrition (RR 0.77, 95% CI 0.55 to 1.06; 4 studies, 192 participants; I^2 = 10%; Analysis 1.13). We analysed non-VAP (RR 0.57, 95% CI 0.29 to 1.11; 2 studies, 105 participants; I^2 = 0%), and VAP (RR 0.89, 95% CI 0.59 to 1.35; 3 studies, 146 participants; I^2 = 1%) separately. The results remained inconclusive, and the analysis showed no subgroup differences (P = 0.27; I^2 = 18.9%; Analysis 1.14).

We rated the certainty of evidence as very low due to the risk of bias, imprecision, and indirectness (Summary of findings for the main comparison).

Subgroup analysis

Subgroups of participants

Four of six included trials, enrolling 231 participants (66.96% of total participants in this review), were performed in trauma patients (Chourdakis 2012; Eyer 1993; Hill 2002; Leiderman 2002).

In the subgroup of trials with trauma patients, the results were inconclusive for length of ICU stay (test subgroup differences P = 0.3; I^2 = 8.3%; Analysis 1.8), and pneumonia (test subgroup differences P = 0.60; I^2 = 0%; Analysis 1.15). We did not find sufficient data to undertake subgroup analyses on ICU mortality (Analysis 1.5), or duration of mechanical ventilation (Analysis 1.11).

There was insufficient information to perform the remaining planned subgroup analyses (Fuentes Padilla 2016). There was insufficient information on nutritionally at-risk or malnourished participants, obesity, and severity of illness scores. There were no trials with participants who were post-cardiac arrest. We contacted the trial's authors to request the individual data but were unsuccessful in our attempts.

Subgroups of the intervention

Concerning intervention subgroups, we found that five of the seven included trials, enrolling 227 participants (65.8% of total participants in this review), used very early enteral nutrition (VEEN (Eyer 1993; Hill 2002; Leiderman 2002; Nguyen 2008; Peck 2004)).

The results from four of these trials with VEEN were inconclusive for length of ICU stay (test subgroup differences P = 0.57; I^2 = 0%; Analysis 1.9), and pneumonia (test subgroup differences P = 0.21; I^2 = 36.3%; Analysis 1.16; Eyer 1993; Hill 2002; Leiderman 2002; Nguyen 2008). We did not find sufficient data to undertake subgroup analysis on ICU mortality (Analysis 1.6).

Comparison 2. Early enteral nutrition with supplemental parenteral nutrition (SPN) compared to delayed enteral nutrition with SPN for critically ill adults

We identified one trial, enrolling 27 participants (7.8% of participants in this review), which examined early enteral nutrition with SPN versus delayed enteral nutrition with SPN (Peck 2004).

Primary outcomes

1. Mortality (measured in hospital within 30 days, within 90 days, and within 180 days)

Peck 2004 did not report the total time of follow-up or the time frame in which they measured mortality. The results for mortality were inconclusive between early and delayed enteral nutrition with supplemental parenteral nutrition (RR 0.74, 95% CI 0.25 to 2.18; 27 participants; Analysis 2.1). We rated the certainty of evidence as very low due to imprecision (-2) and indirectness (Summary of findings 2).

2. Infectious complications

The results for infectious complications were inconclusive between early and delayed enteral nutrition with supplemental parenteral nutrition (MD 0.00, 95% CI -1.94 to 1.94; 27 participants; Analysis 2.2); this trial did not provide a definition or list the types of infectious complications they measured. We rated the certainty of evidence as very low, due to imprecision (-2) and indirectness (Summary of findings 2).

3. Feed intolerance or gastrointestinal complications

We did not identify any studies that measured feed intolerance or gastrointestinal complications for this comparison.

Secondary outcomes

1. ICU mortality

We did not identify any studies that measured ICU mortality for this comparison.

2. Length of ICU stay in days

The results for length of ICU stay were inconclusive between early and delayed enteral nutrition with supplemental parenteral nutrition (MD 3.00, 95% CI -21.55 to 27.55; 27 participants; Analysis 2.3). We rated the certainty of evidence as very low due to imprecision (-2) and indirectness (Summary of findings 2).

3. Hospital length of stay in days

We did not identify any studies that measured hospital length of stay for this comparison.

4. Duration of mechanical ventilation in days

The results for duration of mechanical ventilation were inconclusive between early and delayed enteral nutrition with supplemental parenteral nutrition (MD 9.00, 95% CI -10.99 to 28.99; 27 participants; Analysis 2.4). We rated the certainty of evidence as very low due to imprecision (-2) and indirectness (Summary of findings 2).

5. Weaning failure

We did not identify any studies that measured weaning failure for this comparison.

6. Pneumonia

We did not identify any studies that measured pneumonia for this comparison.

Subgroup analysis

Subgroups of participants

Only one trial was included in this comparison (Peck 2004). We did not perform analysis on participant subgroups.

Subgroups of the intervention

Only one trial was included in this comparison (Peck 2004) with VEEN. We did not perform analysis on intervention subgroups.

Sensitivity analysis

We did not have enough trials to pool the results for the primary outcomes, therefore, we did not perform a sensitivity analysis for this review.

Publication bias

The review did not include the minimum number of trials necessary to produce a funnel plot of the primary outcomes, so funnel plots are not presented.

DISCUSSION

Summary of main results

The objectives of this Cochrane review were to assess the efficacy and safety of early enteral nutrition (EN) administered to adults hospitalized in the intensive care unit (ICU). We included seven RCTs in this review. Six provided data for the first comparison (early versus delayed enteral nutrition (Chourdakis 2012; Eyer 1993; Hill 2002; Leiderman 2002; Moses 2009; Nguyen 2008); and one trial providing data for the second comparison (early enteral nutrition with supplemental parenteral nutrition (SPN) versus delayed enteral nutrition with SPN (Peck 2004). Two trials included clinical outcomes as primary outcomes (Leiderman 2002; Moses 2009).

Comparison 1. Early enteral nutrition versus delayed enteral nutrition

We found very low-certainty evidence from one trial of inconclusive results in mortality within 30 days. No studies reported mortality within 90 and 180 days.

We did not pool the studies that measured infectious complications because of the infectious complications varied across the trials and missing summary data. One trial provided very low-certainty evidence of inconclusive results between treatment groups for infectious complications and feed intolerance.

For the secondary outcome of ICU mortality, we found very low-certainty evidence of inconclusive results between the groups. We did not pool data for length of ICU stay and duration of mechanical ventilation due to high heterogeneity between studies. One trial provided very low-certainty evidence of longer hospital length of stay in the early enteral nutrition group; this was reported in the trial report. We found very low-certainty evidence of inconclusive results for weaning failure and pneumonia.

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

We included one study for this comparison, which provided very low-certainty evidence of inconclusive results for the primary outcomes of mortality and infectious complications. This trial did not report on feed intolerance. We found very low-certainty evidence of inconclusive results for the secondary outcomes of length of ICU stay and duration of mechanical ventilation. The trial did not report any data on ICU mortality, hospital length of stay, weaning failure, or pneumonia.

Overall completeness and applicability of evidence

We identified seven trials on the use of early enteral nutrition in adult participants in the ICU, with or without SPN. Four of these trials included trauma patients (Chourdakis 2012; Eyer 1993; Hill 2002; Leiderman 2002), and five trials included participants who received very early enteral nutrition (VEEN) within 24 hours of admission or injury (Eyer 1993; Hill 2002; Leiderman 2002; Nguyen 2008; Peck 2004). Therefore, the results of this Cochrane Review would be more applicable to the use of VEEN in ICU trauma patients. Trials included data on most outcomes of interest for the early versus delayed enteral nutrition comparison, although there were often few trials that measured each outcome, or they reported heterogeneous data, which could not be combined in a meta-analysis. This also limited the potential for subgroup analyses,

which could have allowed an exploration of heterogeneity among trials. For the second comparison (early versus delayed enteral nutrition with SPN), we included a single trial, and most of the outcomes were not reported (feed intolerance, ICU mortality, hospital length of stay, weaning failure, and pneumonia).

Quality of the evidence

For the early versus delayed enteral nutrition comparison, we did not downgrade the quality of the evidence for blinding (risk of bias) for the outcome mortality, because of the objective nature of the outcome. It is unlikely that this objective outcome was influenced by the unblinded nature of the intervention. However, we downgraded the quality of the evidence due to risk of bias for all of the outcomes we assessed as unclear, or at high risk of bias. We downgraded the certainty of evidence for all of the outcomes due to imprecision when the studies included small sample sizes, a low number of events (or both), and due to indirectness because different population were included in the trials. We also downgraded the certainty of evidence for infectious complications due to indirectness because the included studies included different types of events in the outcome. For example, Chourdakis 2012 reported VAP, non-VAP, central nervous system infection, bacteraemia, urinary system infection, and Moses 2009 reported VAP, catheter-related bloodstream infection, and urinary tract infections as infectious complications. We downgraded the evidence for length of ICU stay and duration of MV for inconsistency, because of substantial heterogeneity in the meta-analysis (Summary of findings for the main comparison).

For the comparison of early versus delayed enteral nutrition with SPN, we downgraded the certainty of evidence for mortality, infectious complications, length of ICU stay, and duration of MV due to imprecision and indirectness. The evidence of a single trial in burn patients, with a small sample size and wide confidence interval neither supported nor refuted either EN strategy (Summary of findings 2).

Potential biases in the review process

We followed the methodology for systematic reviews outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The strengths of the systematic review process include: a detailed electronic search; the independent involvement of at least two review authors in all steps of the review, including study selection and data extraction; and the availability of a third review author to consult and help to achieve consensus when necessary.

The limitations of the systematic review process might include: incomplete information in the reports to enable us to evaluate risk of bias, and unsuccessful requests to study authors for clarifications of the data or study characteristics (e.g. total time of follow-up); the fact that we did not identify RCTs with protocols registered in public registers to enable us to evaluate reporting bias; the small sample size of included studies; the small number of trials included in meta-analysis, which might introduce publication biases, and prevented us from generating a funnel plot.

Agreements and disagreements with other studies or reviews

Most of the evidence regarding early EN is derived from reviews that compare early EN (as defined by the authors) with delayed nutrition intake (including delayed EN, oral diet, PN or standard care) in critically ill participants (Doig 2009; Doig 2011; Heyland 2003; Tian 2018). To answer the question of this Cochrane Review, we included only RCTs that compared early EN (within 48 hours of ICU admission or injury) versus delayed EN in critically ill adults.

Heyland 1998 performed one of the first systematic reviews on critically ill patients, which included one study, and found no preliminary evidence to support the use of early EN to improve clinical outcomes. Since that time, several reviews with meta-analyses have examined the available evidence. Marik 2001 (with 15 RCTs), compared early EN (within 36 hours of hospital admission or surgery) with delayed EN; the results of this review suggested that early feeding decreases infectious complications and length of hospital stay in critically ill patients (including postoperative abdominal surgery, trauma, head-injured, and burn patients). However, the results must be interpreted with caution, because the review authors reported significant heterogeneity between the included studies. Heyland 2003 (eight RCTs) failed to find any statistically significant benefits in clinical outcomes that were attributable to the provision of early EN versus delayed nutrition intake in mechanically ventilated critically ill adults. Doig 2009 (six RCTs) compared early EN (within 24 hours of ICU admission or injury) with all forms of standard care provided later than 24 hours. They found a statistically significant reduction in mortality and pneumonia that was attributable to early EN. In addition, they found a statistically significant reduction in mortality that was attributable to early EN in trauma patients (Doig 2011). Using the same methodology in their most recent publication, which included 16 RCTs, they concluded there was no clear difference between early enteral nutrition and all other forms of nutrition support, and no clear clinical advantages of early enteral nutrition over parenteral nutrition (Tian 2018).

The most recent clinical guidelines published on nutrition in critically ill patients, address the same question as our Cochrane Review but in an indirect way, since the authors focus their recommendations on the use of early EN compared with delayed 'nutrition intake'. For 'nutrition intake' they include different types of nutritional support (delayed EN, delayed oral diet, PN, fluid iv or standard care). The American Society for Parenteral and Enteral Nutrition recommends initiating EN within 24 to 48 hours following the onset of critical illness and admission to the ICU (very low-quality evidence; strong recommendation (ASPEN 2016)). The Working Group on Gastrointestinal Function of the Metabolism, Endocrinology and Nutrition (MEN) Section of the European Society of Intensive Care Medicine (ESICM) recommends the use of early EN in critically ill adult patients rather than delayed nutrition intake (low-quality evidence (ESICM 2017)). Both guidelines evaluated mortality and infectious complications. Although they included five of the seven RCTs we included in our review, we did not find any subgroup analyses of the interventions in the guidelines to adequately address the question of this Cochrane Review (Chourdakis 2012; Eyer 1993; Moses 2009; Nguyen 2008; Peck 2004). The Canadian Guidelines 2015 is the only guideline that evaluates the use of early EN (as defined by the author) versus delayed EN in a subgroup analysis, concluding that early EN did not have a clear effect on either mortality or infectious complications. The European Society of Parenteral and Enteral Nutrition recommends the use of early EN versus delayed EN, based on a reduction of infectious complications (low-quality evidence, including six studies in ICU patients, and four studies that included non-ICU

patients (ESPEN 2019)). However, this was only true when they include studies that also enrolled non-ICU patients. Therefore, they mention that excluding the studies published before 2000, the signal that early EN may reduce infectious complications compared to delaying EN beyond 48 hours is attenuated. There were no clear differences in other outcomes.

Koretz 2014 assessed the presence and effect of bias in trials of early EN in critical care and concluded that the benefits attributed to early EN were either seen only in trials with high risk of bias, or they might have resulted from residual risk of bias. Therefore, there is no reliable evidence to support the guideline recommendations for routine use of early EN in the ICU.

Similarly to Koretz 2014, we were not able to establish certainties about any potential clinical benefits resulting from the use of early EN for adult patients hospitalized in ICU.

AUTHORS' CONCLUSIONS

Implications for practice

Due to very low-quality evidence, we are uncertain whether early enteral nutrition, compared with delayed enteral nutrition, affects the risk of mortality within 30 days, feed intolerance or gastrointestinal complications, or pneumonia.

Due to very low-quality evidence, we are uncertain if early enteral nutrition with supplemental parenteral nutrition compared with delayed enteral nutrition with supplemental parenteral nutrition reduces mortality, infectious complications, or duration of mechanical ventilation.

Implications for research

Large high-quality RCTs, which report on the effects on clinical outcomes from the use of early enteral nutrition (EN, with or without supplemental parenteral nutrition (SPN)) in intensive care unit (ICU) patients, are needed. All protocols of these RCTs should be registered at inception, in a public trial registry, to facilitate early access to study information. A multicentre RCT, involving centres in different countries, would probably be very useful. RCTs should use high-quality methodology in randomization, allocation concealment, and blinding of outcome assessors. The published RCTs that were included in this Cochrane Review lacked important information. We suggest that researchers involved in future trials should seriously consider adopting the CONSORT criteria (at http://www.consort-statement.org). Trials should examine long-term and clinically important outcomes, including long-term mortality, re-admissions, and muscle rehabilitation.

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REFERENCES

References to studies included in this review

Chourdakis 2012 *{published data only}*

Chourdakis M, Kraus MM, Tzellos T, Sardeli C, Peftoulidou M, Vassilakos D, et al. Effect of early compared with delayed enteral nutrition on endocrine function in patients with traumatic brain injury: an open-labeled randomized trial. *JPEN. Journal of Parenteral and Enteral Nutrition* 2012;**36**(1):108-16. [PUBMED: 21965459]

Eyer 1993 *{published data only}*

Eyer SD, Micon LT, Konstantinides FN, Edlund DA, Rooney KA, Luxenberg MG, et al. Early enteral feeding does not attenuate metabolic response after blunt trauma. *Journal of Trauma* 1993;**34**(5):639-43. [PUBMED: 8496997]

Hill 2002 *{published data only}*

Hill DB, Kearney P, Magnuson B, Charash W, Annis K, Mcclain C. Effects of route and timing of nutrition support in critically ill patients. *Gastroenterology* 2002;**122**(Suppl 4):A38. [https://doi.org/10.1016/S0016-5085(02)83878-1]

Leiderman 2002 *{published data only}*

Leiderman IN, Albokrinov AA, Levit AL. Early vs late enteral nutritional support in severe head injury patients: does hypercatabollsm determine clinical outcome?. *Clinical Nutrition* 2002;**21**(Suppl 1):50-1. [https://doi.org/10.1016/S0261-5614(02)80006-1]

Moses 2009 *{published data only}*

Moses V, Mahendri NV, John G, Peter JV, Ganesh A. Early hypocaloric enteral nutritional supplementation in acute organophosphate poisoning – a prospective randomized trial. *Clinical Toxicology* 2009;**47**(5):419-24. [PUBMED: 19492933]

Nguyen 2008 *{published data only}*

Nguyen N, Fraser RJL, Bryant LK, Burgstad CM, Bellon M, Holloway RH. Delayed enteral feeding reduces small intestinal glucose absorption in critically ill patients. *Journal of Gastroenterology and Hepatology* 2009;**24**(Suppl 2):A326. [EMBASE: 70038110]

Nguyen NQ, Besanko LK, Burgstad C, Bellon M, Holloway RH, Chapman M, et al. Delayed enteral feeding impairs intestinal carbohydrate absorption in critically ill patients. *Critical Care Medicine* 2012;**40**(1):50-4. [PUBMED: 21926614]

Nguyen NQ, Fraser RJ, Bryant L, Burgstad CM, Bellon M, Holloway RH. Delayed enteral feeding reduces small intestinal nutrient absorption and impairs clinical outcomes in critically ill patients. *Gastroenterology* 2010;**138**(5 Suppl 1):S39. [EMBASE: 70395051]

* Nguyen NQ, Fraser RJ, Bryant LK, Burgstad C, Chapman MJ, Bellon M, et al. The impact of delaying enteral feeding on gastric emptying, plasma cholecystokinin, and peptide YY concentrations in critically ill patients. *Critical Care Medicine* 2008;**36**(5):1469-74. [PUBMED: 18434906]

Peck 2004 *{published data only}*

Peck MD, Kessler M, Cairns BA, Chang YH, Ivanova A, Schooler W. Early enteral nutrition does not decrease hypermetabolism associated with burn injury. *Journal of Trauma* 2004;**57**(6):1143-9. [PUBMED: 15625442]

References to studies excluded from this review

ACTRN12615000876594 *{unpublished data only}*

ACTRN12615000876594. Targeted full energy and protein delivery in critically ill patients: a pilot randomised control trial. apps.who.int/trialsearch/Trial2.aspx?TrialID=ACTRN12615000876594 (first received 21 August 2015).

