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Enteral versus parenteral nutrition and enteral versus a combination of enteral and parenteral nutrition for adults in the intensive care unit (Review)

Lewis SR, Schofield-Robinson OJ, Alderson P, Smith AF

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[Intervention Review]

Enteral versus parenteral nutrition and enteral versus a combination of enteral and parenteral nutrition for adults in the intensive care unit

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ABSTRACT

Background

Critically ill people are at increased risk of malnutrition. Acute and chronic illness, trauma and inflammation induce stress-related catabolism, and drug-induced adverse effects may reduce appetite or increase nausea and vomiting. In addition, patient management in the intensive care unit (ICU) may also interrupt feeding routines. Methods to deliver nutritional requirements include provision of enteral nutrition (EN), or parenteral nutrition (PN), or a combination of both (EN and PN). However, each method is problematic. This review aimed to determine the route of delivery that optimizes uptake of nutrition.

Objectives

To compare the effects of enteral versus parenteral methods of nutrition, and the effects of enteral versus a combination of enteral and parenteral methods of nutrition, among critically ill adults, in terms of mortality, number of ICU-free days up to day 28, and adverse events.

Search methods

We searched CENTRAL, MEDLINE, and Embase on 3 October 2017. We searched clinical trials registries and grey literature, and handsearched reference lists of included studies and related reviews.

Selection criteria

We included randomized controlled studies (RCTs) and quasi-randomized studies comparing EN given to adults in the ICU versus PN or versus EN and PN. We included participants that were trauma, emergency, and postsurgical patients in the ICU.

Data collection and analysis

Two review authors independently assessed studies for inclusion, extracted data, and assessed risk of bias. We assessed the certainty of evidence with GRADE.

Main results

We included 25 studies with 8816 participants; 23 studies were RCTs and two were quasi-randomized studies. All included participants were critically ill in the ICU with a wide range of diagnoses; mechanical ventilation status between study participants varied. We identified 11 studies awaiting classification for which we were unable to assess eligibility, and two ongoing studies.

Seventeen studies compared EN versus PN, six compared EN versus EN and PN, two were multi-arm studies comparing EN versus PN versus EN and PN. Most studies reported randomization and allocation concealment inadequately. Most studies reported no methods to blind personnel or outcome assessors to nutrition groups; one study used adequate methods to reduce risk of performance bias.

Enteral nutrition versus parenteral nutrition

We found that one feeding route rather than the other (EN or PN) may make little or no difference to mortality in hospital (risk ratio (RR) 1.19, 95% confidence interval (CI) 0.80 to 1.77; 361 participants; 6 studies; low-certainty evidence), or mortality within 30 days (RR 1.02, 95% CI 0.92 to 1.13; 3148 participants; 11 studies; low-certainty evidence). It is uncertain whether one feeding route rather than the other reduces mortality within 90 days because the certainty of the evidence is very low (RR 1.06, 95% CI 0.95 to 1.17; 2461 participants; 3 studies). One study reported mortality at one to four months and we did not combine this in the analysis; we reported this data as mortality within 180 days and it is uncertain whether EN or PN affects the number of deaths within 180 days because the certainty of the evidence is very low (RR 0.33, 95% CI 0.04 to 2.97; 46 participants).

No studies reported number of ICU-free days up to day 28, and one study reported number of ventilator-free days up to day 28 and it is uncertain whether one feeding route rather than the other reduces the number of ventilator-free days up to day 28 because the certainty of the evidence is very low (mean difference, inverse variance, 0.00, 95% CI -0.97 to 0.97; 2388 participants).

We combined data for adverse events reported by more than one study. It is uncertain whether EN or PN affects aspiration because the certainty of the evidence is very low (RR 1.53, 95% CI 0.46 to 5.03; 2437 participants; 2 studies), and we found that one feeding route rather than the other may make little or no difference to pneumonia (RR 1.10, 95% CI 0.82 to 1.48; 415 participants; 7 studies; low-certainty evidence). We found that EN may reduce sepsis (RR 0.59, 95% CI 0.37 to 0.95; 361 participants; 7 studies; low-certainty evidence), and it is uncertain whether PN reduces vomiting because the certainty of the evidence is very low (RR 3.42, 95% CI 1.15 to 10.16; 2525 participants; 3 studies).