Bakiner 2013 *{published data only}*

Bakiner O, Bozkirli E, Giray S, Arlier Z, Kozanoglu I, Sezgin N, et al. Impact of early versus late enteral nutrition on cell mediated immunity and its relationship with glucagon like peptide-1 in intensive care unit patients: a prospective study. *Critical Care / the Society of Critical Care Medicine* 2013;**17**(3):R123. [PUBMED: 23786864]

Ertorer ME, Bakiner OS, Bozkirli E, Giray S, Arlier Z, Kozanoglu I, et al. Impact of early enteral nutrition on cell mediated immunity versus late enteral nutrition and its relationship with glucagon like peptide-1 in intensive care unit patients. The Endocrine Society's 95th Annual Meeting and Expo; 2013 June 15–18; San Francisco (CA). 2013. [EMBASE: 71784311; Poster Board SAT-829]

Bakker 2014 *{published data only}*

Bakker OJ, van Brunschot S, van Santvoort HC, Besselink MG, Bollen TL, Boermeester MA, et al. Early versus on-demand nasoenteric tube feeding in acute pancreatitis. *New England Journal of Medicine* 2014;**371**(21):1983-93. [DOI: 10.1056/NEJMoa1404393; PUBMED: 25409371]

Beale 2008 *{published data only}*

Beale RJ, Sherry T, Lei K, Campbell-Stephen L, McCook J, Smith J, et al. Early enteral supplementation with key pharmaconutrients improves sequential organ failure assessment score in critically ill patients with sepsis: outcome of a randomized, controlled, double-blind trial. *Critical Care Medicine* 2008;**36**(1):131-44. [PUBMED: 18007263]

Koretz R. Comment on:
early enteral supplementation with key pharmaconutrients improves sequential organ failure assessment score in critically ill patients with sepsis: outcome of a randomized, controlled, double-blind trial. *Nutrition in Clinical Practice* 2008;**23**(9):447-9. [DOI: 10.1177/0884533608321134]

Braunschweig 2015 *{published data only}*

Braunschweig CA, Sheean PM, Peterson SJ, Gomez Perez S, Freels S, Lateef O, et al. Intensive nutrition in acute lung injury: a clinical trial (INTACT). *JPEN. Journal of Parenteral and Enteral Nutrition* 2015;**39**(1):13-20. [PUBMED: 24722769]

Cao 2014 *{published data only}*

Cao J, Zhang H, Sun L, Gao L. Effects of enteral plus parenteral nutrition on early nutrition parameters and immune function in neurocritical patients. *Brain Pathology* 2014;**24**(Suppl 1):S46-7. [EMBASE: 71838891]

Casaer 2011a *{published data only}*

Casaer MP, Hermans G, Wilmer A, Van den Berghe G. Impact of early parenteral nutrition completing enteral nutrition in adult critically ill patients (EPaNIC trial): a study protocol and statistical analysis plan for a randomized controlled trial. *Trials* 2011;**12**:21. [PUBMED: 21261975]

Casaer 2011b *{published data only}*

Casaer MP, Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt G, et al. Early versus late parenteral nutrition in critically ill adults. *New England Journal of Medicine* 2011;**365**(6):506-17. [PUBMED: 21714640]

Casaer MP, Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt G, et al. Impact of early parenteral nutrition to complete failing enteral nutrition in adult critically Ill patients: a randomized controlled trial. 93rd Annual Meeting and Expo of the Endocrine Society, ENDO; 2011 Jun 4-7; Boston. 2011. [DOI: 10.1210/endo-meetings.2011.PART2.P20.P1-778; EMBASE: 70676648; P1-778]

Kerrie JP, Bagshaw SM, Brindley PG. Early versus late parenteral nutrition in the adult ICU: feeding the patient or our conscience?. *Canadian Journal of Anaesthesia* 2012;**59**(5):494-8. [PUBMED: 22302305]

Casaer 2013 *{published data only}*

Casaer MP, Langouche L, Coudyzer W, Vanbeckevoort D, De Dobbelaer B, Güiza FG, et al. Impact of early parenteral nutrition on muscle and adipose tissue compartments during critical illness. *Critical Care Medicine* 2013;**41**(10):2298-309. [PUBMED: 23860247]

Chatterjee 2012 *{published data only}*

Chatterjee S, Bala SK, Chakraborty P, Dey R, Sinha S, Ray R, et al. A comparative study between early enteral feeding (within 24 hours) versus conventional enteral feeding after enteric anastomosis. *Bangladesh Journal of Medical Science* 2012;**11**(4):273-83. [EMBASE: 366171414; http://dx.doi.org/10.3329/bjms.v11i4.12597]

ChiCTR-INR-17010741 *{unpublished data only}*

ChiCTR-INR-17010741. Study on the effect of Chengqi Tang combined with early enteral nutrition on intestinal resuscitation in ill patients. apps.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR-INR-17010741 (first received 27 February 2017).

Chuntrasakul 1996 *{published data only}*

Chuntrasakul C, Siltharm S, Chinswangwatanakul V, Pongprasobchai T, Chockvivatanavanit S, Bunnak A. Early nutritional support in severe traumatic patients. *Journal of the Medical Association of Thailand* 1996;**79**(1):21-6. [PUBMED: 8867397]

Couto 2014 *{published data only}*

Couto C, Beck M, Friedman G. A randomized controlled trial comparing early jejunal with gastric nutrition in critical illness. *Intensive Care Medicine* 2014;**40**(Suppl 1):S17. [DOI: 10.1007/s00134-013-3451-5; EMBASE: 71629901]

Davies 2012 *{published data only}*

Davies AR, Morrison SS, Bailey MJ, Bellomo R, Cooper DJ, Doig GS, et al. A multicenter, randomized controlled trial comparing early nasojejunal with nasogastric nutrition in critical illness. *Critical Care Medicine* 2012;**40**(8):2342-8. [PUBMED: 22809907]

De Castro 2012 *{published data only}*

De Castro LG, Pontes-Arruda A, Neto HMC, Do Ceara VDA, Furtado-Lima B, De Lima SM, et al. Enteral feeding with EPA/GLA in malnourished patients with early sepsis without organ dysfunctions: a prospective, randomized and double-blinded study. *Critical Care Medicine* 2012;**40**(12 (Suppl1)):262-3. [DOI: 10.1097/01.ccm.0000425251.51120.0d; EMBASE: 71066175]

Dennis 2005 *{published data only}*

Dennis MS, Lewis SC, Warlow C, Food Trial Collaboration. Effect of timing and method of enteral tube feeding for dysphagic stroke patients (FOOD): a multicentre randomised controlled trial. *Lancet* 2005;**365**(9461):764-72. [PUBMED: 15733717]

Desachy 2008 *{published data only}*

Desachy A, Clavel M, Vuagnat A, Normand S, Gissot V, François B. Initial efficacy and tolerability of early enteral nutrition with immediate or gradual introduction in intubated patients. *Intensive Care Medicine* 2008;**34**(6):1054-9. [PUBMED: 18210092]

Dou 2011 *{published data only}*

Dou C, Ju H, Liu H, Wang H. The research of early enteral nutritional support in head injury. *Journal of Neurotrauma* 2011;**28**(5):A17. [DOI: 10.1089/neu.2011.9946; EMBASE: 70420056]

Dvorak 2004 *{published data only}*

Dvorak MF, Noonan VK, Belanger L, Bruun B, Wing PC, Boyd MC, et al. Early versus late enteral feeding in patients with acute cervical spinal cord injury: a pilot study. *Spine* 2004;**29**(9):E175–80. [PUBMED: 15105682]

Engel 1997 *{published data only}*

Engel JM, Menges T, Neuhäuser C, Schaefer B, Hempelmann G. Effects of various feeding regimens in multiple trauma patients on septic complications and immune parameters [Auswirkungen verschiedener Ernährungsregime bei polytraumatisierten Patienten auf septische Komplikationen und Immunparameter]. *Anasthesiol Intensivmed Notfallmed Schmerzther* 1997;**32**(4):234-9. [PUBMED: 9289023]

Grahm 1989 *{published data only}*

Grahm TW, Zadrozny DB, Harrington T. The benefits of early jejunal hyperalimentation in the head-injured patient. *Neurosurgery* 1989;**25**(5):729-35. [PUBMED: 2511499]

Grau-Carmona 2011 *{published data only}*

Grau-Carmona T, Morán-García V, García-de-Lorenzo A, Heras-de-la-Calle G, Quesada-Bellver B, López-Martínez J, et al. Effect of an enteral diet enriched with eicosapentaenoic acid, gamma-linolenic acid and anti-oxidants on the outcome of mechanically ventilated, critically ill, septic patients. *Clinical Nutrition (Edinburgh, Scotland)* 2011;**30**(5):578-84. [PUBMED: 21474219]

Hasse 1995 *{published data only}*

Hasse JM, Blue LS, Liepa GU, Goldstein RM, Jennings LW, Mor E, et al. Early enteral nutrition support in patients undergoing liver transplantation. *JPEN. Journal of Parenteral and Enteral Nutrition* 1995;**19**(6):437-43. [PUBMED: 8748357]

Heslin 1997 *{published data only}*

Heslin MJ, Latkany L, Leung D, Brooks AD, Hochwald SN, Pisters PW, et al. A prospective, randomized trial of early enteral feeding after resection of upper gastrointestinal malignancy. *Annals of Surgery* 1997;**226**(4):567-77. [PUBMED: 9351723]

Ibrahim 2002 *{published data only}*

Ibrahim EH, Mehringer L, Prentice D, Sherman G, Schaiff R, Fraser V, et al. Early versus late enteral feeding of mechanically ventilated patients: results of a clinical trial. *JPEN. Journal of Parenteral and Enteral Nutrition* 2002;**26**(3):174-81. [PUBMED: 12005458]

ISRCTN12233792 *{unpublished data only}*

ISRCTN12233792. To improve clinical outcomes of critically ill patients with enteral feeding protocol [Effectiveness of enteral feeding protocol on critically ill patients: a clustered randomized controlled trial]. isrctn.com/ISRCTN12233792 (first received 24 November 2017).

ISRCTN63461816 *{unpublished data only}*

ISRCTN63461816. The effect of early enteral feeding in patients suffering severe head injury and requiring mechanical ventilation. apps.who.int/trialsearch/Trial2.aspx?TrialID=ISRCTN63461816 (first received 23 January 2004).

Jana 2014 *{published data only}*

Jana M, Bose PP. Effect of early nasojejunal feeding in severe acute pancreatitis. *Indian Journal of Gastroenterology* 2014;**33**(Suppl1):A92. [DOI: 10.1007/s12664-014-0518-3; EMBASE: 71905694]

Jazayeri 2016 *{published and unpublished data}*

Jazayeri S, Ostadrahimi A, Safaiyan A, Hashemzadeh S, Salehpour F. Effects of four different enteral feeding methods on tumor necrosis factor-α (TNF-α) and high sensitive C-reactive protein (hs-CRP) in critically Ill patients: double blinded, randomized controlled trial. *Progress in Nutrition* 2016;**18**(3):236-41.

Jazayeri 2018 *{published data only}*

Jazayeri S, Ostadrahimi A, Hashemzadeh S, Safaiyan A, Salehpour F, Barati, et al. Proportions of prognostic scoring models among ICU patients receiving enteral nutrition. *Progress in Nutrition* 2018;**20**(4):635-41. [DOI: 10.23751/pn.v20i4.6580]

JPRN-UMIN000003569 *{unpublished data only}*

JPRN-UMIN000003569. The effects of Rikkunshito for the early enteral feeding in the critically ill patients. apps.who.int/trialsearch/Trial2.aspx?TrialID=JPRN-UMIN000003569 (first received 1 April 2010).

JPRN-UMIN000009552 *{unpublished data only}*

JPRN-UMIN000009552. The tolerability study of oligomeric formula for early enteral nutrition in critically ill patients. apps.who.int/trialsearch/Trial2.aspx?TrialID=JPRN-UMIN000009552 (first received 15 December 2012).

Kemen 1995 *{published data only}*

Kemen M, Senkal M, Homann HH, Mumme A, Dauphin AK, Baier J, et al. Early postoperative enteral nutrition with arginine-omega-3 fatty acids and ribonucleic acid-supplemented diet versus placebo in cancer patients: an immunologic evaluation of Impact. *Critical Care Medicine* 1995;**23**(4):652-9. [PUBMED: 7536138]

Kompan 1999 *{published data only}*

Kompan L, Kremzar B, Gadzijev E, Prosek M. Effects of early enteral nutrition on intestinal permeability and the development of multiple organ failure after multiple injury. *Intensive Care Medicine* 1999;**25**(2):157-61. [PUBMED: 10193541]

Kompan 2004 *{published data only}*

Kompan L, Vidmar G, Spindler-Vesel A, Pecar J. Is early enteral nutrition a risk factor for gastric intolerance and pneumonia?. *Clinical Nutrition (Edinburgh, Scotland)* 2004;**23**(4):527-32. [PUBMED: 15297088]

Liu 2018 *{published data only}*

Liu Y, Zhao W, Chen W, Shen X, Fu R, Zhao Y, et al. Effects of early enteral nutrition on immune function and prognosis of patients with sepsis on mechanical ventilation. Journal of Intensive Care Medicine 2018 Nov 1 [Epub ahead of print]. [DOI: 10.1177/0885066618809893]

Maude 2011 *{published data only}*

Maude R, Hoque MG, Hasan MMU, Abu Sayeed M, Akter S, Samad R, et al. Timing of enteral feeding in cerebral malaria in resource-poor settings: a randomized trial category: scientific free paper. *Journal of Infection* 2011;**63**(6):e101. [http://dx.doi.org/10.1016/j.jinf.2011.04.171]

Maude RJ, Hoque G, Hasan MU, Sayeed A, Akter S, Samad R, et al. Timing of enteral feeding in cerebral malaria in resource-poor settings: a randomized trial. *PLoS One* 2011;**6**(11):e27273. [PUBMED: 22110624]

Minard 2000 *{published data only}*

Minard G, Kudsk KA, Melton S, Patton JH, Tolley EA. Early versus delayed feeding with an immune-enhancing diet in patients with severe head injuries. *JPEN. Journal of Parenteral and Enteral Nutrition* 2000;**24**(3):145-9. [PUBMED: 10850938]

NCT00883948 *{published and unpublished data}*

NCT00883948. Early versus delayed enteral feeding to treat people with acute lung injury or acute respiratory distress syndrome (The EDEN Study) EDEN [Prospective, randomized,

multi-center trial of initial trophic enteral feeding followed by advancement to full-calorie enteral feeding vs. early advancement to full-calorie enteral feeding in patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS)]. clinicaltrials.gov/show/NCT00883948 (first received 17 April 2009).

NCT01432769 *{unpublished data only}*

NCT01432769. Enteral nutrition after cardiovascular surgery [Effect of enteral nutrition in the outcome of patients with cardiovascular surgery]. clinicaltrials.gov/show/NCT01432769 (first received 7 September 2011).

NCT02837861 *{unpublished data only}*

NCT02837861. Early and adequate protein feeding post-traumatic injury EMS [Early metabolomic support study]. clinicaltrials.gov/show/NCT02837861 (first received 7 March 2017).

Ohbe 2019 *{published data only}*

Ohbe H, Jo T, Matsui H, Fushimi K, Yasunaga H. Differences in effect of early enteral nutrition on mortality among ventilated adults with shock requiring low-, medium-, and high-dose noradrenaline: A propensity-matched analysis. Clinical Nutrition (Edinburgh, Scotland) 2019 Feb 15 [Epub ahead of print]. [DOI: 10.1016/j.clnu.2019.02.020]

Ostadrahimi 2016 *{published data only}*

Ostadrahimi A, Nagili B, Asghari-Jafarabadi M, Beigzali S, Zalouli H, Lak S. A proper enteral nutrition support improves sequential organ failure score and decreases length of stay in hospital in burned patients. *Iranian Red Crescent Medical Journal* 2016;**18**(2):e21775. [PUBMED: 27186387]

Perez-Guisado 2013 *{published data only}*

Pérez-Guisado J, de Haro-Padilla JM, Rioja LF, Derosier LC, de la Torre JI. The potential association of later initiation of oral/enteral nutrition on euthyroid sick syndrome in burn patients. *International Journal of Endocrinology* 2013;**2013**:707360. [DOI: 10.1155/2013/707360]

Petrova 2017 *{published data only}*

Petrova MV, Butrov AV, Vatsik MV, Nakade MFI, Mohan R, Storchai MN. The role of early enteral nutrition in the prevention of postoperative intestinal failure. *Intensive Care Medicine Experimental* 2017;**5**(Suppl 2):0814. [DOI: 10.1186/s40635-017-0151-4]

Pilika 2015 *{published data only}*

Pilika K, Roshi E. Insulin resistance in early vs late nutrition and complications of sirs in neurosurgical intensive care unit (ICU). *Medical Archives* 2015;**69**(1):46-8. [PUBMED: 25870478]

Pupelis 2001 *{published data only}*

Pupelis G, Selga G, Austrums E, Kaminski A. Jejunal feeding, even when instituted late, improves outcomes in patients with severe pancreatitis and peritonitis. *Nutrition* 2001;**17**(2):91-4. [PUBMED: 11240334]

Singh 1998 *{published data only}*

Singh G, Ram RP, Khanna SK. Early postoperative enteral feeding in patients with nontraumatic intestinal perforation and peritonitis. *Journal of the American College of Surgeons* 1998;**187**(2):142-6. [PUBMED: 9704959]

Su 2018 *{published data only}*

Su S, Sun R, Liu R, Xu Z. Effect of enteral nutrition time on pH value of gastric juice and ventilator-associated pneumonia in critically ill patient. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue [Chinese Critical Care Medicine]* 2018;**30**(8):768-70. [DOI: 10.3760/cma.j.issn.2095-4352.2018.08.011]

Sun 2013 *{published data only}*

Sun JK, Mu XW, Li WQ, Tong ZH, Li J, Zheng SY. Effects of early enteral nutrition on immune function of severe acute pancreatitis patients. *World Journal of Gastroenterology* 2013;**19**(6):917-22. [PUBMED: 23431120]

Vicic 2013 *{published data only}*

Vicic VK, Radman M, Kovacic V. Early initiation of enteral nutrition improves outcomes in burn disease. *Asia Pacific Journal of Clinical Nutrition* 2013;**22**(4):543-7. [PUBMED: 24231014]

Wang 1997 *{published data only}*

Wang S, Wang S, Li A. A clinical study of early enteral feeding to protect the gut function in burned patients. *Chinese Journal of Plastic Surgery and Burns* 1997;**13**(4):267-71. [PUBMED: 10452011]

Wang 2007 *{published data only}*

Wang Y-Z, Ding Y-B, Wu J, Deng B, Xiao W-M. Treatment of 64 cases of severe acute pancreatitis with early enteral nutrition and intestinal barrier protective agents. *World Chinese Journal of Digestology* 2007;**15**(33):3545-48. [EMBASE: 351155326]

Wang 2015 *{published data only}*

Wang G, Chen H, Liu J, Ma Y, Jia H. A comparison of postoperative early enteral nutrition with delayed enteral nutrition in patients with esophageal cancer. *Nutrients* 2015;**7**(6):4308-17. [DOI: 10.3390/nu7064308; PUBMED: 26043031]

Weijs 2018 *{published data only}*

Weijs PJM. Route, early or energy? ... Protein improves protein balance in critically ill patients. *Critical Care* 2018;**22**(1):91. [DOI: 10.1186/s13054-018-2015-z]

Wereszczynska-Siemiatkowska 2013 *{published data only}*

Wereszczynska-Siemiatkowska U, Swidnicka-Siergiejko A, Siemiatkowski A, Dabrowski A. Early enteral nutrition is superior to delayed enteral nutrition for the prevention of infected necrosis and mortality in acute pancreatitis. *Pancreas* 2013;**42**(4):640-6. [PUBMED: 23508012]

Woo 2010 *{published data only}*

Woo SH, Finch CK, Broyles JE, Wan J, Boswell R, Hurdle A. Early vs delayed enteral nutrition in critically ill medical patients. *Nutrition in Clinical Practice* 2010;**25**(2):205-11. [PUBMED: 20413702]

Yan 2019 *{published data only}*

Yan XX, Zhang X, Ai H, Wang D, Song KY. Changes of intestinal mucosal barrier function and effects of early enteral nutrition in patients with severe organophosphorus poisoning. *Zhonghua Yi Xue Za Zhi* 2019;**99**(6):442-46. [DOI: 10.3760/cma.j.issn.0376-2491.2019.06.012]

Yi 2015 *{published data only}*

Yi H, Fu B, An Y, Yi X, Lv H, Chen G. Early enteral nutrition support in patients undergoing liver transplantation decreased the incidence of postoperative infection. *Transplantation* 2015;**99**(Suppl 1):263-4. [EMBASE: 72118695; P-429]

Yuan 2019 *{published data only}*

Yuan F, Yang F, Zhang W, Jia Y, Ma Y, Qu Y, et al. Optimizing early enteral nutrition in severe stroke (OPENS): protocol for a multicentre randomized controlled trial. *BMC Neurology* 2019;**19**(1):24. [DOI: 10.1186/s12883-019-1253-2]

Zhang 2018 *{published data only}*

Zhang P, Xie K, Huang X, Li RC, Song Y, Li B, et al. Early nutrition support therapy to improve the nutrition status of head and neck cancer patients accepted concurrent chemoradiotherapy (NSTIP): interim analysis from a prospective randomized controlled clinical study. *Journal of Clinical Oncology* 2018;**102**(3):e744–45. [DOI: 10.1016/j.ijrobp.2018.07.1988]

Zhong 2014 *{published data only}*

Zhong GY, Li YH, Ma LP, Huang CP. Early enteral nutrition and nursing care for prevention of complications of severe cerebrovascular diseases. *World Chinese Journal of Digestology* 2014;**22**(11):1612-5. [DOI: 10.11569/wcjd.v22.i11.1612; EMBASE: 372885628]

Zou 2014 *{published data only}*

Zou J, Liu Y, Shan Y, Li D, Shuai W, Zhu Y, et al. Effect of early enteral nutrition on mechanically ventilated patients. *Chinese Journal of Clinical Nutrition* 2014;**22**(1):34-7. [DOI: 10.3760/cma.j.issn.1674-635X.2014.01.007; EMBASE: 372839575]

References to ongoing studies

ChiCTR-INR-17012709 *{unpublished data only}*

ChiCTR-INR-17012709. The effect of early enteral nutrition intervention on patients with severe infections after cardiac surgery to intestinal microflora and metabolize. apps.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR-INR-17012709 (first received 18 Sept 2017).

ChiCTR-IOR-17011914 *{unpublished data only}*

ChiCTR-IOR-17011914. A protocol for early enteral nutrition in mechanical ventilated patients. apps.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR-IOR-17011914 (first received 9 July 2017).

Additional references

Academy of Nutrition and Dietetics 2012

Academy of Nutrition, Dietetics Evidence Analysis Library. Evidence-based nutrition practice guideline on critical illness, updated 2012. www.andeal.org (accessed 5 November 2015).

Alberda 2009

Alberda C, Gramlich L, Jones N, Jeejeebhoy K, Day AG, Dhaliwal R, et al. The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study. *Intensive Care Medicine* 2009;**35**(10):1728-37. [PUBMED: 19572118]

ANZICS 2018

TARGET Investigators, for the ANZICS Clinical Trials Group. Energy-dense versus routine enteral nutrition in the critically ill. *New England Journal of Medicine* 2018;**379**(19):1823-34. [DOI: 10.1056/NEJMoa1811687; PUBMED: 30346225]

Artinian 2006

Artinian V, Krayem H, DiGiovine B. Effects of early enteral feeding on the outcome of critically ill mechanically ventilated medical patients. *Chest* 2006;**129**(4):960-7. [PUBMED: 16608945]

ASPEN 2015

American Society for Parenteral and Enteral Nutrition (ASPEN). American Society for Parenteral and Enteral Nutrition (ASPEN) definition of terms, style, and conventions used in ASPEN board of directors–approved documents. www.nutritioncare.org/Guidelines_and_Clinical_Resources/Clinical_Practice_Library/Special_Reports/ (accessed prior to 20 November 2018).

ASPEN 2016

McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, 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 (ASPEN). *JPEN. Journal of Parenteral and Enteral Nutrition* 2016;**40**(2):159-211. [PUBMED: 26773077]

Barr 2004

Barr J, Hecht M, Flavin KE, Khorana A, Gould MK. Outcomes in critically ill patients before and after the implementation of an evidence-based nutritional management protocol. *Chest* 2004;**125**(4):1446-57. [PUBMED: 15078758]

Bost 2014

Bost RB, Tjan DH, van Zanten AR. Timing of (supplemental) parenteral nutrition in critically ill patients: a systematic review. *Annals of Intensive Care* 2014;**4**(31):1-13. [DOI: 10.1186/s13613-014-0031-y; PUBMED: 25593747]

Bouharras 2015

Bouharras H, Molina J, Pérez I, Florea DI, Lobo G, Herrera-Quintana L, et al. Imbalances in protein metabolism in critical care patient with systemic inflammatory response syndrome at admission in intensive care unit. *Nutrición Hospitalaria* 2015;**32**(6):2848-54. [PUBMED: 26667743]

Bradburn 2007

Bradburn MJ, Deeks JJ, Berlin JA, Russell Localio A. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. *Statistics in Medicine* 2007;**26**(1):53-77. [PUBMED: 16596572]

Canadian Guidelines 2015

Critical Care Nutrition. Canadian Clinical Practice Guidelines, updated 29 May 2015. www.criticalcarenutrition.com (accessed 2 November 2015).

Casaer 2011

Casaer MP, Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt G, et al. Early versus late parenteral nutrition in critically ill adults. *New England Journal of Medicine* 2011;**365**(6):506-17. [PUBMED: 21714640]

DerSimonian 1986

DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**:177-88.

Doig 2009

Doig GS, Heighes PT, Simpson F, Sweetman EA, Davies AR. Early enteral nutrition, provided within 24 h of injury or intensive care unit admission, significantly reduces mortality in critically ill patients: a meta-analysis of randomised controlled trials. *Intensive Care Medicine* 2009;**35**(12):2018-27. [PUBMED: 19777207]

Doig 2011

Doig GS, Heighes PT, Simpson F, Sweetman EA. Early enteral nutrition reduces mortality in trauma patients requiring intensive care: a meta-analysis of randomised controlled trials. *Injury* 2011;**42**(1):50-6. [PUBMED: 20619408]

EDEN 2012

National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. *JAMA* 2012;**307**(8):795-803. [PUBMED: 22307571]

Egger 1997

Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. *BMJ* 1997;**315**(7121):1533-7. [PUBMED: 9432252]

ESICM 2017

Reintam Blaser A, Starkopf J, Alhazzani W, Berger MM, Casaer MP, Deane AM, et al. Early enteral nutrition in critically ill patients: ESICM clinical practice guidelines. *Intensive Care Medicine* 2017;**43**(3):380-98. [PUBMED: 28168570]

ESPEN 2009

Singer P, Berger MM, Van den Bergue G, Biolo G, Calder P, Forbes A, et al. ESPEN guidelines on parenteral nutrition: intensive care. *Clinical Nutrition (Edinburgh, Scotland)* 2009;**28**(4):387-400. [PUBMED: 19505748]

ESPEN 2019

Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. *Clinical Nutrition (Edinburgh, Scotland)* 2019;**38**(1):48-79. [DOI: 10.1016/j.clnu.2018.08.037; PUBMED: 30348463]

Fahy 2009

Fahy BG, Sheehy AM, Coursin DB. Glucose control in the intensive care unit. *Critical Care Medicine* 2009;**37**(5):1769-76. [PUBMED: 19325461]

Faisy 2009

Faisy C, Lerolle N, Dachraoui F, Savard JF, Abboud I, Tadie JM, et al. Impact of energy deficit calculated by a predictive method on outcome in medical patients requiring prolonged acute mechanical ventilation. *British Journal of Nutrition* 2009;**101**(7):1079-87. [PUBMED: 18778528]

Fukatsu 2011

Fukatsu K, Kudsk KA. Nutrition and gut immunity. *Surgical Clinics of North America* 2011;**91**(4):755-70. [PUBMED: 21787966]

GRADEpro GDT [Computer program]

McMaster University (developed by Evidence Prime). GRADEpro GDT. Version accessed 6 August 2017. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015.

Guyatt 2008

Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ, GRADE Working Group. What is "quality of evidence" and why is it important to clinicians. *BMJ* 2008;**336**(7651):995-8. [PUBMED: 18456631]

Heyland 1998

Heyland D. Nutritional support in the critically ill patients. A critical review of the evidence. *Critical Care Clinics* 1998;**14**(3):423-40. [PUBMED: 9700440]

Heyland 2003

Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P, Canadian Critical Care Clinical Practice Guidelines Committee. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. *JPEN. Journal of Parenteral and Enteral Nutrition* 2003;**27**(5):355-73. [PUBMED: 12971736]

Heyland 2004

Heyland DK, Dhaliwal R, Day A, Jain M, Drover J. Validation of the Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients: results of a prospective observational study. *Critical Care Medicine* 2004;**32**(11):2260-6. [PUBMED: 15640639]

Heyland 2010

Heyland DK, Cahill NE, Dhaliwal R, Sun X, Day AG, McClave SA. Impact of enteral feeding protocols on enteral nutrition delivery: results of a multicenter observational study. *JPEN. Journal of Parenteral and Enteral Nutrition* 2010;**34**(6):675-84. [PUBMED: 21097768]

Heyland 2011

Heyland DK, Cahill N, Day AG. Optimal amount of calories for critically ill patients: depends on how you slice the cake!. *Critical Care Medicine* 2011;**39**(12):2619-26. [PUBMED: 21705881]

Heyland 2015

Heyland DK, Dhaliwal R, Wang M, Day AG. The prevalence of iatrogenic underfeeding in the nutritionally 'at-risk' critically ill patient: results of an international, multicenter, prospective study. *Clinical Nutrition (Edinburgh, Scotland)* 2015;**34**(4):659-66. [PUBMED: 25086472]

Higgins 2011

Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Huang 2012

Huang HH, Hsu CW, Kang SP, Liu MY, Chang SJ. Association between illness severity and timing of initial enteral feeding in critically ill patients: a retrospective observational study. *Nutrition Journal* 2012;**11**:30. [PUBMED: 22554240]

Jabbar 2003

Jabbar A, Chang WK, Dryden GW, McClave SA. Gut immunology and the differential response to feeding and starvation. *Nutrition in Clinical Practice* 2003;**18**(6):461-82. [PUBMED: 16215082]

Jensen 2010

Jensen GL, Mirtallo J, Campher C, Dhaliwal R, Forbes A, Grijalba RF, et al. International Consensus Guideline Committee. Adult starvation and disease-related malnutrition: a proposal for etiology-based diagnosis in the clinical practice setting from the International Consensus Guideline Committee. *JPEN. Journal of Parenteral and Enteral Nutrition* 2010;**34**(2):156-9. [PUBMED: 20375423]

Khalid 2010

Khalid I, Doshi P, DiGiovine B. Early enteral nutrition and outcomes of critically ill patients treated with vasopressors and mechanical ventilation. *American Journal of Critical Care* 2010;**19**(3):261-8. [PUBMED: 20436064]

Koretz 2014

Koretz RL, Lipman TO. The presence and effect of bias in trials of early enteral nutrition in critical care. *Clinical Nutrition (Edinburgh, Scotland)* 2014;**33**(2):240-5. [PUBMED: 23845382]

Kudsk 2001

Kudsk K. Importance of enteral feeding in maintaining gut integrity. *Techniques in Gastrointestinal Endoscopy* 2001;**3**(1):2-8. [DOI: 10.1053/tgie.2001.19906]

Kudsk 2002

Kudsk K. Current aspects of mucosal immunology and its influence by nutrition. *American Journal of Surgery* 2002;**183**(4):390-8. [DOI: 10.1016/S0002-9610(02)00821-8; PUBMED: 11975926]

Kudsk 2007

Kudsk KA. Beneficial effect of enteral feeding. *Gastrointestinal Endoscopy Clinics of North America* 2007;**17**(4):647-62. [PUBMED: 17967372]

Lewis 2018

Lewis SR, Schofield-Robinson OJ, Alderson P, Smith AF. Enteral versus parenteral nutrition and enteral versus a combination of enteral and parenteral nutrition for adults in the intensive care unit. *Cochrane Database of Systematic Reviews* 2018, Issue 6. [DOI: 10.1002/14651858.CD012276.pub2]

Lochs 2006

Lochs H, Allison SP, Meier R, Pirlich M, Kondrup J, Schneider S, et al. Introductory to the ESPEN guidelines on enteral nutrition: terminology, definitions and general topics. *Clinical Nutrition (Edinburgh, Scotland)* 2006;**25**(2):180-6. [PUBMED: 16697086]

Marik 2001

Marik PE, Zaloga GP. Early enteral nutrition in acutely ill patients: a systematic review. *Critical Care Medicine* 2001;**29**(12):2264-70. [PUBMED: 11801821]

Martin 2004

Martin CM, Doig GS, Heyland DK, Morrison T, Sibbald WJ. Multicentre, cluster-randomized clinical trial of algorithms for critical-care enteral and parenteral therapy (ACCEPT). *Canadian Medical Association Journal* 2004;**170**(2):197-204. [PUBMED: 14734433]

Mault 2000

Mault J. Energy balance and outcome in critically ill patients: results of a multi-center, prospective, randomized trial by the ICU Nutrition Study Group. *JPEN. Journal of Parenteral and Enteral Nutrition* 2000;**24**(1):S4. [DOI: 10.1177/0148607100024001111]

McClave 2009

McClave SA, Heyland DK. The physiologic response and associated clinical benefits from provision of early enteral nutrition. *Nutrition in Clinical Practice* 2009;**24**(3):305-15. [PUBMED: 19483060]

McClave 2014

McClave SA, Martindale RG, Rice TW, Heyland DK. Feeding the critically ill patient. *Critical Care Medicine* 2014;**42**(12):2600-10. [PUBMED: 25251763]

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;**339**:2535. [PUBMED: 19622551]

Preiser 2015

Preiser JC, van Zanten AR, Berger MM, Biolo G, Casaer MP, Doig GS, et al. Metabolic and nutritional support of critically ill patients: consensus and controversies. *Critical Care (London, England)* 2015;**19**(35):1-11. [DOI: 10.1186/s13054-015-0737-8; PUBMED: 25886997]

Review Manager 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rice 2012

Rice TW, Wheeler AP, Thompson BT, Steingrub J, Hite RD, Moss M, et al. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. *JAMA* 2012;**307**(8):795-803. [PUBMED: 22307571]

Rubinson 2004

Rubinson L, Diette GB, Song X, Brower RG, Krishnan JA. Low caloric intake is associated with nosocomial bloodstream infections in patients in the medical intensive care unit. *Critical Care Medicine* 2004;**32**(2):350-7. [PUBMED: 14758147]

SENPE 2011

Fernández-Ortega JF, Herrero Meseguer JI, Martínez García P. Guidelines for specialized nutritional and metabolic support in the critically-ill patient: update. Consensus SEMICYUC-SENPE: indications, timing and routes of nutrient delivery [Recomendaciones para el soporte nutricional y metabólico especializado del paciente crítico. Actualización. Consenso SEMICYUC-SENPE: Indicaciones, momento de inicio y vías de aporte]. *Nutrición Hospitalaria* 2011;**26**(S2):7-11. [PUBMED: 22411511]

Singh 2009

Singh N, Gupta D, Aggarwal AN, Agarwal R, Jindal SK. An assessment of nutritional support to critically ill patients and its correlation with outcomes in a respiratory intensive care unit. *Respiratory Care* 2009;**54**(12):1688-96. [PUBMED: 19961635]

Soguel 2012

Soguel L, Revelly JP, Schaller MD, Longchamp C, Berger MM. Energy deficit and length of hospital stay can be reduced by a two-step quality improvement of nutrition therapy: the intensive care unit dietitian can make the difference. *Critical Care Medicine* 2012;**40**(2):412-9. [PUBMED: 21926572]

Sutton 2000

Sutton AJ, Duval SJ, Tweedie RL, Abrams KR, Jones DR. Empirical assessment of effect of publications bias on meta-analyses. *BMJ* 2000;**320**:1574-7. [PUBMED: 10845965]

Taylor 1999

Taylor SJ, Fettes SB, Jewkes C, Nelson RJ. Prospective, randomized, controlled trial to determine the effect of early enhanced enteral nutrition on clinical outcome in mechanically ventilated patients suffering head injury. *Critical Care Medicine* 1999;**27**:2525-31. [PUBMED: 10579275]

Tian 2018

Tian F, Heighes PT, Allingstrup MJ, Doig GS. Early enteral nutrition provided within 24 hours of ICU admission: a meta-analysis of randomized controlled trials. Critical Care Medicine 2018 Apr 6 [Epub ahead of print]. [DOI: 10.1097/CCM.0000000000003152]

Villet 2005

Villet S, Chiolero RL, Bollmann MD, Revelly JP, Cayeux RNM, Delarue J, et al. Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients. *Clinical Nutrition (Edinburgh, Scotland)* 2005;**24**(4):502-9. [PUBMED: 15899538]

Wei 2015

Wei X, Day AG, Ouellette-Kuntz H, Heyland DK. The association between nutritional adequacy and long-term outcomes in critically ill patients requiring prolonged mechanical ventilation: a multicenter cohort study. *Critical Care Medicine* 2015;**43**(8):1569-79. [PUBMED: 25855901]

References to other published versions of this review

Fuentes Padilla 2016

Fuentes Padilla P, Martínez G, Vernooij RWM, Urrútia G, Roqué i Figuls M, Bonfill Cosp X. Early versus delayed enteral nutrition support for critically ill adults. *Cochrane Database of Systematic Reviews* 2016, Issue 9. [DOI: 10.1002/14651858.CD012340]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Chourdakis 2012

Methods	**Study design:** randomized controlled trial
	Unit of allocation: by individuals
	Start date recruitment: August 2003
	End date recruitment: May 2005
	Duration of participation: not reported

Chourdakis 2012 *(Continued)*

Participants	**Participants:** all patients were admitted to the ICU of AHEPA University Hospital in Greece, with traumatic brain injury (TBI). **Inclusion criteria** 1. Age > 18 < 70 years 2. TBI patients admitted to the ICU **Exclusion criteria** 1. Age < 18 or ≥ 70 years 2. GCS score ≥ 9 3. Obesity (> 30 BMI) 4. Pregnancy 5. Lactation 6. Received corticosteroids or thyroidal hormones, or both, during the previous months 7. Any of the following conditions: heart failure, respiratory problems, metabolic syndrome, immunodeficiency, diabetes, neurological problems, internal bleeding, indication for total parenteral nutrition (TPN) 8. Delay of admission to ICU > 24 hours from injury **Population description:** TBI ICU patients **Setting:** ICU teaching hospital in Greece **Total number** randomized**:** 34 patients to the early enteral nutrition group and 25 in the delayed enteral nutrition group **Baseline imbalances:** no significant differences were found between study groups **Age:** early EN group: 36.13 (SD: 14.72); delayed EN group: 33.3 (SD: 12.96) **Sex (male):** early EN group: 26 of 34; delayed EN group: 21 of 25 **Disease status, type**: traumatic brain injury **Score severity of illness at ICU admission, APACHE II:** early EN group: 15.35 ± 5.26; delayed EN group: 16.00 ± 6.01 **Comorbidities:** not reported **Sepsis (N° / %):** not reported **Weight (kg):** early EN group: 75.03 (SD: 10.10); delayed EN group: 77.43 (SD: 8.56) **BMI:** early EN group: 24.86 (SD: 2.06); delayed EN group: 25.18 (SD:1.97)
Interventions	**Types of intervention:** In the early EN group, enteral feeding was established through the nasogastric tube and feeding began within 24 to 48 hours from admission to the ICU **Types of comparison:** delayed EN was initiated when gastroparesis was resolved (> 48 hours) but no later than 5 days after admission to the ICU, and the goal for the administration rate was to reach 100% of the needs within 4 days **Common interventions:** all patients were intubated and mechanically ventilated to maintain blood gases at PaO^2 ≥ 100 mm Hg and $PaCO^2$ = 35 mm to 40 mm Hg. Endocranial pressure was monitored with an additional catheter placed in the brain parenchyma or in the brain ventricles. An arterial catheter, endotracheal tube, nasogastric tube, and urinary catheter were placed in each patient after intubation. All patients were placed in a recumbent position 30° from horizontal. When a central vein catheter was available, fluid administration to TBI patients was adjusted according to central vein pressure data and monitoring of cardiac output.