Enteral nutrition versus enteral nutrition and parenteral nutrition

We found that one feeding regimen rather than another (EN or combined EN or PN) may make little or no difference to mortality in hospital (RR 0.99, 95% CI 0.84 to 1.16; 5111 participants; 5 studies; low-certainty evidence), and at 90 days (RR 1.00, 95% CI 0.86 to 1.18; 4760 participants; 2 studies; low-certainty evidence). It is uncertain whether combined EN and PN leads to fewer deaths at 30 days because the certainty of the evidence is very low (RR 1.64, 95% CI 1.06 to 2.54; 409 participants; 3 studies). It is uncertain whether one feeding regimen rather than another reduces mortality within 180 days because the certainty of the evidence is very low (RR 1.00, 95% CI 0.65 to 1.55; 120 participants; 1 study).

No studies reported number of ICU-free days or ventilator-free days up to day 28. It is uncertain whether either feeding method reduces pneumonia because the certainty of the evidence is very low (RR 1.40, 95% CI 0.91 to 2.15; 205 participants; 2 studies). No studies reported aspiration, sepsis, or vomiting.

Authors' conclusions

We found insufficient evidence to determine whether EN is better or worse than PN, or than combined EN and PN for mortality in hospital, at 90 days and at 180 days, and on the number of ventilator-free days and adverse events. We found fewer deaths at 30 days when studies gave combined EN and PN, and reduced sepsis for EN rather than PN. We found no studies that reported number of ICU-free days up to day 28. Certainty of the evidence for all outcomes is either low or very low. The 11 studies awaiting classification may alter the conclusions of the review once assessed.

PLAIN LANGUAGE SUMMARY

Delivery of nutrition (food) to critically ill adults other than by the person eating and swallowing the food/nutrition

Background

Critically ill adults in the intensive care unit (ICU) are at an increased risk of malnutrition because the body responds to serious illness or injury by increasing the metabolic rate. Also, the person's feeding routine may be disrupted because they are unconscious or too ill to feed themselves or eat normally. This means alternative ways to ensure people receive adequate nutrition must be used. People may be given artificial nutrition in three ways: enteral feeding (through a tube placed into the stomach or small intestine; parenteral feeding (through a tube inserted into a vein whereby nutrients enter the bloodstream directly); or by a combination of both routes. This review compared the effects of these routes.

Study characteristics

The evidence is current to 3 October 2017. We included 25 studies with 8816 participants who had trauma, emergency, medical or postsurgical conditions and were in the ICU. Eleven studies are awaiting classification (because we did not have enough details to assess them) and two studies are ongoing. Included studies compared enteral feeding with parenteral feeding, or with combined enteral and parenteral feeding.

Key results

Studies reported the number of people who died from any cause at different time points. We found no evidence that enteral feeding compared to parenteral feeding or compared to a combination of routes was more or less likely to reduce the number of deaths in hospital, within 90 days and 180 days. We found evidence from three small studies that fewer people died within 30 days when feeding was given through combined enteral and parenteral routes. No studies reported number of ICU-free days up to day 28 (i.e. length of stay in the ICU by taking account of expected participant loss because of death) and one study reported that the feeding route did not affect the number of ventilator-free days.

We found no evidence that enteral feeding compared to parenteral feeding was likely to increase or decrease cases of aspiration (the entry of materials such as food from the digestive system to the lungs) or pneumonia (swelling of the tissue in one or both lungs that is usually caused by a bacterial infection). Enteral nutrition may reduce sepsis (a life-threatening condition that arises when the body's response to infection causes injury to its own tissues and organs), although evidence was from studies of people with different conditions (such as trauma, medical, or postsurgical conditions). We found that fewer participants vomited if they were given parenteral feeding rather than enteral feeding, although there were few studies with very few reported events.

Certainty of the evidence

It was not possible for researchers to mask the ICU staff to the type of feeding route, which may have biased the findings, and study authors did not consistently report good study methods. People in each study had different types of critical illness (such as trauma, medical, or postsurgical conditions) which may have affected how they responded to the type of feeding route, and there were limited data for many of our measurements. We believed that the certainty of the evidence was low or very low.