Chourdakis 2012 *(Continued)*

	Standard care of head injuries was offered according to trauma type and daily clinical observations. Medications administered included pentothal, benzodiazepines, propofol, and opioids (fentanyl) for sedation and control of endocranial pressure; antimicrobial agents for prevention and treatment of infections; low molecular weight heparin for thromboprophylaxis; and gastroprotective drugs against development of stress ulcers, as indicated. Antidiarrheal drugs and laxatives were offered as needed. None of the patients received systemic glucocorticoids or mineralocorticoids. The initial administration rate was 30 mL/h; the rate reached 80 mL/h to 100 mL/h within 48 hours by subsequently increasing by 10 mL/h every 4 to 6 hours. Tolerance of administration of enteral feeding was evaluated daily based on the gastric residue collected between the intervals among nutrition administration. The administration rate was continuous for 6 hours followed by a 1-hour interval for the drainage of the gastric residue. Tracheal secretions were also routinely checked for feeding residuals. Feedings were stopped when gastric residue volume was > 200 mL and were only reinitiated when gastric residue volume measurement was < 200 mL. Prokinetic agents (cisapride or domperidone) were provided in cases of early feeding administration intolerance (nearly 45% of the cases) and were mostly withdrawn after a period of 48 hours. The administration rate for the prescribed quantity was calculated for < 24 hours in order to include the 'dead time' of the residue calculation and drainage, resulting in a continuous provision of 21 to 22 hours per day. Reasons for terminating administration of enteral feeding were excessive gastric residue, frequent diarrhoea, ileus, and thrombocytopenia. An elemental solution was provided for the first 2 to 3 days to both groups, whereas a polymeric compound was used for target attainment. The solution (Fresubin HP Energy, Fresenius Kabi AG, Bad Homburg, Germany) was chosen to cover the calculated requirements, not only in kilocalories (as estimated by indirect calorimetry) but also for macro- and micronutrients. The administration of nutrition components was based first on the provided quantity of proteins, and the remaining calories were divided into 60% carbohydrates and 40% lipids. The recommended daily protein intake was 1.5 g/kg body weight. **Energy delivered** (kcal/day or kcal/kg/day)**:** early EN group: 1862.0 (SD: 279.7) kcal/day; delayed EN group: 1792.0 (SD: 260.3) kcal/day **Protein delivered** (g/kg/day): not reported
Outcomes	1. Infectious complications 2. Feed intolerance or gastrointestinal complications 3. ICU mortality 4. Length of ICU stay 5. Pneumonia
Notes	Financial disclosure: none declared We contacted the author by email: kouvelas@auth.gr on 18 and 26 May 2017. We received no reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "patients were randomly assigned to 1 of the 2 treatment groups using a restricted randomization in order to achieve equality in baseline characteristics" **Comment:** no methodology for generating the random sequence was reported
Allocation concealment (selection bias)	Unclear risk	**Comment:** no methods for allocation concealment were identified
Blinding of participants and personnel (performance bias)	High risk	**Quote:** "comparative, prospective, open-labeled, randomized study included..."

Chourdakis 2012 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	High risk	**Quote:** "comparative, prospective, open-labeled"
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Quote:** "Intention-to-treat analyses were carried out for all outcomes" **Comment:** the analysis was performed with the intention-to-treat principle and it is considered adequate
Selective reporting (reporting bias)	Unclear risk	**Quote:** "the study protocol was approved by the School of Medicine, Democritus University of Thrace (protocol no. 3857/01.07.2002)" **Comment:** protocol was not available to evaluate selective reporting
Other bias	Low risk	**Comment:** none identified

Eyer 1993

Methods	**Study design:** randomized controlled trial **Unit of allocation:** by individuals. **Start date recruitment:** December 1988 **End date recruitment:** May 1991 **Duration of participation:** not reported
Participants	**Participants:** all patients were admitted to the trauma ICU at the St. Paul-Ramsey Medical Center, St. Paul, Minnesota, in the USA, with blunt trauma. **Inclusion criteria** 1. Age > 17 years 2. Injury Severity Score (ISS) > 13 3. Feeding support anticipated for at least 7 days, and an ability to start enteral feeding via a tube placed distal to the pylorus within 24 hours after ICU admission **Exclusion criteria** 1. Contraindication to enteral feeding, e.g. new upper intestinal suture line 2. Contraindication to placement of an enteral tube within 24 hours after ICU admission, e.g. unstable cervical fracture 3. Admission creatinine level > 2 mg/dL 4. Admission bilirubin > 3 mg/dL 5. Pre-existing malnutrition according to history and physical examination 6. Use of steroids, radiation, or chemotherapy 7. Malignancy 8. Acute spinal cord injury **Population description:** blunt trauma ICU patients **Setting:** trauma ICU teaching hospital in the USA **Total number randomized:** 38 patients were randomized, 19 patients to the early EN group and 19 to the delayed EN group

Eyer 1993 *(Continued)*

	Baseline imbalances: patients in early EN group had worse respiratory failure at admission (PaO^2/FiO^2) 201, SD: 114 (11 patients with $PaO^2/FiO^2 < 150$) compared with delayed EN group (PaO^2/FiO^2) 247, SD: 100 (4 patients with $PaO^2/FiO^2 < 150$) **Age:** early EN group: 44 (SD: 22); delayed EN group: 41 (SD: 18) **Sex (male):** early EN group: 14 of 19; delayed EN group: 8 of 19 **Disease status, type**: blunt trauma **Score severity of illness at ICU admission, Injury Severity Score (ISS):** early EN group: 34 ± 11; delayed EN group: 32 ± 9 **Comorbidities:** not reported **Sepsis (N° / %):** not reported **Weight (kg):** not reported **BMI:** not reported (note: exclusion criteria was pre-existing malnutrition according to history and physical examination)
Interventions	**Types of intervention**: In the early EN group, enteral feeding was established through nasoduodenal tube, and feeding began < 24 hours after ICU admission The day of trauma admission was considered day 0 (zero). Enteral feeding was begun immediately after patients returned to the ICU post nasoenteric tube installation **Types of comparison:** delayed EN was initiated > 72 hours after ICU admission. Patients received no nutrients for the first 72 hours other than intravenous crystalloid solutions containing dextrose, and plasma products as necessary. Nasoenteric tubes in the late group were usually not placed until the day feeding began **Common interventions:** 10 F nasoenteric feeding tube placed distal to the pylorus by experienced radiologists under fluoroscopic guidance. The tip was usually positioned at the ligament of Treitz. In both groups, enteral feeding was with a peptide-based formula (Reabilan HN, O'Brien Pharmaceuticals, Parsippany, NJ). Riablian HN contains 1.33 kcal/mL, 490 mOsm/kg water, and a 125:1 non-protein kcal/g nitrogen ratio. Per litre, there are 58 g protein, 158 g carbohydrate, and 52 g fat. Full-strength formula was started at 25 mL/hour every 4 hours, until patient's target rate was reached. Target was to provide 1.5 g protein/kg/day unless fluid restriction was necessary to manage closed head injury. Nitrogen balance determination was then performed, and enteral administration rates were adjusted to achieve nitrogen equilibrium All patients in the study were placed on stress gastritis prophylaxis with a sucralfate or antacid regimen. Fluid resuscitation, antibiotics, and inotropic agents were given as clinically indicated The study was completed after the tenth study day, when oral intake could be resumed, or on the day a patient went 24 hours without receiving any nutrients **Energy delivered** (kcal/day or kcal/kg/day)**:** early EN group: 30 (SD: 6) kcal/kg/day; delayed EN group: 19 (SD: 5) kcal/kg/day **Protein delivered** (g/kg/day): early EN group: 1.3 (SD: 0.3); delayed EN group: 0.9 (SD: 0.2)
Outcomes	1. Mortality 2. Infectious complications 3. Length of ICU stay 4. Duration of mechanical ventilation in days 5. Pneumonia
Notes	Funding source: this study was supported in part by a grant from Hoechst-Roussel, Paris, France

Eyer 1993 *(Continued)*

We contacted the last author by email: cerra001@umn.edu on 18 May 2017. We received a reply on 23 May 2017.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "randomization was by card draw"
Allocation concealment (selection bias)	Unclear risk	**Quote:** "randomization was by card draw from sealed envelopes" **Comment:** it is not clear if the sealed envelopes used were opaque
Blinding of participants and personnel (performance bias) All outcomes	High risk	**Comment:** study was unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	**Comment:** study was unblinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** analysis with intention-to-treat principle; it was considered adequate
Selective reporting (reporting bias)	Unclear risk	**Comment:** no protocol was identified for this study
Other bias	Low risk	**Comment:** none identified

Hill 2002

Methods	**Study design:** randomized controlled trial **Unit of allocation:** by individuals **Start date recruitment:** not reported **End date recruitment:** not reported **Duration of participation:** not reported
Participants	**Participants:** multiple trauma patients ≥ 18 years old and having an injury severity score (ISS) ≥ 20 were randomized to 1 of 3 groups within 24 hours of injury; TPN for 7 days, followed by enteral nutrition, early EN started within 24 hours of injury, and delayed EN where enteral feeds started at day 5 post injury **Population description:** multiple trauma ICU patients **Setting:** ICU in the USA **Total number randomized:** 22 patients to the early EN group and 24 to the delayed EN group **Baseline imbalances:** no data were reported regarding baseline data **Age:** Mean of 41 ± 2.1 years old for all participants. No data were reported for each group

Hill 2002 *(Continued)*

	Sex (male): no data were reported regarding sex **Disease status, type**: multiple trauma patients **Score severity of illness at ICU admission, Injury Severity Score (ISS):** median of 29 ± 1.0 for all patients, no data were reported regarding each group **Comorbidities:** not reported **Sepsis (N° / %):** not reported **Weight (kg):** not reported **BMI:** not reported
Interventions	**Types of intervention**: early EN started within 24 hours of injury **Types of comparison:** delayed EN started at day 5 post injury **Energy delivered** (kcal/day or kcal/kg/day)**:** not reported **Protein delivered** (g/kg/day): not reported No data were reported regarding details of the interventions
Outcomes	1. Mortality 2. Pneumonia
Notes	Funding source: not reported Data extracted from conference abstract We contacted the author by email: daniell.hill@louisville.edu on 18 and 26 May 2017. We received no reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "the patients were randomised to one of three groups" **Comment:** no methodology for generating the random sequence was reported
Allocation concealment (selection bias)	Unclear risk	**Comment:** no methods for allocation concealment were identified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** no methods for blinding of participants and personnel were identified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** no methods for blinding of outcome assessment were identified
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** there were no dropouts

Hill 2002 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	**Comment:** no protocol was identified for this study
Other bias	Low risk	**Comment:** none identified

Leiderman 2002

Methods	**Study design:** randomized controlled trial **Unit of allocation:** by individuals **Start date recruitment:** 2000 **End date recruitment:** 2001 **Duration of participation:** not reported
Participants	**Participants:** ICU patients older than 18 years and mechanically ventilated were randomized to 1 of 2 groups; early EN group started within the first 24 hours; delayed EN group started 72 hours after ICU admission **Population description:** severe head injury patients **Setting:** ICU in a hospital in Russia **Total number randomized:** 38 patients to the early EN group; 50 to the delayed EN group **Baseline imbalances:** there were no differences in sex, age, ISS score, caloric requirements. No further details were given **Age:** not reported **Sex (female):** not reported **Disease status, type**: severe head injury **Score severity of illness at ICU admission, Injury Severity Score (ISS):** early EN group:34.5 ± 3.23; delayed EN group: 36.6 ± 1.35 **Comorbidities:** not reported **Sepsis (N° / %):** not reported **Weight (kg):** not reported **BMI:** not reported
Interventions	**Types of intervention**: early EN group started within the first 24 hours of ICU admission through nasogastric tube feeding; standard isocaloric enteral diet **Types of comparison:** delayed EN group started at 72 hours post ICU admission through nasogastric tube feeding **Energy delivered** (kcal/day or kcal/kg/day)**:** not reported **Protein delivered** (g/kg/day): not reported No data were reported regarding details of the interventions
Outcomes	1. Mortality

Leiderman 2002 *(Continued)*

Notes	Funding source: not reported Data extracted from conference abstract We wrote to the author by email: inl@urmail.ru. We received no reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "patients were randomly assigned to the study and control group" **Comment:** no methodology for generating the random sequence has been reported
Allocation concealment (selection bias)	Unclear risk	**Comment:** no methods for allocation concealment were identified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** no methods for blinding of participants and personnel were identified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** no methods for blinding of outcome assessment were identified
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Quote:** "88 patients were included for analysis" **Comment:** all randomized patients were analysed in the study
Selective reporting (reporting bias)	Unclear risk	**Comment:** no protocol was identified for this study
Other bias	Low risk	**Comment:** none identified

Moses 2009

Methods	**Study design:** randomized controlled trial **Unit of allocation:** by individuals **Start date recruitment:** not reported **End date recruitment:** not reported (time of recruitment 13 months) **Duration of participation:** not reported
Participants	**Inclusion criteria:** adult patients admitted to the medical ICU with a diagnosis of organophosphate poisoning (OP), who needed invasive mechanical ventilatory support **Exclusion criteria: r**efractory hypotension or features of intestinal obstruction or ileus at the time of randomization **Population description:** ICU patients with organophosphate poisoning **Setting:** medical ICU of a tertiary care university teaching hospital in South India

Moses 2009 *(Continued)*

	Total number randomized: 29 patients to the early EN group; 31 to the delayed EN group. The analysis was done on 59 patients (1 patient of the delayed EN group was excluded as the diagnosis was revised) **Baseline imbalances:** no significant differences were found between study groups **Age:** early EN group: 29.41 (SD:11.8); delayed EN group: 30.83 (SD 12.4) **Sex (male):** early EN group: 22 of 29; delayed EN group: 22 of 31 **Disease status, type**: organophosphate poisoning (OP) **Score severity of illness at ICU admission, APACHE II:** not reported **Comorbidities:** diabetes in early EN group: 2 of 29; diabetes in delayed EN group: 3 of 31 **Sepsis (N° / %):** not reported **Weight (kg):** not reported **BMI:** not reported
Interventions	**Types of intervention: i**n the early hypocaloric EN group, enteral feeding was established through a nasogastric tube and feeding starting within 48 hours of intubation. Enteral feeds were prepared in the dietary department of the hospital and delivered by a nasogastric tube. The maximum feed given per day was 1000 calories with a concentration of 1 cal/mL (the feed on day 1 was 0.5 cal/mL). The total fluid intake through the nasogastric tube was restricted to a maximum of 1000 mL in 24 hours in view of the reduced gut motility with atropine use. The goal rate of feeding was calculated for 16 to 18 h/day, taking into consideration interruptions in delivery. Feeds were interrupted 6 to 12 hours before tracheostomy, transfers for therapeutic or diagnostic procedures, and before extubation. The head of the bed was maintained at 30° elevation to minimise aspiration risk. The duration of the intervention was from the time of intubation to either the time of tracheostomy, extubation, transfer out of the medical ICU to the ward, or death. If the patient was re-intubated in the ward after being transferred from the ICU, the event was noted and included in the analysis, but the study feed protocol was not restarted **Types of comparison:** in the control group, enteral feeds were started following tracheostomy **Common interventions: t**he nasogastric tube was placed before randomization for all patients with OP in the emergency department. Both groups received intravenous fluids containing glucose and electrolyte supplements according to fluid and electrolyte requirements. OP patients received atropine according to the following protocol: a loading dose of 1 mg was administered with increasing doses of atropine (generally doubled) every 5 to 10 minutes if not adequately atropinised. Atropinisation targets were: a. heart rate > 110/min (day 1), > 100/min (day 2), > 90/min (day 3); b. clear lung fields; c. systolic blood pressure > 90 mmHg. Although pupillary dilatation and bowel sounds (reduction) were also monitored, these were not used to assess adequacy of atropinisation. Once atropinised, an infusion of atropine was continued to maintain the above targets. Generally, by about day 3, atropine requirements came down, and the dose was tapered under close monitoring. Tracheostomy was done at the clinician's discretion, if ventilation was required or expected for more than 7 to 10 days **Energy delivered** (kcal/day or kcal/kg/day)**:** early EN group: 604 kcal/day (IQR 500 kcal/day to 713 kcal/day); delayed EN group: 447 kcal/day (IQR 423.5 kcal/day to 484.2 kcal/day) **Protein delivered** (g/kg/day): not reported
Outcomes	1. Mortality

Moses 2009 *(Continued)*

2. Infectious complications
3. Length of ICU stay
4. Hospital length of stay
5. Duration of mechanical ventilation in days
6. Weaning failure
7. Pneumonia

Notes	The data for length of ICU stay, duration of MV, hospital length of stay, and energy delivered were reported in mean and IQR (authors did not report SD) Funding source: not reported We contacted the authors on 18 and 26 May 2017 by email: vijumoses@gmail.com. We received no reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "randomization of patients was based on published random digits"
Allocation concealment (selection bias)	High risk	**Quote**: "the allocation sequence was generated before the study. The allocation sequence was kept with the ICU nursing staff and accessed only by them. The medical ICU nursing staff allocated the patient to the appropriate treatment arm once the patient was recruited by the principal investigator. Sealed envelopes were not used" **Comment:** it is important that sealed envelopes were not used
Blinding of participants and personnel (performance bias) All outcomes	High risk	**Quote**: "blinding was not possible in view of the nature of the study"
Blinding of outcome assessment (detection bias) All outcomes	High risk	**Quote:** "blinding was not possible in view of the nature of the study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Quote:** "patients who died were excluded from the analysis of duration on ventilator, and length of stay in ICU and hospital" ... "The final analysis was done on 30 control and 29 intervention patients. One patient randomised to the control group was excluded as the diagnosis was revised." **Comment:** the number of dropouts was not enough to have a clinically relevant impact on the intervention effect estimate
Selective reporting (reporting bias)	Unclear risk	**Comment:** no protocol was identified for this study
Other bias	Low risk	**Comment:** none identified

Nguyen 2008

Methods	**Study design:** randomized controlled trial **Unit of allocation:** by individuals