Conclusion

We found insufficient evidence to determine with confidence whether one feeding route was better at reducing the number of deaths, the number of ventilator-free days, and side effects. No studies reported number of ICU-free days up to day 28. Evidence was of low and very low certainty, and we could not be confident in the findings of our review.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Enteral versus parenteral nutrition for adults in the intensive care unit

Enteral versus parenteral nutrition for adults in the intensive care unit

Patient or population: critically ill adults admitted to the ICU for trauma, emergency, or surgical care; population excluded people with acute pancreatitis
Setting: intensive care units in: Brazil, China, Germany, Iran, Italy, Turkey, UK, and USA
Intervention: EN
Comparison: PN

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)
	Risk with EN	Risk with PN			
Mortality	**In-hospital mortality**		**RR 1.19** (0.80 to 1.77)	361 (6 studies)	⊕⊕⊖⊖ **Low**[a]
	Study population				
	229 per 1000 (154 to 340)	192 per 1000			
	Mortality within 30 days		**RR 1.02** (0.92 to 1.13)	3148 (11 studies)	⊕⊕⊖⊖ **Low**[b]
	Study population				
	304 per 1000 (274 to 336)	298 per 1000			
	Mortality within 90 days		**RR 1.06** (0.95 to 1.17)	2461 (3 studies)	⊕⊖⊖⊖ **Very low**[c]
	Study population				
	393 per 1000 (352 to 434)	371 per 1000			
	Mortality within 180 days		**RR 0.33** (0.04 to 2.97)	46 (1 study)	⊕⊖⊖⊖ **Very low**[d]
	Study population				
	130 per 1000	43 per 1000 (5 in 387)			

Number of ICU-free days up to day 28	–	–	–	–	Not measured
Number of ventilator-free days up to day 28	Mean number of ventilator-free days: 14.2 (SD ± 12.2)	Mean difference 0 days (0.97 fewer to 0.97 more)	N/A	2388 (1 study)	⊕⊖⊖⊖ **Very low**[d]
Adverse events: aspiration (as reported by study authors at end of study follow-up period)	Study population 5 per 1000 (2 to 17)	3 per 1000	**RR 1.53** (0.46 to 5.03)	2437 (2 studies)	⊕⊖⊖⊖ **Very low**[e]
Adverse events: sepsis (as reported by study authors at end of study follow-up period)	Study population 123 per 1000 (77 to 199)	209 per 1000	**RR 0.59** (0.37 to 0.95)	361 (7 studies)	⊕⊕⊖⊖ **Low**[f]
Adverse events: pneumonia (as reported by study authors at end of study follow-up period)	Study population 314 per 1000 (234 to 423)	268 per 1000	**RR 1.10** (0.82 to 1.48)	415 (7 studies)	⊕⊕⊖⊖ **Low**[f]
Adverse events: vomiting (as reported by study authors at end of study follow-up period)	Study population 11 per 1000 (4 to 32)	3 per 1000	**RR 3.42** (1.15 to 10.16)	2525 (3 studies)	⊕⊖⊖⊖ **Very low**[g]

*__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; **EN:** enteral nutrition; **ICU:** intensive care unit; **N/A:** not applicable; **PN:** parenteral nutrition; **RR:** risk ratio; **SD:** standard deviation.

GRADE Working Group grades of evidence
High: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate: 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: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]All studies had a high risk of performance bias; downgraded one level for study limitations. Studies included a variety of primary diagnoses and evidence was less direct; downgraded one level for indirectness.
[b]All studies had a high risk of performance bias; downgraded one level for study limitations. Studies included a variety of primary diagnoses and study designs and evidence were less direct; downgraded one level for indirectness.

[c]All studies had a high risk of performance bias; downgraded one level for study limitations. Studies included a variety of primary diagnoses and study designs and evidence were less direct; downgraded one level for indirectness. Few studies and one included study had a large number of participants relative to other included studies; downgraded one level for imprecision.

[d]Data from only one study that had a high risk of performance bias; downgraded one level for study limitations and two levels for imprecision.

[e]All studies had a high risk of performance bias; downgraded one level for study limitations. Studies included a variety of primary diagnoses and evidence was less direct; downgraded one level for indirectness. Few studies and one included study had a large number of participants relative to other included studies; downgraded one level for imprecision.

[f]All studies had a high risk of performance bias; downgraded one level for study limitations. Studies included a variety of primary diagnoses and evidence was less direct; downgraded one level for indirectness.

[g]All studies had a high risk of performance bias; downgraded one level for study limitations. Studies included a variety of primary diagnoses and study designs and evidence were less direct; downgraded one level for indirectness. Few studies, with very few events, and one included study had a large number of participants relative to other included studies; downgraded one level for imprecision.

Summary of findings 2. Enteral versus enteral and parenteral nutrition for adults in the intensive care unit

Enteral versus enteral and parenteral nutrition for adults in the intensive care unit

Patient or population: critically ill adults admitted to the ICU for trauma, emergency, or post-surgical care; population excludes participants with acute pancreatitis
Setting: intensive care units in: France, Italy, Switzerland, Turkey, and USA
Intervention: EN
Comparison: EN + PN

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)
	Risk with EN	Risk with EN + PN			
Mortality	**In-hospital mortality**		**RR 0.99** (0.84 to 1.16)	5111 (5 studies)	⊕⊕⊖⊖ **Low**[a]
	Study population				
	106 per 1000 (90 to 124)	107 per 1000			
	Mortality within 30 days		**RR 1.64** (1.06 to 2.54)	409 (3 studies)	⊕⊖⊖⊖ **Very low**[b]
	Study population				
	216 per 1000 (140 to 335)	132 per 1000			
	Mortality within 90 days		**RR 1.00** (0.86 to 1.18)	4760 (2 studies)	⊕⊕⊖⊖ **Low**[c]
	Study population				

	115 per 1000 (99 to 135)	115 per 1000			
	Mortality within 180 days		**RR 1.00** (0.65 to 1.55)	120 (1 RCT)	⊕⊖⊖⊖ **Very low**[d]
	Study population				
	400 per 1000 (260 to 620)	400 per 1000			
Number of ICU-free days up to day 28	–	–	–	–	Not measured
Number of ventilator-free days up to day 28	–	–	–	–	Not measured
Adverse events: aspiration (as reported by study authors at end of study follow-up period)	–	–	–	–	Not measured
Adverse events: sepsis (as reported by study authors at end of study follow-up period)	–	–	–	–	Not measured
Adverse events: pneumonia (as reported by study authors at end of study follow-up period)	350 per 1000 (228 to 538)	250 per 1000	**RR 1.40** (0.91 to 2.15)	205 (2 studies)	⊕⊖⊖⊖ **Very low**[d]
Adverse events: vomiting (as reported by study authors at end of study follow-up period)	–	–	–	–	Not measured

*__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; **EN:** enteral nutrition; **ICU:** intensive care unit; **PN:** parenteral nutrition; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate: 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: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]All studies had high risk of performance bias; downgraded one level for study limitations. Studies included a variety of primary diagnoses and evidence was less direct; downgraded one level for indirectness.

[b]All studies had high risk of performance bias; downgraded one level for study limitations. Studies included a variety of primary diagnoses and evidence was less direct; downgraded one level for indirectness. Few studies with increased risk of imprecision; downgraded one level.

[c]Both studies had high risk of performance bias; downgraded one level for study limitations. Studies included a variety of primary diagnoses and evidence was less direct; downgraded one level for indirectness.

[d]Data from only one study that had a high risk of performance bias; downgraded one level for study limitations and two levels for imprecision.

BACKGROUND

Description of the condition

Malnutrition is associated with increased mortality and morbidity to include susceptibility to infectious complications, such as pulmonary infections, urinary infections, wound infections, and sepsis, and susceptibility to non-infectious complications, such as respiratory failure and cardiac arrhythmias (Correia 2003; Mogensen 2015).

Acute and chronic illness, trauma, and inflammation induce stress-related catabolism, increasing the metabolic rate at which the body breaks down food. In addition to this, drug-related side effects may affect ingestion and lead to loss of appetite or nausea and vomiting, or both, and it has been suggested that hospital routines and lack of awareness among nursing staff may affect nutritional care (Norman 2008). Critically ill people, who may be unconscious, unable to feed themselves or unable to receive oral nutritional support, or both, are at increased susceptibility to malnutrition.

Nutritional support is a complex aspect of care for critically ill people. This systematic review aimed specifically to address the route of delivery that will optimize uptake of nutrition. It did not deal with supplementation of specific nutrients as a number of these are reviewed already (Allingstrup 2016; Dushianthan 2016; Tao 2014).