Nguyen 2008 *(Continued)*

	Start date recruitment: not reported **End date recruitment:** not reported **Duration of participation:** not reported
Participants	**Participants:** studies were performed in medical and surgical critically ill patients, who were admitted to a level 3, mixed medical and surgical intensive care unit (ICU). **Inclusion criteria:** patients sedated; mechanically ventilated; able to receive EN; older than 17 years of age **Exclusion criteria:** patients receiving parenteral nutrition; recent (less than 4 weeks) major surgery that involved opening the abdominal cavity or gastrointestinal tract; previous surgery of the oesophagus or stomach; inability to place a naso- or orogastric feeding tube for feeding, due to either technical failure or safety concerns (e.g. acute oesophageal or gastric variceal bleeding); administration of prokinetic therapy (erythromycin or another macrolide antibiotic or metoclopramide) within 24 hours prior to the study; pregnant or breast-feeding. Early enteral nutrition participants received feeding within 24 hours of admission; delayed enteral nutrition participants received feeding on day 4 of admission, after gastric emptying assessment **Population description:** critically ill patients, admitted to a mixed medical and surgical ICU **Setting:** mixed medical and surgical ICU in South Australia **Total number randomized:** 14 patients to the early EN group; 14 to the delayed EN group **Baseline imbalances:** no significant differences were found between study groups **Age:** early EN group: 54.9 (SD 3.3); delayed EN group: 56.3 (SD 3.4) **Sex (male):** early EN group: 8 of 14; delayed EN group: 10 of 14 **Disease status, type**: early EN: head injury 6 (42%), sepsis 6 (42%), respiratory failure 5 (36%), trauma 4 (29%), dissecting aortic aneurysm 1 (7%), burns 1 (7%); delayed EN: head injury 7 (50%), sepsis 6 (42%), respiratory failure 4 (29%), trauma 6 (42%), dissecting aortic aneurysm 2 (14%), burns 0 (0%) **Score severity of illness at ICU admission, APACHE II:** early EN group: 24.0 ± 1.7; delayed EN group: 22.9 ± 1.7 **Comorbidities:** not reported **Sepsis (N° / %): e**arly enteral nutrition; 6 (42%); delayed enteral nutrition; 6 (42%) **Weight (kg):** not reported **BMI:** early EN group: 28.3 (SD 1.7); delayed EN group: 27.4 (SD 1.9)
Interventions	**Types of intervention:** the early enteral group started feeding within 24 hours of admission. EN was commenced at a rate of 40 mL/h. Gastric aspirates were collected every 6 hours as per clinical practice. If feeding was tolerated (aspirate volume 250 mL), the rate was increased by 20 mL/hr until the prescribed maximum was reached. In accordance with usual practice in the ICU, nutritional requirements were determined by a dietician and based on the patient's body mass index (BMI), with feeding prescribed by an intensive care physician. If an aspirate of 250 mL occurred, the feeding rate was reduced by half, or to the minimum rate of 20 mL/h. Prokinetic therapy was not administered throughout the study period. The amount of calories administered, as well as the administered:prescribed caloric ratio over the first 4 days before the assessment of gastric emptying were collected. Measurements of GE and gut hormones were performed on day 4 of admission. Feeding was stopped 6 hours before the study. The stomach was emptied by aspiration of the nasogastric tube, and the volume of aspirate obtained was recorded.

Nguyen 2008 *(Continued)*

	Types of comparison: in the control group, enteral feeding was started on day 4 of admission, after gastric emptying assessment. The delayed feeding group did not receive any other form of nutritional support, including parenteral nutrition. The nasogastric tube was placed on free drainage. **Common interventions:** a nasogastric tube (NGT) was inserted on admission in all patients, and correct position of the tube was confirmed by routine X-ray. All patients received an insulin infusion, according to a standard protocol, designed to maintain the blood glucose concentration between 6 mmol/L to 8 mmol/L **Energy delivered** (kcal/day or kcal/kg/day)**:** at day 4 of the study: early EN group: 2894 kcal/day (SD 198); delayed EN group: 0 kcal/day **Protein delivered** (g/kg/day): not reported
Outcomes	1. Mortality 2. ICU mortality 3. Length of ICU stay 4. Duration of mechanical ventilation in days 5. Pneumonia
Notes	Funding source: Drs. Nguyen, Fraser, Bryant, Burgstad, Chapman, and Horowitz have received Australian National Health and Medical Research Council (HMRC) grants. The remaining authors did not disclose any potential conflicts of interest We contacted the authors on 23 May 2017 and 6 June 2017 by email: Qnguyen@mail.rah.sa.gov.au. We received no reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "patients were enrolled within the first 10 hrs after admission to the ICU and were randomised to receive either early feeding within 24 hrs of admission or delayed feeding on day 4 of admission after GE assessment" **Comment:** no methodology for generating the random sequence was reported
Allocation concealment (selection bias)	Unclear risk	**Comment:** no methods for allocation concealment were identified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** no methods for blinding of participants and personnel were identified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** no methods for blinding of outcome assessment were identified
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** all randomized patients were analysed in the study
Selective reporting (reporting bias)	High risk	**Comment:** no data for the outcome, hospital length of stay, in the results. No protocol was identified for this study

Nguyen 2008 *(Continued)*

Other bias	Low risk	**Comment:** none identified

Peck 2004

Methods	**Study design:** randomized controlled trial **Unit of allocation:** by individuals **Start date recruitment:** not reported **End date recruitment:** not reported **Duration of participation:** not reported
Participants	**Participants:** all patients admitted to the North Carolina Jaycee Burn Center, in the USA. **Inclusion criteria:** patients between 18 and 50 years of age, who had at least a 20% total body surface area (TBSA) burn, or patients who were younger than 18 years or older than 50 years, and had at least 10% TBSA burns Admitted within 24 hours of injury **Exclusion criteria:** medical conditions that led to inanition and wasting (such as adult immunodeficiency syndrome, cancer); had high-voltage electrical injuries; were admitted to the burn centre for treatment of an exfoliative skin disorder; treated with the volumetric diffusive respirator (VDR) for smoke inhalation injury **Population description:** patients admitted in a burn ICU **Setting:** burn ICU in the USA **Total number randomized:** 14 patients to the early EN group; 13 to the delayed EN group **Baseline imbalances:** no significant differences were found in demographics and operative management between study groups. However, 4 patients with inhalation injury were randomized to the early group, and none to the delayed group **Age:** early EN group: 44 (SD 24); delayed EN group: 49 (SD 19) **Sex (male):** early EN group: 9 of 14; delayed EN group: 10 of 13 **Disease status, type:** early EN group % total body surface area (TBSA) burn: 36 ± 13; delayed EN group % TBSA burn: 43 ± 27 **Score severity of illness at ICU admission, APACHE II:** not reported **Comorbidities:** early EN group inhalation injury: 4/14 (28%); delayed EN group inhalation injury: 0/13 (0%) **Sepsis (N° / %):** not reported **Weight (kg):** not reported **BMI:** not reported
Interventions	**Types of intervention:** nutritional support was initiated within 24 hours of burn injury. The rate of infusion was increased every 6 hours, as tolerated by the patient, until the goal rate was achieved. Oral intake for the early group was encouraged for non-intubated subjects, and supplemented in exactly the same way for patients randomized to the late group. Tube feedings were discontinued when oral intake exceeded 80% of the caloric goal for 2 consecutive days.

Peck 2004 *(Continued)*

Types of comparison: EN was started 7 days after burn injury. Nasogastric tube was removed when bowel function returned, and the subjects were advanced to a regular diet, as above. Daily calorie and protein counts were performed, and if by day 7 the subjects were unable to consume at least 80% of their calorie and protein needs, a soft silastic feeding tube was passed nasally into the stomach, and enterogastric feedings were advanced, as in the early group

Common Interventions: nasogastric tube at the time of admission. Central venous TPN supplementation was used only as a last resort. Indications for TPN included: paralytic ileus, gastric atony, malabsorption, and pancreatitis

Diarrhoea was treated initially with diphenoxylate HCl with atropine SO_4 (Lomotil, G.D. Searle & Co., Chicago, IL) after ensuring that it was not of infectious origin. If the patient failed therapy with Lomotil, the rate of infusion of tube feedings was decreased until the diarrhoea resolved.

The basal energy expenditure (BEE) for each subject was calculated shortly after admission, using the Harris-Benedict equations. The estimated BEE served as the starting point for calculations of the estimated daily caloric need, and provided a standard against which subsequent measurements of resting energy requirements (REE), using indirect calorimetry, were compared over time. Initial estimates of daily energy expenditure were made by multiplying the BEE by 1.2 to 1.3 and then by an injury factor proportional to burn size. The amount of protein given was 1.5 g/kg/day for burns under 30% TBSA, 2 g/kg/day to 3 g/kg/day for 30% to 50% TBSA burns, and up to 3 g/kg/day for burns of 50% TBSA or more. Transferrin and transthyretin were measured every Monday morning, and the amount of dietary protein was adjusted to keep transthyretin levels higher than 12 mg/dL. Collection of 24-hour urinary urea nitrogen was performed weekly. Subjects remained in the study during the acute phase of their hospitalization, and until at least 90% of the wounds were closed. Oxandrolone, growth hormone, or any other anabolic agent were not used in any of the subjects.

Patients in burn shock were initially resuscitated with lactated Ringer's solution. Subjects with smoke inhalation injury were intubated, and ventilatory support was provided until patients passed appropriate criteria for weaning and extubation. Deep second degree (deep partial thickness) and third degree (full thickness) burns were surgically excised within the first 10 days after injury; superficial partial thickness burns were allowed to heal for up to 21 days post injury, before excision. Steps were taken, as tolerated by the patient, on an individual basis to cover the open wounds, with either synthetic materials, such as Biobrane (Bertek Pharmaceuticals, Inc., Morgantown, WV), artificial dermis (INTEGRA Artificial Skin, Integra Life Sciences, Plainsboro, NJ), or biologics, such as cadaver skin (Ohio Valley Tissue and Skin Center, Cincinnati, OH) or autograft. Topical antimicrobials applied to wounds included silver sulfadiazine cream 1%, and mafenide acetate cream or mafenide acetate 5% solution (Sulfamylon cream or solution, Bertek Pharmaceuticals). Pain management was accomplished with a combination of narcotics and benzodiazepines. Physical and occupational therapy were initiated on the day of admission

Energy delivered (kcal/day or kcal/kg/day)**:** early EN group: 2234 kcal/day (SD not reported); delayed EN group: 2207 kcal/day (SD not reported)

Protein delivered (g/kg/day): not reported

Outcomes	1. Mortality 2. Infectious complications 3. Length of ICU stay 4. Duration of mechanical ventilation in days
Notes	Funding source: this study was supported by the North Carolina Jaycee Burn Center, and in part, by grant RR00046 from the General Clinical Research Center Program of the Division of Research Resources, National Institutes of Health We contacted the author on 6 June 2017 by email: mpeck47@hotmail.com. We received a reply on 7 June 2017.

Risk of bias

Bias	Authors' judgement	Support for judgement

Peck 2004 *(Continued)*

Random sequence generation (selection bias)	Low risk	**Comment:** the trial used a computer random number generator (information reported by the author)
Allocation concealment (selection bias)	Low risk	**Comment:** the trial used opaque sealed envelopes (information reported by the author)
Blinding of participants and personnel (performance bias) All outcomes	High risk	**Comment:** study was unblinded (information reported by the author)
Blinding of outcome assessment (detection bias) All outcomes	High risk	**Comment:** study was unblinded (information reported by the author)
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** analysis was with intention-to-treat principle, and was considered adequate
Selective reporting (reporting bias)	Unclear risk	**Comment:** no protocol was available for this study (information reported by the author)
Other bias	Low risk	**Comment:** none identified

Acronyms and abbreviations used in this table
AHEPA: hospital name, from Greek (Πανεπιστημιακό Νοσοκομείο ΑΧΕΠΑ); APACHE: acute physiology and chronic health evaluation; BEE: basal energy expenditure ; BMI: body mass index; EN: enteral nutrition; GCS: Glasgow coma scale; GE: gastric emptying; g/kg/day: grams per kilogram per day; h: hours; ICU: Intensive care unit; IQR: interquartile range; ISS: injury severity score; kcal/day: kilocalories per day; kcal/kg/day: kilocalories per kilogram per day; mg/dL: milligrams per decilitre; mL/h: millilitre per hour; mOsm/kg: milliosmoles per kilogram; MV: mechanical ventilation; NGT: nasogastric tube; OP: organophosphate-poisoning; REE: resting energy expenditure; SD: standard deviation; TBI: traumatic brain injury; TBSA: total body surface area; TPN: total parenteral nutrition; VDR: volumetric diffusive respirator; yrs: years

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
ACTRN12615000876594	Wrong intervention; early initiation of EN was applied to both groups
Bakiner 2013	Wrong study design; quasi-randomised controlled trial
Bakker 2014	Wrong intervention; oral diet comparator study
Beale 2008	Wrong intervention; early initiation of EN was applied to both groups
Braunschweig 2015	Wrong intervention; standard care (including PN) comparator study
Cao 2014	Wrong intervention; early initiation of EN was applied to all the groups with EN (this study included 3 groups)
Casaer 2011a	Wrong intervention; protocol; early initiation of EN was applied to both groups (compared early SPN versus delayed SPN)
Casaer 2011b	Wrong intervention; early initiation of EN was applied to both groups (compared early SPN versus delayed SPN)

Study	Reason for exclusion
Casaer 2013	Wrong intervention; early initiation of EN was applied to both groups (compared early SPN versus delayed SPN)
Chatterjee 2012	Wrong patient population; did not include patients in ICU
ChiCTR-INR-17010741	Wrong intervention
Chuntrasakul 1996	Wrong intervention; oral diet comparator study
Couto 2014	Wrong intervention; enteral administration by gastric versus jejunal tube study
Davies 2012	Wrong intervention; enteral administration by gastric versus jejunal tube study
De Castro 2012	Wrong intervention; hypercaloric high in antioxidants (eicosapentaenoic acid and gamma-linolenic acid) enteral formula versus isocaloric isonitrogenous standard ICU diet study
Dennis 2005	Wrong intervention; the enrolment was within 7 days of admission, it was not reported if it included ICU patients
Desachy 2008	Wrong intervention; early initiation of EN was applied to both groups (compared different flow rates)
Dou 2011	Wrong intervention; delayed EN was applied to both groups, also it was a standard care comparator study
Dvorak 2004	Wrong intervention; delayed EN was applied to both groups (compared EN started before 72 hours after injury versus EN started 120 hours after injury)
Engel 1997	Wrong intervention; early initiation of EN was applied to 2 groups with EN (supplemented EN, enteral standard group and PN group)
Grahm 1989	Wrong study design; quasi-randomized controlled trial
Grau-Carmona 2011	Wrong intervention; early initiation of EN was applied to both groups (compared different formulas of EN)
Hasse 1995	Wrong intervention; IV fluids and oral feeding comparator study
Heslin 1997	Wrong intervention; IV fluids and oral feeding comparator study, also early EN was defined according surgical time
Ibrahim 2002	Wrong study design; quasi-randomized controlled trial
ISRCTN12233792	Wrong intervention; compared the effectiveness of enteral feeding protocols in critically ill patients
ISRCTN63461816	Wrong intervention; early initiation of EN was applied to both groups
Jana 2014	Wrong intervention; oral or nasogastric feeding comparator study
Jazayeri 2016	Study outcomes not of interest to our review (study did not include clinical outcomes, it only measured inflammatory markers). We contacted the authors on 15 May 2017 and 22 May 2017 by email: ostadrahimi@tbzmed.ac.ir. We received no reply.
Jazayeri 2018	Wrong outcomes; study outcomes not of interest to our review (study did not include clinical outcomes)

Study	Reason for exclusion
JPRN-UMIN000003569	Wrong intervention
JPRN-UMIN000009552	Wrong intervention; early initiation of EN was applied to both groups
Kemen 1995	Wrong intervention; early initiation of EN was applied to both groups (compared different formulas of EN)
Kompan 1999	Wrong intervention; early initiation of EN was applied to both groups (compared EN started within 6 hours versus later than 24 hours after ICU admission)
Kompan 2004	Wrong intervention; early initiation of EN was applied to both groups
Liu 2018	Wrong study design; retrospective study
Maude 2011	Wrong intervention; no enteral feeding until able to take oral food or up to a maximum starvation period of 60 hours in adults comparator study, this study also included children
Minard 2000	Wrong intervention; delayed EN was applied to both groups (EN started after 60 hours of injury versus EN started when gastroparesis was resolved)
NCT00883948	Wrong intervention; early initiation of EN was applied to both groups (compared full versus trophic enteral nutrition)
NCT01432769	Wrong intervention; early initiation of EN was applied to both groups (compared two different compounds of enteral formulas)
NCT02837861	Wrong intervention; early initiation of EN was applied to both groups (compared enteral nutrition plus support of amino acids versus enteral nutrition alone)
Ohbe 2019	Wrong study design; retrospective study
Ostadrahimi 2016	Wrong intervention; hospital routine diet ad libitum comparator study
Perez-Guisado 2013	Wrong study design; retrospective study
Petrova 2017	Wrong intervention; early initiation of EN was applied to three groups (compared glutamine, semi-elemental feeding diet, and enteral administration of saline solutions)
Pilika 2015	Wrong intervention; delayed EN was applied to both groups (EN started within 72 hours versus after 72 hours of ICU admission)
Pupelis 2001	Wrong intervention; IV fluids only until reintroduction of the normal diet comparator study
Singh 1998	Wrong intervention; IV fluids and electrolyte supplements comparator study
Su 2018	Wrong study design
Sun 2013	Wrong intervention; early EN versus EN + PN study
Vicic 2013	Wrong intervention; standard manner per os (3 standard hospital meals) comparator study
Wang 1997	Wrong intervention; early initiation of EN was applied to patients of both groups; oral intake as tolerated; study outcomes not of interest to our review
Wang 2007	Wrong intervention; delayed EN was applied to 3 groups (conventional therapy, EN by nasogastric feeding, and EN and intestinal barrier protective agents by nasogastric feeding)

Study	Reason for exclusion
Wang 2015	Wrong patient population; did not include patients in ICU
Weijs 2018	Review or comment
Wereszczynska-Siemiatkowska 2013	Wrong study design; not a RCT; this was an observational study with retrospective analysis
Woo 2010	Wrong study design; not a RCT; this was an observational study
Yan 2019	Wrong outcomes; study outcomes not of interest to our review (study did not include clinical outcomes)
Yi 2015	Wrong intervention; PN comparator study
Yuan 2019	Wrong intervention (three groups with EEN: full EEN, full EEN plus prokinetic drugs, and trophic EEN)
Zhang 2018	Wrong patient population; did not include patients in ICU
Zhong 2014	Wrong intervention; delayed EN was applied to both groups (EN started after 72 hours of admission versus conventional nutritional treatment). To clarify the definition of conventional nutritional treatment, we contacted the authors on 9 July 2017 and 18 July 2017 by email: 1679237107@qq.com. We received no reply.
Zou 2014	Wrong intervention; PN comparator study

Acronyms and abbreviations used in this table
EEN: early enteral nutrition; EN: enteral nutrition; ICU: intensive care unit; IV: intravenous; PN: parenteral nutrition; SPN: supplemental parenteral nutrition; RCT: randomized controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

ChiCTR-INR-17012709

Trial name or title	The effect of early enteral nutrition intervention on patients with severe infections after cardiac surgery to intestinal microflora and metabolize
Methods	Study type: interventional study Study design: randomized parallel controlled trial
Participants	Patients with sepsis and septic shock
Interventions	EEN of high soluble dietary fibre in 48h; EEN of non high soluble dietary fibre in 48h; DEN of non high soluble dietary fibre after 48h
Outcomes	Intestinal microflora, basic data, respiratory parameters, circulation parameters, organ function, enteral nutrition tolerance
Starting date	Date of registration: 18 September 2017. Date of first enrolment: 10 January 2017
Contact information	Qinghe Hu (huqinghe1274@126.com) Yun Long (ly_icu@aliyun.com)
Notes	Recruitment status: pending

ChiCTR-IOR-17011914	
Trial name or title	A protocol for early enteral nutrition in mechanical ventilated patients
Methods	Study type: interventional study Study design: randomized parallel controlled trial
Participants	Inclusion criteria: 1. ICU patients; 2. receiving mechanical ventilation (MV), both non-invasive ventilation and invasive ventilation; 3. expecting MV more than 72 hours. Exclusion criteria: pregnancy
Interventions	Standard care and treating in protocol
Outcomes	Fulfilling the nutrition target, mortality
Starting date	Date of registration: 9 July 2017. Date of first enrolment: 1 December 2017
Contact information	Erzhen Chen (chenerzhen@hotmail.com) Ming Zhong (zm11716@rjh.com.cn)
Notes	Recruitment status: pending

DEN: delayed enteral nutrition; EEN: early enteral nutrition

DATA AND ANALYSES

Comparison 1. Early enteral nutrition versus delayed enteral nutrition

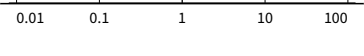
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	5		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2 Infectious Complications	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3 Feed intolerance or gastrointestinal complications	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4 ICU Mortality	2	87	Risk Ratio (IV, Random, 95% CI)	1.03 [0.39, 2.71]
5 ICU Mortality (subgroup analysis by trauma)	2		Risk Ratio (IV, Random, 95% CI)	Totals not selected
5.1 Trauma	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Non-trauma	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6 ICU Mortality (subgroup analysis by VEEN)	2		Risk Ratio (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 VEEN	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 Early enteral nutrition	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7 Length of ICU stay	3	125	Mean Difference (IV, Random, 95% CI)	-2.26 [-6.12, 1.60]
8 Length of ICU stay (subgroup analysis by trauma)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1 Trauma	2	97	Mean Difference (IV, Random, 95% CI)	-0.97 [-6.46, 4.52]
8.2 Non-trauma	1	28	Mean Difference (IV, Random, 95% CI)	-4.6 [-8.64, -0.56]
9 Length of ICU stay (subgroup analysis by VEEN)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
9.1 VEEN	2	66	Mean Difference (IV, Random, 95% CI)	-1.46 [-7.82, 4.91]
9.2 Early enteral nutrition	1	59	Mean Difference (IV, Random, 95% CI)	-3.70 [-8.02, 0.62]
10 Duration in mechanical ventilation	2	66	Mean Difference (IV, Random, 95% CI)	-1.31 [-7.78, 5.15]
11 Duration in mechanical ventilation (subgroup analysis by trauma)	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
11.1 Trauma	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
11.2 Non-trauma	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
12 Weaning failure	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
13 Pneumonia	4	192	Risk Ratio (IV, Random, 95% CI)	0.77 [0.55, 1.06]
14 Non-VAP and VAP	4	251	Risk Ratio (IV, Random, 95% CI)	0.79 [0.55, 1.12]
14.1 Non-VAP	2	105	Risk Ratio (IV, Random, 95% CI)	0.57 [0.29, 1.11]
14.2 VAP	3	146	Risk Ratio (IV, Random, 95% CI)	0.89 [0.59, 1.35]
15 Pneumonia (subgroup analysis by trauma)	4	192	Risk Ratio (IV, Random, 95% CI)	0.77 [0.55, 1.06]
15.1 Trauma	2	105	Risk Ratio (IV, Random, 95% CI)	0.71 [0.51, 0.98]
15.2 Non-trauma	2	87	Risk Ratio (IV, Random, 95% CI)	0.90 [0.38, 2.11]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16 Pneumonia (subgroup analysis by VEEN)	4	192	Risk Ratio (IV, Random, 95% CI)	0.77 [0.55, 1.06]
16.1 VEEN	2	74	Risk Ratio (IV, Random, 95% CI)	0.49 [0.23, 1.06]
16.2 Early enteral nutrition	2	118	Risk Ratio (IV, Random, 95% CI)	0.88 [0.54, 1.44]

Analysis 1.1. Comparison 1 Early enteral nutrition versus delayed enteral nutrition, Outcome 1 Mortality.

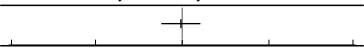
Study or subgroup	Early enteral nutrition n/N	Delayed enteral nutrition n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Eyer 1993	2/19	2/19		1[0.16,6.38]
Hill 2002	0/22	2/24		0.22[0.01,4.29]
Leiderman 2002	5/38	13/50		0.51[0.2,1.3]
Moses 2009	3/29	3/30		1.03[0.23,4.71]
Nguyen 2008	6/14	6/14		1[0.43,2.35]



Favours early enteral nutrition — Favours delayed enteral nutrition

Analysis 1.2. Comparison 1 Early enteral nutrition versus delayed enteral nutrition, Outcome 2 Infectious Complications.

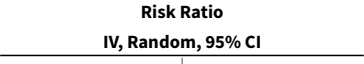
Study or subgroup	Early enteral nutrition n/N	Delayed enteral nutrition n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Moses 2009	14/29	15/30		0.97[0.57,1.62]



Favours early enteral — Favours delayed enteral

Analysis 1.3. Comparison 1 Early enteral nutrition versus delayed enteral nutrition, Outcome 3 Feed intolerance or gastrointestinal complications.

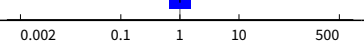
Study or subgroup	Early enteral nutrition n/N	Delayed enteral nutrition n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Chourdakis 2012	8/34	7/25		0.84[0.35,2.01]



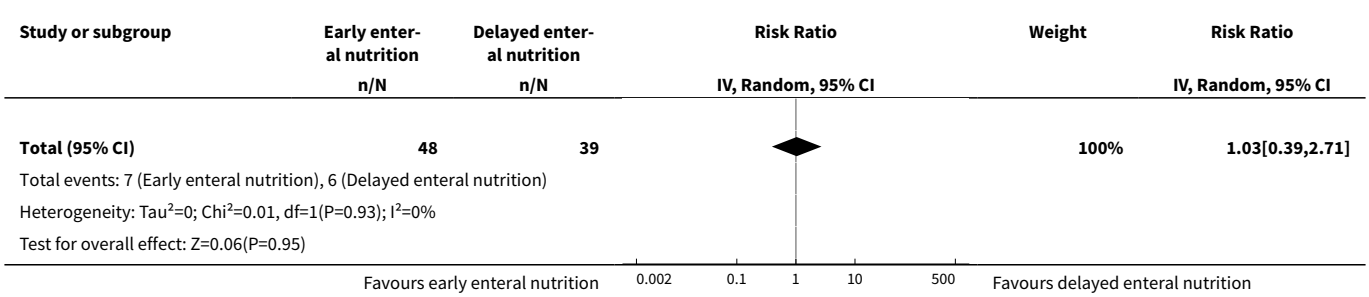
Favours early enteral — Favours delayed enteral

Analysis 1.4. Comparison 1 Early enteral nutrition versus delayed enteral nutrition, Outcome 4 ICU Mortality.

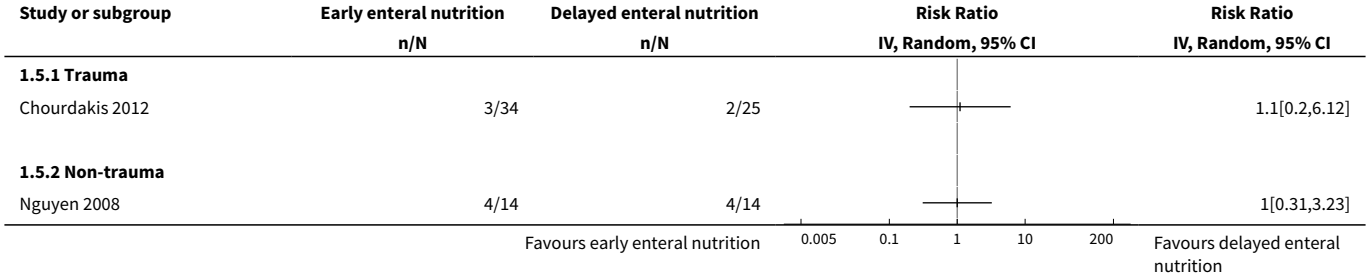
Study or subgroup	Early enteral nutrition n/N	Delayed enteral nutrition n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Chourdakis 2012	3/34	2/25		31.86%	1.1[0.2,6.12]
Nguyen 2008	4/14	4/14		68.14%	1[0.31,3.23]



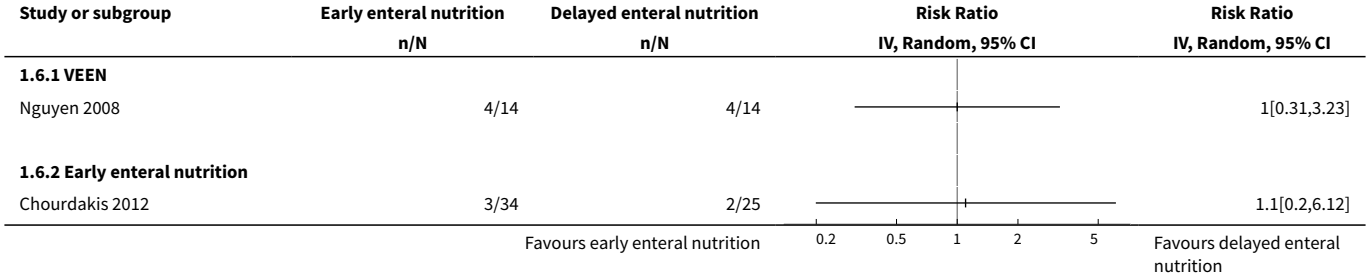
Favours early enteral nutrition — Favours delayed enteral nutrition



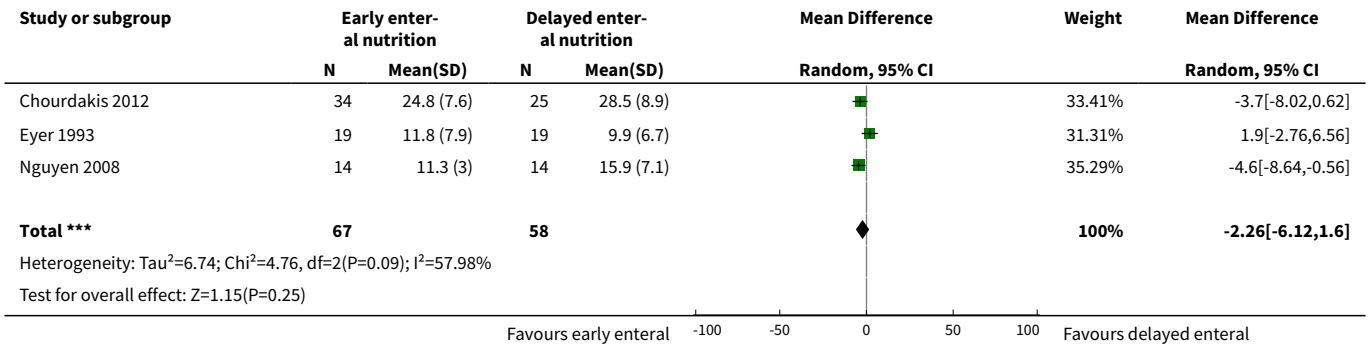
Analysis 1.5. Comparison 1 Early enteral nutrition versus delayed enteral nutrition, Outcome 5 ICU Mortality (subgroup analysis by trauma).



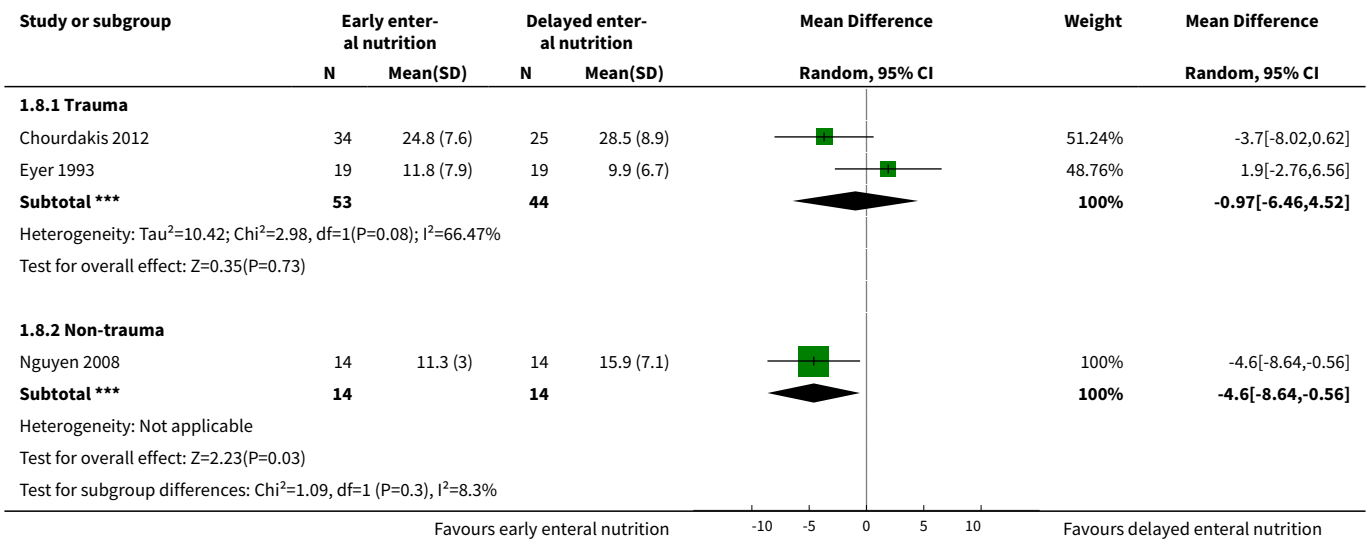
Analysis 1.6. Comparison 1 Early enteral nutrition versus delayed enteral nutrition, Outcome 6 ICU Mortality (subgroup analysis by VEEN).



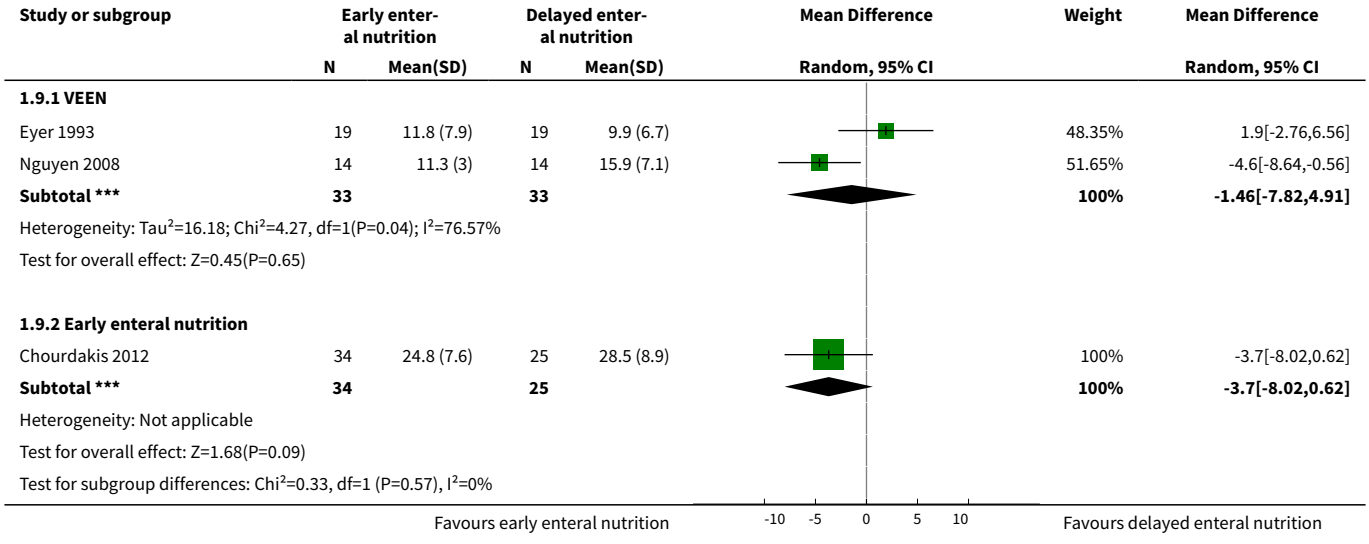
Analysis 1.7. Comparison 1 Early enteral nutrition versus delayed enteral nutrition, Outcome 7 Length of ICU stay.



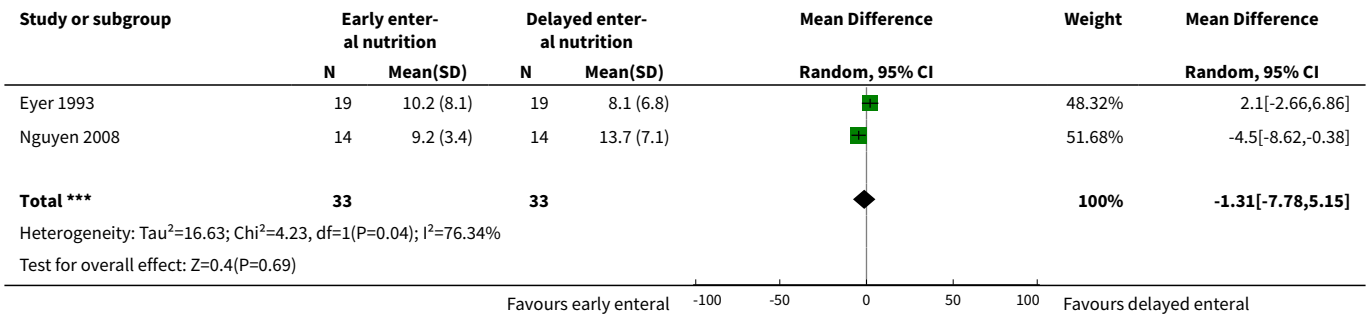
Analysis 1.8. Comparison 1 Early enteral nutrition versus delayed enteral nutrition, Outcome 8 Length of ICU stay (subgroup analysis by trauma).



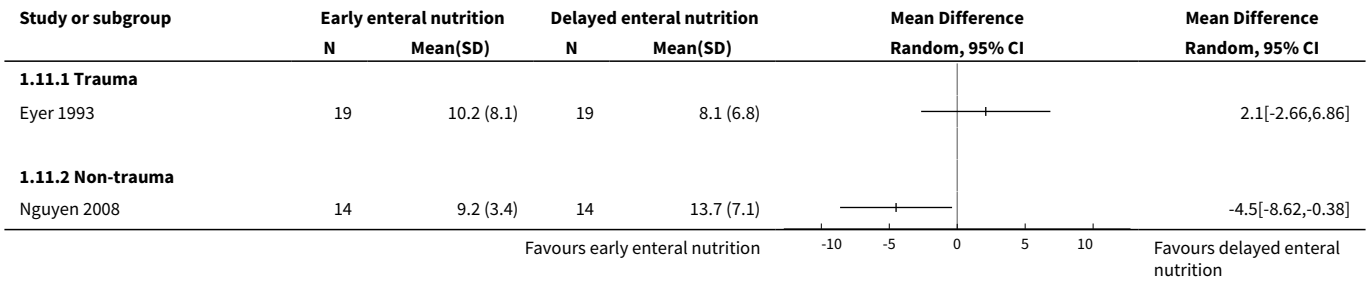
Analysis 1.9. Comparison 1 Early enteral nutrition versus delayed enteral nutrition, Outcome 9 Length of ICU stay (subgroup analysis by VEEN).