Description of the intervention

Enteral nutrition (EN) refers to the delivery of a nutritionally complete feed via a tube into the stomach, duodenum, or jejunum (NICE 2006). This method is suitable for people who have inadequate oral intake but a functional gastrointestinal tract, and some evidence suggests that it is an effective method of providing nutrition to particular patient groups (e.g. people with sepsis (Elke 2013); people with acute pancreatitis (Al-Omran 2010)). EN may help to maintain the function and integrity of the gut barrier (Altintas 2011; King 1999; Kyle 2006), and is associated with increased immunoglobulin A production, which in turn may provide increased protection against airway infections. However, critically ill people may not tolerate enteral feeding well, and side effects such as nausea and vomiting may occur (Harvey 2015), and non-occlusive bowel necrosis (Marvin 2000). In addition, high volumes of gastric residual may allow bacteria to colonize, and increase the risk of aspiration and complications, such as ventilator-associated pneumonia (Altintas 2011), although one study assessing monitoring of gastric residual volume showed no difference in ventilator-associated pneumonia with absence of monitoring (Reignier 2013). Furthermore, EN can be disturbed by patient care and diagnostic interventions, particularly among people receiving respiratory support (Corley 2017), and this may affect the capacity for EN to maintain nutritional goals (Kyle 2006; Seres 2013). Some benefit has been found from placing the tube into the duodenum or jejunum rather than the stomach (Alkhawaja 2015).

Parenteral nutrition (PN) is unphysiological and bypasses the gastrointestinal tract and portal venous system. It delivers a nutritionally complete feed intravenously via a central or peripheral venous catheter, and may be used as an alternative for people in need of nutritional support. It confers the advantage of ease of administration to the person (Seres 2013), often with no further intervention needed to provide nutritional support when all components are administered via an 'all in one bag' system. Whilst interrupting feeding during patient care is not necessary, PN may increase the risk of overfeeding (Singer 2009). PN is associated with a higher rate of hyperglycaemia; subsequently, people may require glycaemic control alongside PN. Earlier studies have reported increased susceptibility to infectious complications, such as catheter-related bloodstream infections (Peter 2005).

PN may be used to supplement EN to achieve target energy requirements when EN alone is inadequate (Singer 2011).

Research findings are unclear regarding sufficient caloric intake needed to meet the energy requirements of critically ill people, and no evidence currently supports the assumption that these people benefit from a normocaloric intake (80% to 100% of energy requirements) rather than permissive underfeeding (less than 70% of energy requirements) (Marik 2016). Similarly, a target time for initiation of nutrition has been debated by researchers, with large randomized controlled trials (RCTs) (e.g. the EDEN (Early versus delayed enteral feeding to treat people with acute lung injury or acute respiratory distress syndrome) study (ARDS Clinical Trials Network 2012); the EPaNIC (Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients) study (Casaer 2011)), providing evidence that conflicts with European nutrition guidelines (ESPEN; Singer 2009), which advise early feeding during critical illness (Casaer 2014). Whilst this review aimed specifically to address the route of nutrition, both caloric intake and initiation time are also important considerations.

Why it is important to do this review

The most current American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines recommend use of EN over PN (Taylor 2016), suggesting a reduction in infectious morbidity and length of stay in the intensive care unit (ICU) for people given EN. This is comparable with guidelines of the European Society for Parenteral and Enteral Nutrition (ESPEN) (Kreymann 2006; Singer 2009), and the UK National Institute for Health and Care Excellence (NICE) (NICE 2006). However, these guidelines reflect only research findings of small RCTs published prior to these guidelines, and current evidence contradicts some outcomes, for example, risk of infectious complications with PN.

It is highly debated if, how, and when nutritional support may contribute to improved patient outcomes (Casaer 2014; Preiser 2015; Schetz 2013). Nutrition for critically ill people has global relevance, achieving benefits for the patient and reducing impact on healthcare resources. This review aimed specifically to consider whether the route of delivery of nutrition is a significant factor in the treatment of critically ill adults, and incorporates recent findings to assess both evidence of benefit and risk of adverse events.

OBJECTIVES

To compare the effects of enteral versus parenteral methods of nutrition, and the effects of enteral versus a combination of enteral and parenteral methods of nutrition, among critically ill adults, in terms of mortality, number of ICU-free days up to day 28 and adverse events.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomized controlled trials (RCTs), including quasi-randomized studies (e.g. studies in which the method of assignment was based on alternation, date of birth, or medical record number) and cluster-randomized studies.

Types of participants

We included all adults, over 16 years of age, who had been in an ICU for at least 24 hours.

We included participants admitted for all conditions, except acute pancreatitis as this patient group is reviewed elsewhere (Al-Omran 2010). We aimed to include studies that had a mixed population that included acute pancreatitis, if fewer than 50% of participants had acute pancreatitis; we aimed to contact study authors to request additional information if necessary.

We included trauma, emergency, medical, and elective postsurgical participants. We included mechanically ventilated and non-mechanically ventilated participants.

If studies included participants of which not all were in the ICU, we included the study if study authors reported that more than 75% of participants were in the ICU.

Types of interventions

We included studies that compare EN versus PN, and studies that compared EN versus EN and PN. These represent two comparison groups; we analysed separately data from studies comparing EN versus PN and studies comparing EN versus EN and PN.

We included EN that was given via a tube into the stomach, duodenum, or jejunum, and PN that was given via a central venous catheter or a peripheral venous catheter. We anticipated that the protocol used to administer nutrition would differ between studies. We included EN and PN initiated early or delayed, and given to meet a normocaloric or hypocaloric goal.

Types of outcome measures

We aimed to establish whether one type of feeding method reduced the rate of mortality among study participants and considered data gathered at different time points, up to 180 days. Length of stay in the ICU was an important outcome for this review topic. Given that rates of mortality may be high in the included population, and to avoid the effect of death on this outcome, we planned to report data presented as ICU-free days. Similarly, we planned to assess duration of mechanical ventilation as the number of ventilator-free days. These outcomes account for the number of days that a person is alive or is no longer using mechanical ventilation; therefore, a participant who has died would be counted as having zero ICU-free or ventilator-free days. Adverse events represent an important outcome for this review, and EN and PN may lead to different adverse events. For each adverse event reported by study authors, we collected data during the study follow-up period.

Primary outcomes

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

Secondary outcomes

1. Number of ICU-free days up to day 28.
2. Number of ventilator-free days up to day 28.
3. Adverse events as reported by study authors (to include hyperglycaemia, aspiration pneumonia, catheter-related bloodstream infections, and gastrointestinal events).

Search methods for identification of studies

Electronic searches

We identified RCTs through literature searching with systematic and sensitive search strategies as outlined in Chapter 6.4 of the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011). We applied no restrictions to language or publication status.

We searched the following databases for relevant trials:

1. Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 9);
2. MEDLINE (OvidSP, 1946 to 3 October 2017);
3. Embase (OvidSP, 1974 to 3 October 2017).

We developed a subject-specific search strategy in MEDLINE and used that as the basis for the search strategies in the other listed databases. The search strategy was developed in consultation with the Information Specialist. Search strategies can be found in Appendix 1; Appendix 2; and Appendix 3.

We scanned the following trial registries for ongoing and unpublished trials (8 January 2018):

1. World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp/en/);
2. ClinicalTrials.gov (clinicaltrials.gov).

Searching other resources

We carried out citation searching of identified included studies in Web of Science (apps.webofknowledge.com), on 24 March 2017 and conducted a search of grey literature through Opengrey (www.opengrey.eu./), on 27 April 2017. We scanned reference lists of relevant systematic reviews to search for additional trials. We did not contact study authors or organizations to ask if they were aware of other completed or ongoing studies.

Data collection and analysis

Two review authors (SL and OSR) independently completed all data collection and analyses before comparing results and reaching consensus. We consulted with a third review author (AS) to resolve conflicts when necessary.

Selection of studies

We used reference management software to collate the results of searches and to remove duplicates (Endnote). We used Covidence software to screen results of the search of titles and abstracts and identify potentially relevant studies (Covidence). We sourced the full texts of all potentially relevant studies and considered whether

they meet the inclusion criteria (see Criteria for considering studies for this review). We reviewed abstracts at this stage and included these in the review only if they provided sufficient information and relevant results that included denominator figures for each intervention/comparison group. We recorded the number of papers retrieved at each stage and reported this information using a PRISMA flow chart. We reported in the review brief details of closely related but excluded papers.