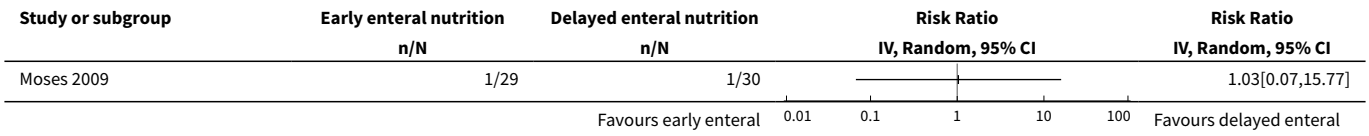
Analysis 1.10. Comparison 1 Early enteral nutrition versus delayed enteral nutrition, Outcome 10 Duration in mechanical ventilation.



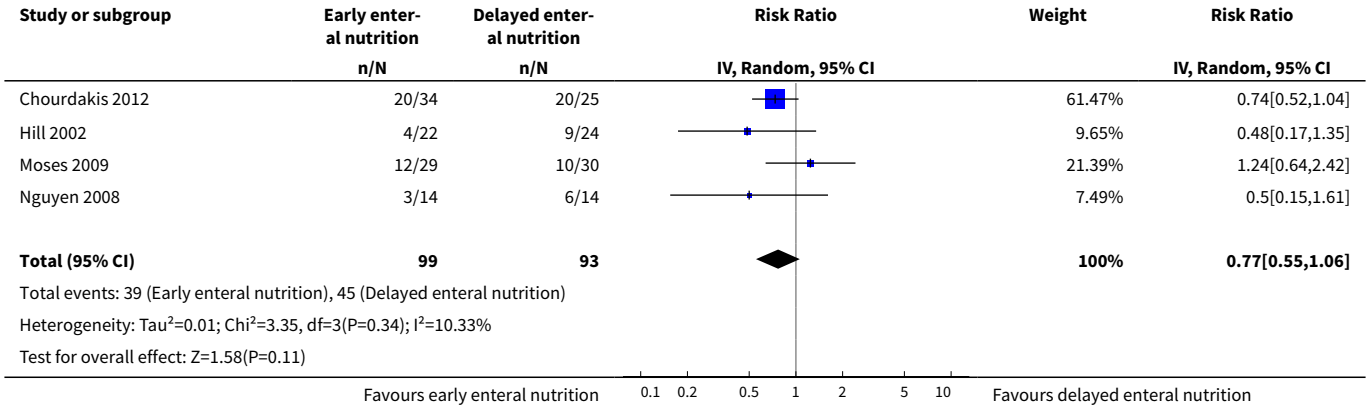
Analysis 1.11. Comparison 1 Early enteral nutrition versus delayed enteral nutrition, Outcome 11 Duration in mechanical ventilation (subgroup analysis by trauma).



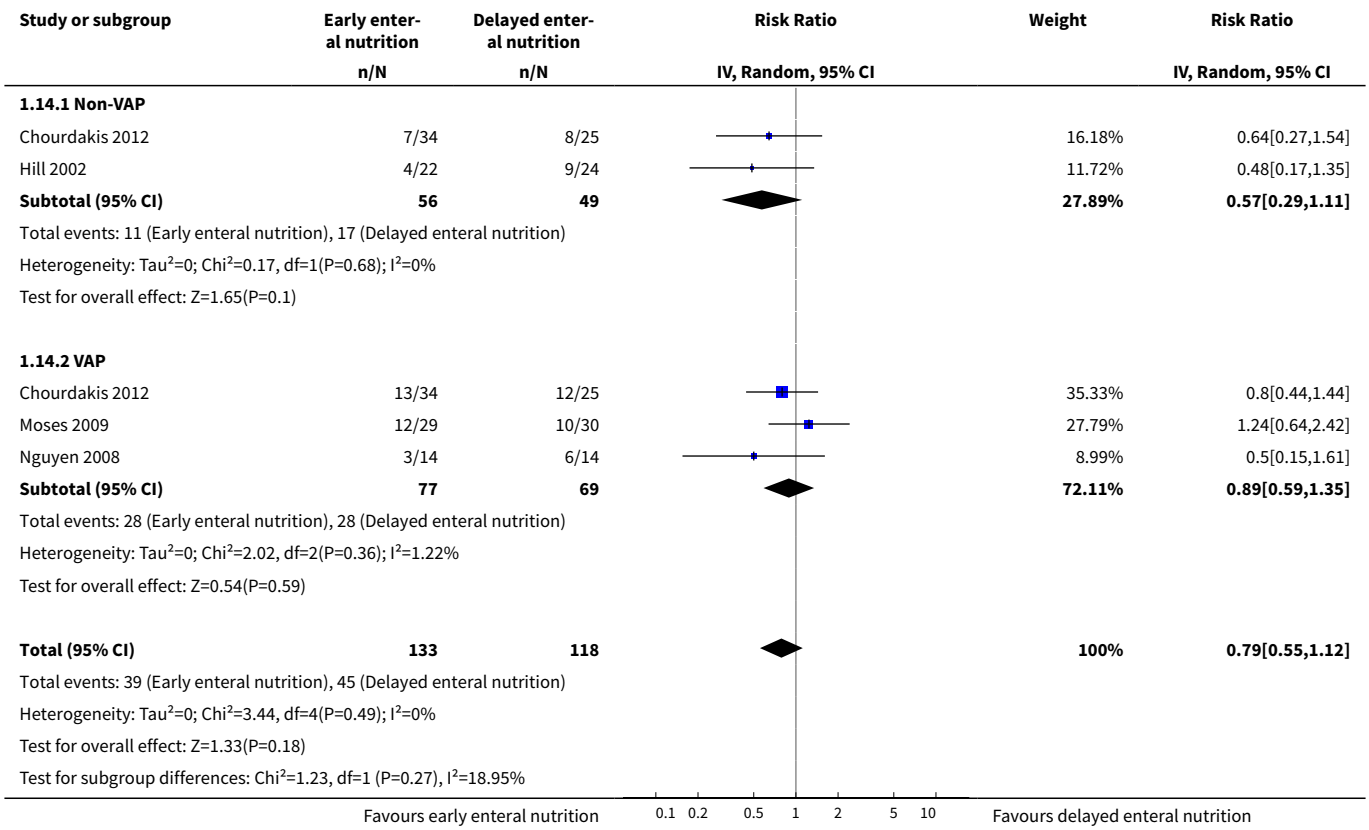
Analysis 1.12. Comparison 1 Early enteral nutrition versus delayed enteral nutrition, Outcome 12 Weaning failure.



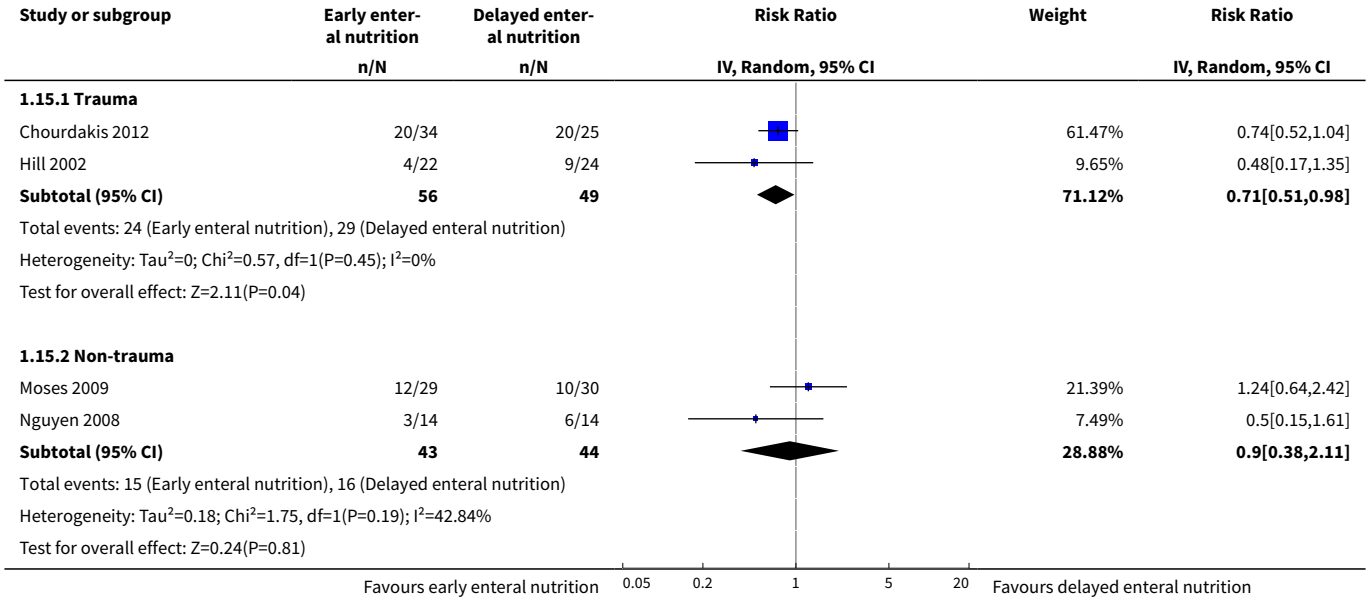
Analysis 1.13. Comparison 1 Early enteral nutrition versus delayed enteral nutrition, Outcome 13 Pneumonia.

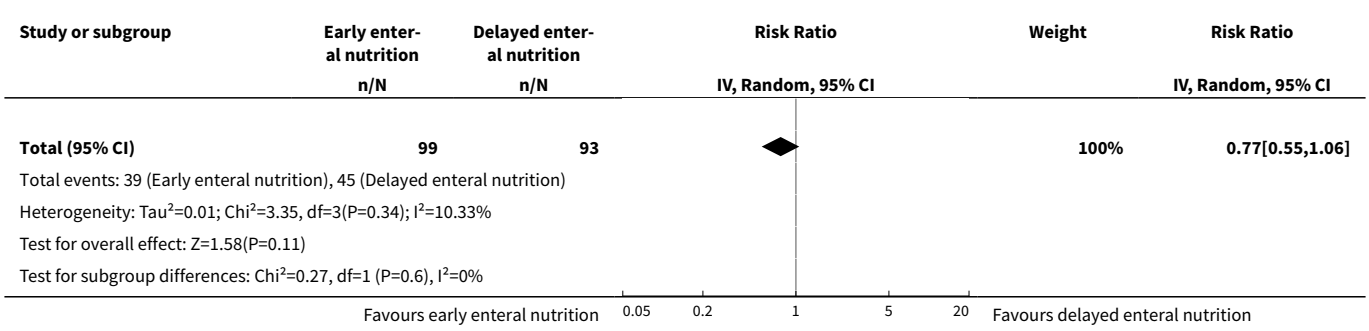


Analysis 1.14. Comparison 1 Early enteral nutrition versus delayed enteral nutrition, Outcome 14 Non-VAP and VAP.

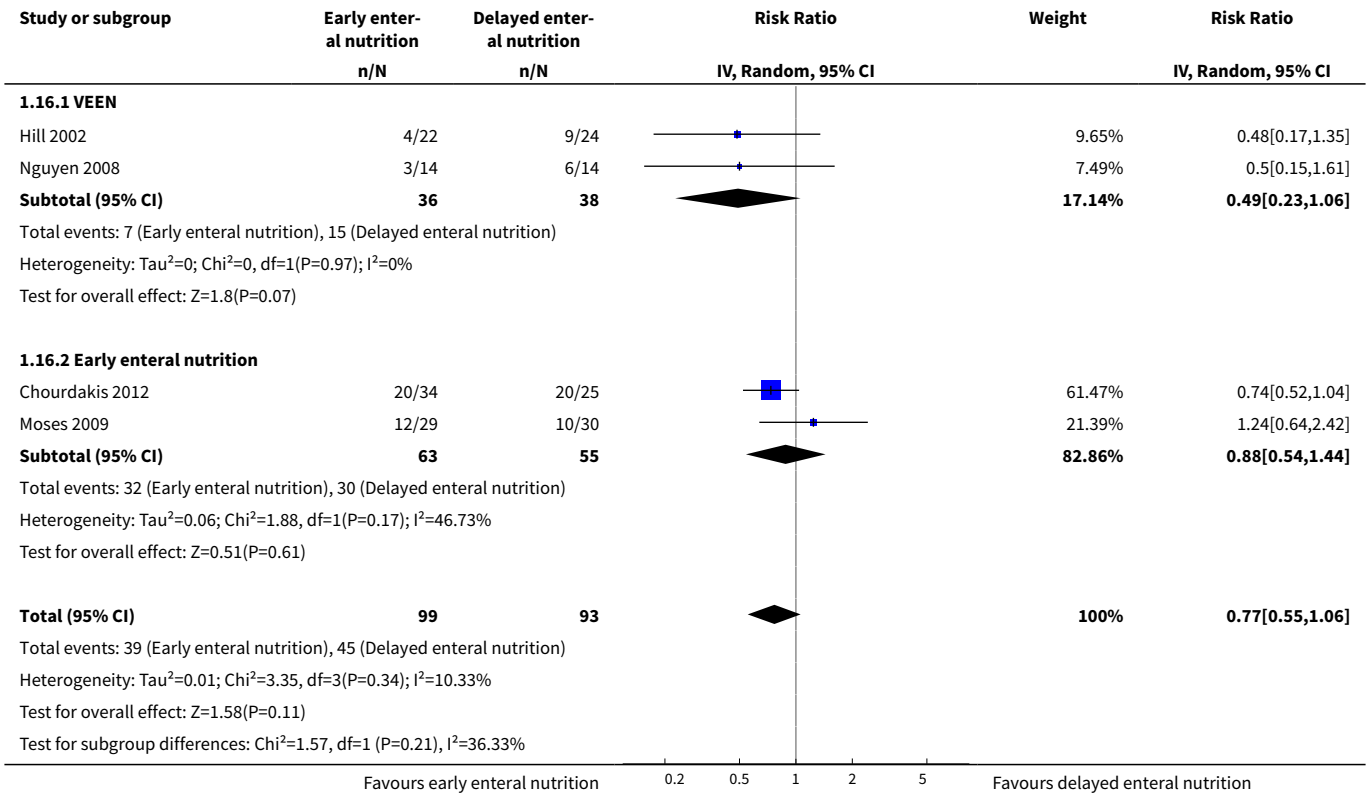


Analysis 1.15. Comparison 1 Early enteral nutrition versus delayed enteral nutrition, Outcome 15 Pneumonia (subgroup analysis by trauma).





Analysis 1.16. Comparison 1 Early enteral nutrition versus delayed enteral nutrition, Outcome 16 Pneumonia (subgroup analysis by VEEN).



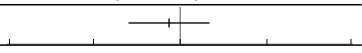
Comparison 2. Early enteral nutrition with supplemental parenteral nutrition (SPN) compared to delayed enteral nutrition with SPN for critically ill adults

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2 Infectious complications	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Length of ICU stay	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Duration of mechanical ventilation	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

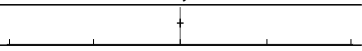
Analysis 2.1. Comparison 2 Early enteral nutrition with supplemental parenteral nutrition (SPN) compared to delayed enteral nutrition with SPN for critically ill adults, Outcome 1 Mortality.

Study or subgroup	Early enteral nutrition n/N	Delayed enteral nutrition n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Peck 2004	4/14	5/13		0.74[0.25,2.18]



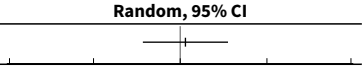
Analysis 2.2. Comparison 2 Early enteral nutrition with supplemental parenteral nutrition (SPN) compared to delayed enteral nutrition with SPN for critically ill adults, Outcome 2 Infectious complications.

Study or subgroup	Early enteral nutrition N	Mean(SD)	Delayed enteral nutriton N	Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Peck 2004	14	3 (2)	13	3 (3)		0[-1.94,1.94]



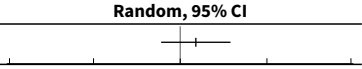
Analysis 2.3. Comparison 2 Early enteral nutrition with supplemental parenteral nutrition (SPN) compared to delayed enteral nutrition with SPN for critically ill adults, Outcome 3 Length of ICU stay.

Study or subgroup	Early enteral nutrition N	Mean(SD)	Delayed enteral nutrition N	Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Peck 2004	14	40 (32)	13	37 (33)		3[-21.55,27.55]



Analysis 2.4. Comparison 2 Early enteral nutrition with supplemental parenteral nutrition (SPN) compared to delayed enteral nutrition with SPN for critically ill adults, Outcome 4 Duration of mechanical ventilation.

Study or subgroup	Early enteral nutrition N	Mean(SD)	Delayed enteral nutrition N	Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Peck 2004	14	32 (27)	13	23 (26)		9[-10.99,28.99]



ADDITIONAL TABLES

Table 1. Infectious complications

Study	Participants	Events in early enteral group	Events in delayed enteral group	P value (reported by study authors)	Events included as infectious complications
Chourdakis 2012	59	28 (N = 34 participants)	29 (N = 25 participants)	not reported	VAP, non-VAP, CNS infection, bacteraemia, urinary system infection
Eyer 1993	38	29 (N = 19 participants)	14 (N = 19 participants)	P < 0.05	pneumonia, urinary tract infection, abdominal abscess, wound infection, catheter sepsis, bacteraemia, sinusitis, eye infection
Moses 2009	59	17 events in 14 participants (N = 29 participants)	19 events in 15 participants (N = 30 participants)	not reported	VAP, catheter-related bloodstream infection, urinary tract infection

Acronyms and abbreviations used in this table
CNS: central nervous system; non-VAP: non ventilator-associated pneumonia; VAP: ventilator-associated pneumonia.

Table 2. Pneumonia

Study	Definition of events included in the outcome
Chourdakis 2012	VAP and non-VAP (definitions were not reported)
Eyer 1993	Pneumonia was defined as significant growth on sputum culture with < 10 epithelial cells, > 25 leukocytes/HPF on a Gram stain of tracheal secretions and a new infiltrate on chest films, or increased purulent tracheal secretions associated with new fever or elevated WBC (tracheobronchitis).
Hill 2002	Pneumonia definition was not reported.
Moses 2009	VAP was defined as the appearance of a new or progressive pulmonary infiltrate, and any two of the following: (a) temperature > 38 °C or < 36 °C, (b) WBC count > 10,000 or < 4000/µL, (c) purulent tracheobronchial secretions. Quantitative endotracheal aspirates with cultures were performed in patients suspected to have VAP, with ≥ 105 colony-forming units taken as significant.
Nguyen 2008	VAP was defined as the presence of a new or progressive infiltrate with at least two of the following signs and symptoms: (a) purulent respiratory secretions; (b) fever (body temperature > 38 °C) or hypothermia (body temperature < 35 °C); or (c) leukocytosis (WCB ≥ 10,000/mm^3), or leukopenia (total white blood cell count < 4500/mm^3 or > 15% immature neutrophils, regardless of total peripheral WBC count)

Acronyms and abbreviations used in this table
EN: enteral nutrition; HPF: high-power field; non-VAP: non ventilator-associated pneumonia; VAP: ventilator-associated pneumonia; WBC: white blood cell.