Data extraction and management

We used Covidence software to extract data from individual studies (Covidence). A basic template for data extraction forms is available at www.covidence.org. We adapted this template to include the following information.

1. Methods: type of study design; setting; dates of study; funding sources.
2. Participants: number of participants randomized to each group; baseline characteristics (to include "Acute Physiology and Chronic Health Evaluation II" (APACHE II) scores, whether mechanically ventilated and length of time in the ICU before study commencement).
3. Interventions: details of intervention and comparison nutrition (kilocalories per kilogram received, time of initiation, duration of delivery, use of glycaemic controls).
4. Outcomes: all relevant review outcomes as measured and reported by study authors.
5. Outcome data: results of outcome measures.

We considered the applicability of information from individual studies and the generalizability of data to our intended study population (i.e. the potential for indirectness in our review). If we found associated publications from the same study, we created a composite dataset based on all eligible publications.

Assessment of risk of bias in included studies

Two review authors (SL and OSR) independently assessed study quality, study limitations, and the extent of potential bias by using the Cochrane 'Risk of bias' tool (Higgins 2011). We considered the following domains.

1. Sequence generation (selection bias).
2. Allocation concealment (selection bias).
3. Blinding of participants, personnel, and outcome assessors (performance and detection bias).
4. Incomplete outcome data (attrition bias).
5. Selective outcome reporting (reporting bias).
6. Other: use of concomitant drugs.

We anticipated that it would not be feasible for studies to blind participants and personnel and, in the absence of any description of personnel blinding, we assumed that no blinding occurred. However, we anticipated that it was feasible to blind outcome assessors and we considered risk of detection bias (outcome assessor blinding) by each outcome. We considered whether investigators used standard criteria for diagnosis of outcomes, for example, aspiration pneumonia or ventilator-acquired pneumonia, which may be subject to clinician bias.

For each domain, we judged whether study authors had made sufficient attempts to minimize bias in their study design. We made judgements using three measures; high, low, and unclear risk of bias. We recorded this judgement in 'Risk of bias' tables and presented a summary 'Risk of bias' figure.

Measures of treatment effect

We collected dichotomous data for mortality and adverse events, and continuous data for number of ICU-free days and number of ventilator-free days. We reported dichotomous data as risk ratios (RR) to compare groups, and continuous data as a mean difference (MD). We reported 95% confidence intervals (CI).

Unit of analysis issues

(See Differences between protocol and review.) We conducted separate analysis for the comparison arms PN, and EN and PN; this method avoided double-counting in multi-arm studies.

In the event of cluster trials, we would have defined the unit of allocation as the ICU or the hospital rather than the individual participant and analysed data accordingly, calculating effect estimates using the generic inverse variance method (Higgins 2011).

Dealing with missing data

In the event that study authors did not account for missing data, we would have contacted them for information. We considered data to be complete if losses were reported and explained by study authors and we combined no incomplete data in the meta-analysis.

Assessment of heterogeneity

We assessed whether evidence of inconsistency was apparent in our results by considering heterogeneity. We assessed clinical heterogeneity by comparing similarities in our included studies between study designs, participants, interventions, and outcomes, and used the data collected as stated under Data extraction and management. We assessed statistical heterogeneity by calculating the Chi^2 test or I^2 statistic and judged any heterogeneity above an I^2 value of 60% and a Chi^2 P value less than or equal to 0.05 to indicate moderate to substantial statistical heterogeneity (Higgins 2011).

In addition to looking at statistical results, we considered point estimates and overlap of CIs. If CIs overlap, then results are more consistent. Combined studies may show a large consistent effect but with significant heterogeneity. Therefore, we planned to interpret heterogeneity with caution (Guyatt 2011a).

Assessment of reporting biases

We attempted to source published protocols for each of our included studies by using clinical trials registers. We compared published protocols with published study results to assess the risk of selective reporting bias. If we identified sufficient studies reporting on an outcome (i.e. more than 10 studies (Higgins 2011)), we planned to generate a funnel plot to assess risk of publication bias in the review; an asymmetrical funnel plot may suggest publication of only positive results (Egger 1997).