APPENDICES

Appendix 1. 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, or proteins, minerals, vitamins, trace elements, or a combination.

Hypocaloric or underfeeding: an energy administration below 70% of the defined target.

Isocaloric diet or full feeding: an energy administration of approximately the defined target (over 70% of the defined target).

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 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: 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, such as powder, dessert-style, or bars.

Overfeeding: energy administration of 110% above the defined target.

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

1. central: using a central venous catheter to deliver parenteral nutrition directly into a large-diameter vein, such as the superior vena cava, adjacent to the right atrium;
2. peripheral: using a narrow gauge peripheral venous cannula to deliver parenteral nutrition into a peripheral vein, usually in the forearm.

Supplemental parenteral nutrition (SPN): parenteral nutrition combined with enteral nutrition, for example when enteral nutrition alone is unlikely to meet the target nutritional goals.

These definitions are based on ASPEN 2015, ASPEN 2016, and Lochs 2006.

Appendix 2. Electronic searches

CENTRAL; 2019, Issue 4 in the Cochrane Library (searched April 2019)

#1 MeSH descriptor: [Enteral Nutrition] explode all trees
#2 MeSH descriptor: [Nutritional Support] explode all trees

#3 (enteral next nutrition*):TI,AB,KW

#4 (enteral next feed*):TI,AB,KW

#5 (tube next feed*):TI,AB,KW

#6 (nutritional next support):TI,AB,KW

#7 (nutrition next support):TI,AB,KW

#8 nasogastric:TI,AB,KW

#9 nasoenteral:TI,AB,KW

#10 (percutaneous next tube*):TI,AB,KW

#11 (oral next feed*):TI,AB,KW

#12 (sip next feed*):TI,AB,KW

#13 (tube next feed*):TI,AB,KW

#14 (gastrostomy next tube*):TI,AB,KW

#15 (jejunostomy next tube*):TI,AB,KW

#16 (gastric next feed*):TI,AB,KW

#17 (Nutrition next Enteral):TI,AB,KW

#18 (Artificial next Feeding):TI,AB,KW

#19 (feeding next tube*):TI,AB,KW

#20 (enteral next formula):TI,AB,KW

#21 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20

#22 MeSH descriptor: [Time-to-Treatment] explode all trees

#23 MeSH descriptor: [Time Factors] explode all trees

#24 early:TI,AB,KW

#25 earlier:TI,AB,KW

#26 late:TI,AB,KW

#27 later*:TI,AB,KW

#28 delay*:TI,AB,KW

#29 time:TI,AB,KW

#30 timely:TI,AB,KW

#31 timing:TI,AB,KW

#32 hour:TI,AB,KW

#33 hours:TI,AB,KW

#34 soon:TI,AB,KW

#35 sooner:TI,AB,KW

#36 (window next of next opportunity):TI,AB,KW

#37 #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36

#38 MeSH descriptor: [Critical Illness] explode all trees

#39 MeSH descriptor: [Critical Care] explode all trees

#40 MeSH descriptor: [Intensive Care Units] explode all trees

#41 (critical* NEAR ill*):TI,AB,KW

#42 (intensive NEAR care):TI,AB,KW

#43 (critical NEAR care):TI,AB,KW

#44 ICU:TI,AB,KW

#45 (head NEAR injur*):TI,AB,KW

#46 #38 OR #39 OR #40 OR #41 OR #42 OR 43 OR #44 OR #45

#47 #21 AND #37 AND #46, in Trials

MEDLINE Ovid ALL (1946 to April 2019)

1 Enteral Nutrition/

2 Nutritional Support/

3 enteral nutrition*.ti,ab,kw.

4 enteral feed*.ti,ab,kw.

5 tube feed*.ti,ab,kw.

6 nutritional support.ti,ab,kw.

7 nutrition support.ti,ab,kw.

8 nasogastric.ti,ab,kw.

9 nasoenteral.ti,ab,kw.

10 percutaneous tube*.ti,ab,kw.

11 oral feed*.ti,ab,kw.

12 sip feed*.ti,ab,kw.

13 tube feed*.ti,ab,kw.

14 gastrostomy tube*.ti,ab,kw.

15 jejunostomy tube*.ti,ab,kw.

16 gastric feed*.ti,ab,kw.

17 Nutrition Enteral.ti,ab,kw.

18 Artificial Feeding.ti,ab,kw.

19 feeding tube*.ti,ab,kw.

20 enteral formula.ti,ab,kw.

21 or/1-20

22 Time-to-Treatment/

23 Time factors/

24 early.ti,ab,kw.

25 earlier.ti,ab,kw.

26 late.ti,ab,kw.

27 later*.ti,ab,kw.

28 delay*.ti,ab,kw.

29 time.ti,ab,kw.

30 timely.ti,ab,kw.

31 timing.ti,ab,kw.

32 hour.ti,ab,kw.

33 hours.ti,ab,kw.

34 soon.ti,ab,kw.

35 sooner.ti,ab,kw.

36 window of opportunity.ti,ab,kw.

37 or/22-36

38 Critical Illness/

39 Critical Care/

40 Intensive Care Units/

41 (critical* adj3 ill*).ti,ab,kw.

42 (intensive adj2 care).ti,ab,kw.

43 ICU.ti,ab,kw.

44 ((head or burn) adj3 injur*).ti,ab,kw.

45 (critical adj2 care).ti,ab,kw.

46 or/38-45

47 randomized controlled trial.pt.

48 controlled clinical trial.pt.

49 randomi?ed.ab.

50 placebo.ab.

51 drug therapy.fs.

52 randomly.ab.

53 trial.ab.

54 groups.ab.

55 or/47-54

56 exp animals/ not humans.sh.

57 55 not 56

58 21 and 37 and 46 and 57

Embase Ovid (1974 to April 2019)

1 exp enteric feeding/

2 exp nutritional support/

3 enteral nutrition*.ti,ab.

4 enteral feed*.ti,ab.

5 tube feed*.ti,ab.

6 nutritional support.ti,ab.

7 nutrition support.ti,ab.

8 nasogastric.ti,ab.

9 nasoenteral.ti,ab.

10 percutaneous tube*.ti,ab.

11 oral feed*.ti,ab.

12 sip feed*.ti,ab.

13 tube feed*.ti,ab.

14 gastrostomy tube*.ti,ab.

15 jejunostomy tube*.ti,ab.

16 gastric feed*.ti,ab.

17 Nutrition Enteral.ti,ab.

18 Artificial Feeding.ti,ab.

19 feeding tube*.ti,ab.

20 enteral formula.ti,ab.

21 or/1-20

22 exp time factor/

23 early.ti,ab.

24 earlier.ti,ab.

25 late.ti,ab.

26 later*.ti,ab.

27 delay*.ti,ab.

28 time.ti,ab.

29 timely.ti,ab.

30 timing.ti,ab.

31 hour.ti,ab.

32 hours.ti,ab.

33 soon.ti,ab.

34 sooner.ti,ab.

35 window of opportunity.ti,ab.

36 or/22-35

37 exp critical illness/

38 exp intensive care/

39 exp intensive care unit/

40 (critical* adj3 ill*).ti,ab.

41 (intensive adj2 care).ti,ab.

42 ICU.ti,ab.

43 (head adj3 injur*).ti,ab.

44 intensive care.ti,ab.

45 critical care.ti,ab.

46 critically ill.ti,ab.

47 or/37-46

48 randomized controlled trial/

49 controlled clinical trial/

50 random*.ti,ab.

51 randomization/

52 intermethod comparison/

53 placebo.ti,ab.

54 (compare or compared or comparison).ti.

55 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.

56 (open adj label).ti,ab.

57 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.

58 double blind procedure/

59 parallel group$1.ti,ab.

60 (crossover or cross over).ti,ab.

61 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.

62 (assigned or allocated).ti,ab.

63 (controlled adj7 (study or design or trial)).ti,ab.

64 (volunteer or volunteers).ti,ab.

65 trial.ti.

66 or/48-65

67 21 and 36 and 47 and 66

CINAHL EBSCO (1982 to April 2019)

S1 MM "Enteral Nutrition"

S2 MM "Enteral Nutrition"

S3 MM "Nutritional Support"

S4 TX "enteral nutrition*"

S5 TX "enteral feed*"

S6 TX "tube feed*"

S7 TX "nutritional support"

S8 TX "nutrition support"

S9 TX nasogastric

S10 TX nasoenteral

S11 TX "percutaneous tube*"

S12 TX "oral feed*"

S13 TX "sip feed*"

S14 TX "tube feed*"

S15 TX "gastrostomy tube*"

S16 TX "jejunostomy tube*"

S17 TX "gastric feed*"

S18 TX "Nutrition Enteral"

S19 TX "Artificial Feeding"

S20 TX "feeding tube*"

S21 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20

S22 MM "Time Factors"

S23 TX early

S24 TX earlier

S25 TX late

S26 TX later*

S27 TX delay*

S28 TX time

S29 TX timely

S30 TX timing

S31 TX hour

S32 TX hours

S33 TX soon

S34 TX sooner

S35 TX "window of opportunity"

S36 S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35

S37 MM "Critical Illness"

S38 MH "Intensive Care Units+"

S39 MH "Critical Care+"

S40 TX (critical* N3 ill*)

S41 TX (intensive N2 care)

S42 TX ICU

S43 TX (head N3 injur*)

S44 TX "intensive care"

S45 TX "critical care"

S46 TX "critically ill"

S47 S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46

S48 MH "Clinical Trials"

S49 TX trial

S50 TX "single-blind*"

S51 TX "double-blind*"

S52 TX "treatment as usual"

S53 TX randomly

S54 S48 OR S49 OR S50 OR S51 OR S52 OR S53

S55 S21 AND S36 AND S47 AND S54

ISI Web of Science includes: Web of Science (1945 to April 2019); BIOSIS Previews (1926 to April 2019); MEDLINE (1950 to April 2019)

#1 TS=("Enteral Nutrition" OR "Nutritional Support" OR "enteral feed*")
#2 TS=(early OR earlier OR late OR later)
#3 TS=("Critical Care" OR ICU OR "Intensive Care Unit*")
#4 TS=(randomly OR randomised OR randomized OR "random allocat*" OR RCT OR CCT OR "double blind*" OR "single blind*" OR "double blind*" OR "single blind*")
#5 #4 AND #3 AND #2 AND #1

Appendix 3. Study selection form

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

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

Study eligibility

Study characteristics	**Eligibility criteria**	**Eligibility criteria met?**			**Location in text or source**
		Yes	**No**	**Unclear**	
Type of study	Randomized controlled trial				

(Continued)

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 (measured in-hospital within 30 days, within 90 days, and within 180 days)	
	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. ICU mortality	
	5. Length of ICU stay	
	6. Hospital length of stay	
	7. Duration of mechanical ventilation in days (follow-up from the day of starting mechanical ventilation (invasive or non-invasive) until discontinued)	
	8. Weaning failure (the re-initiation of mechanical ventilation after discontinuation, or the requirement for protracted mechanical ventilation)	
	9.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
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	

(Continued)

Withdrawals and exclusions *(if not provided below by outcome)*
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)
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 (measured in hospital within 30 days, within 90 days, and within 180 days)	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 Hospital length of stay	Yes/No
Outcome 7 Duration of mechanical ventilation in days	Yes/No
Outcome 8 Weaning failure	Yes/No
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)	

(Continued)

Outcome 5. Length of ICU stay in days
Outcome 6. Length of hospital stay in days
Outcome 7. Duration of mechanical ventilation in days
Other outcome
Other information that 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 (measured in-hospital within 30 days, within 90 days, and within 180 days)			
Outcome 2. Infectious complications, independent of specific site			
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 that you feel is relevant to the results			

Results	**data**
Number of participants allocated to each treatment arm	
Number who received each treatment arm	
Number who did not receive intended treatment and why	
Number followed up	
Number lost to follow-up and why	

(Continued)

Number included in the final analysis
Analysis
Method
Sample size details
Reported effect size
Authors conclusions
Funding source
Reviewer comments

'Risk of bias' assessment

Domain	Support for judgement	Judgement
Random sequence generation *Was the allocation sequence adequately generated?*		Low High Unclear
Allocation concealment *Was allocation adequately concealed?*		Low High Unclear
Blinding of participants and personnel *Was knowledge of the allocated intervention adequately prevented during the study?*		Low High Unclear
Blinding of outcome assessment *Was knowledge of the allocated intervention adequately prevented during the study?*		Low High Unclear
Incomplete outcome data *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*		Low High Unclear
Selective outcome reporting *Are reports of the study free of suggestion of selective outcome reporting?*		Low High Unclear

(Continued)

Other bias	Low
Role of possible conflicts of interest for study authors	High
	Unclear

Appendix 5. Assessment of risk of bias in included studies

Random sequence generation

We considered that there was a low risk of bias for allocation sequence generation when it was generated by a computer or a random number table algorithm, coin tossing, shuffling cards, envelopes, throwing dice, drawing lots, or minimisation (it may be implemented without a random element and this is considered to be equivalent to being random).

Allocation concealment

We considered that there was a low risk of bias for allocation concealment when the participant recruiters and investigators enrolling participants were unable to anticipate the treatment assignment. Adequate methods included 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 described the methods used, if any, by each included study to blind study participants and personnel from knowing which intervention a participant received. We judged studies at 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 were comatose.

Blinding of outcome assessment

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

Incomplete outcome data

We considered that there was a low risk of bias for incomplete outcome data if any of the following criteria were fulfilled: no missing outcome data; the reasons for missing outcome data were unlikely to be related to true outcome (for survival data, censoring was unlikely to introduce bias); missing outcome data were 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 was not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, the plausible effect size (mean difference or standardised mean difference) among missing outcomes was not enough to have a clinically relevant impact on the observed effect size or missing data were imputed using appropriate methods.

Selective outcome reporting

We considered that there was a low risk of selective reporting bias if any one of the following criteria were fulfilled: the study protocol was available and all of the study's prespecified (primary and secondary) outcomes that were of interest for the systematic review were reported in the prespecified way; or when the study protocol was not available, but it was clear that the published reports included all expected outcomes, including those that were prespecified (convincing text of this nature may be uncommon).

Other bias

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

WHAT'S NEW

Date	Event	Description
14 November 2019	Amended	Figure 1 updated to improve view

HISTORY

Protocol first published: Issue 9, 2016
Review first published: Issue 10, 2019

Date	Event	Description
31 October 2019	Amended	Figure 1 updated to improve view
3 January 2019	Amended	Editorial team changed to Cochrane Emergency and Critical Care

CONTRIBUTIONS OF AUTHORS

Paulina Fuentes Padilla (PFP), Gabriel Martinez (GM), Robin WM Vernooij (RV), Gerard Urrútia (GU), Marta Roqué i Figuls (MRF), Xavier Bonfill Cosp (XBC).

Conceiving the review: PFP, GM, RV

Co-ordinating the review: PFP

Undertaking manual searches: PFP, GM, RV

Screening search results: PFP, GM, RV

Organizing retrieval of papers: PFP, GM

Screening retrieved papers against inclusion criteria: PFP, GM, RV

Appraising quality of papers: PFP, GM, RV

Abstracting data from papers: PFP, GM, RV

Writing to authors of papers for additional information: PFP, GM

Providing additional data about papers: PFP

Obtaining and screening data on unpublished studies: PFP

Data management for the review: PFP

Entering data into Review Manager 5 (RevMan 5): PFP, GM, RV

RevMan 5 statistical analysis: PFP, RV, MRF

Other statistical analysis not using RevMan 5: MRF, RV

Interpretation of data: All authors

Statistical inferences: All authors

Writing the review: PFP, GM, RV

Securing funding for the review: None

Guarantor for the review (one author): PFP

Person responsible for reading and checking review before submission: XB, GU, MRF

DECLARATIONS OF INTEREST

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.

Gabriel Martinez: none known

Robin WM Vernooij: none known

Gerard Urrútia has received consultant fees from Novartis and payments for methodological workshops (critical appraisal) from RIMA, Novartis, MSD, and GSK (addressed to lab representatives or doctors).

Marta Roqué i Figuls: none known

Xavier Bonfill Cosp: none known

SOURCES OF SUPPORT

Internal sources

- Iberoamerican Cochrane Centre, Barcelona, Spain.
- Universitat Autònoma de Barcelona, Barcelona, Spain.

External sources

- National Commission for Scientific and Technological Research (CONICYT), Chile.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes from the published Cochrane Review protocol (Fuentes Padilla 2016).

1. The title "Early versus delayed enteral nutrition support for critically ill adults" was changed to "Early enteral nutrition (within 48 hours) versus delayed enteral nutrition (after 48 hours) with or without supplemental parenteral nutrition in critically ill adults", in order to accurately reflect the review question.
2. In the Types of studies section, we made explicit that we would exclude cross-over trials, as they are unsuitable for the comparisons conducted in the review.
3. According to the available source of database searches, we changed the start date of the search for Embase Ovid (1966 to 1974), and ISI Web of Science (1973 to 1945).
4. For Types of outcome measures, we redefined the outcome 'mortality' to avoid the potential heterogeneity of follow-up times among the included studies. We modified the outcome 'mortality' (at the end of the follow-up) to 'mortality' (measured: in hospital within 30 days, within 90 days, and within 180 days). For the outcome 'infectious complications' and 'pneumonia', we clarified that we collected information on tallies of infectious complications and pneumonia, as well as on the risk of infectious complications and pneumonia.
5. In the Assessment of risk of bias in included studies section, we removed the sentences: "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". The aforementioned was removed in order to avoid a summary of the overall risk of bias of a review as a whole, following the recommendations of Higgins 2011.
6. In the Measures of treatment effect section, we added that: "For count variables collecting the number of events, we had intended to calculate rate ratios with 95% CI to combine trials that measure the same outcome (infectious complications and pneumonia)". The aforementioned was added to clarify the results.
7. In the Unit of analysis issues section, we added that: "No cluster trials were included, and therefore, no adjustment was necessary for clustering. If cluster trials are included in the future, we will use the analytical methods described by the *Cochrane Handbook for Systematic Reviews of Interventions*".
8. In the Data synthesis section, we clarified that: "We pooled the treatment effect measures across studies with the generic inverse variance method in all cases, based on the DerSimonian and Laird method (DerSimonian 1986). We assumed that there would be clinical heterogeneity due to the diversity of the patients, therefore, we used random-effects models throughout". This did not change any of our results in terms of statistical significance.
9. As we explained before, we did not use the overall risk of bias of the included studies. By the aforementioned, we amended the Sensitivity analysis to: "We planned to perform sensitivity analyses, excluding all the studies that we judged at high or unclear risk of selection and performance risk of bias, as determined with the Cochrane tool for assessing risk of bias (Higgins 2011). We aimed to perform sensitivity analyses on primary outcomes".

INDEX TERMS

Medical Subject Headings (MeSH)

Combined Modality Therapy [methods]; Critical Illness [*therapy]; Enteral Nutrition [*methods]; Humans; Intensive Care Units; Malnutrition [prevention & control]; Parenteral Nutrition [*methods]; Randomized Controlled Trials as Topic; Time Factors