Data synthesis

We completed meta-analyses of outcomes for which we had comparable effect measures from more than one study, and when

measures of heterogeneity indicated that pooling of results was appropriate. We did not pool studies that had a high level of clinical heterogeneity and moderate to high statistical heterogeneity indicated by I^2 statistics and Chi^2 P values. We used the statistical calculator provided in Review Manager to perform meta-analysis (Review Manager 2014).

For dichotomous outcomes, for example, mortality rate, we calculated the RR using summary data presented in each trial. We used the Mantel-Haenszel effects model. If events had been extremely rare (one per 1000), we would have used the Peto odds ratio (Higgins 2011). For continuous outcomes, we aimed to use the MD. We used a fixed-effect statistical model. In the event of finding evidence of moderate statistical or clinical heterogeneity, we would have investigated this by performing subgroup analyses, as below, and analysed data using a random-effects model to incorporate unexplained heterogeneity.

We calculated CIs at 95% and used a P value less than or equal to 0.05 to judge whether a result was statistically significant. We considered imprecision in the results of analyses by assessing the CI around an effects measure; a wide CI would suggest a higher level of imprecision in our results. A small number of identified studies may also reduce precision (Guyatt 2011b).

Subgroup analysis and investigation of heterogeneity

Study designs may differ in relation to time of initiation of feeding and target energy requirements given to participants. Therefore, we considered these subgroups for each of our outcomes. We used cut-offs for time of feeding from the most recent ASPEN guidelines (Taylor 2016), and cut-offs for target energy requirements from Marik 2016. Critically ill people who are elderly may have different nutritional requirements and metabolism (ASPEN 2002), leading to different responses to EN and PN methods as compared with younger participants. We did not supply a cut-off age for this subgroup but aimed to separate participants described as 'frail elderly' by study authors from remaining participants. Heterogeneity may be introduced by the types of procedures that participants have undergone or by their reason for admission; people who have had abdominal or bowel surgery and people admitted with gastrointestinal complications may have greater difficulty with ingestion and digestion. In summary, we aimed to perform subgroup analysis as follows.

1. Early initiation of feeding (less than 48 hours) versus late initiation of feeding (48 hours or greater).
2. Normocaloric intake (to match 80% to 100% of energy expenditure) versus hypocaloric intake (less than 70% of energy expenditure).
3. 'Frail elderly' versus other participants.
4. Gastrointestinal medical or surgical participants versus non-gastrointestinal medical or surgical participants.

We performed subgroup analysis only when study authors reported outcome data for identified subgroups. In the absence of numerical data, we planned to present qualitative analysis of these factors as a possible source of heterogeneity.

We aimed to perform subgroup analyses on the following outcomes: mortality, number of ICU-free days up to day 28, and number of ventilator-free days up to day 28.

Sensitivity analysis

We explored the potential effects of decisions made as part of the review process as follows.

1. We excluded all studies that we judged at high or unclear risk of selection bias.
2. We assessed decisions made regarding missing data, excluding studies that provided incomplete data.
3. We conducted meta-analysis using the alternate meta-analytical effects model (fixed-effect or random-effects).

We compared effect estimates from the above results with effect estimates from the main analysis. We aimed to report differences that altered interpretation of effects.

We aimed to perform sensitivity analyses on the following outcomes: mortality, number of ICU-free days up to day 28, and number of ventilator-free days up to day 28.

'Summary of findings' table and GRADE

Two review authors (SL and OSR) independently used the GRADE system to assess the certainty of the body of evidence associated with the following outcomes (Guyatt 2008):

1. mortality (at time points: in-hospital, 30 days, 90 days, 180 days);
2. number of ICU-free days up to day 28;
3. number of ventilator-free days up to day 28;
4. adverse events as reported by study authors (aspiration, sepsis, pneumonia, and vomiting).

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. Evaluation of the certainty of a body of evidence considers within-study risk of bias, directness of the evidence, heterogeneity of the data, precision of effect estimates, and risk of publication bias.

We constructed two 'Summary of findings' tables using the GRADE profiler software for the following comparisons in this review (www.guidelinedevelopment.org/):

1. EN versus PN for adults in the ICU;
2. EN versus EN and PN for adults in the ICU.

We reached consensus without consulting a third review author.

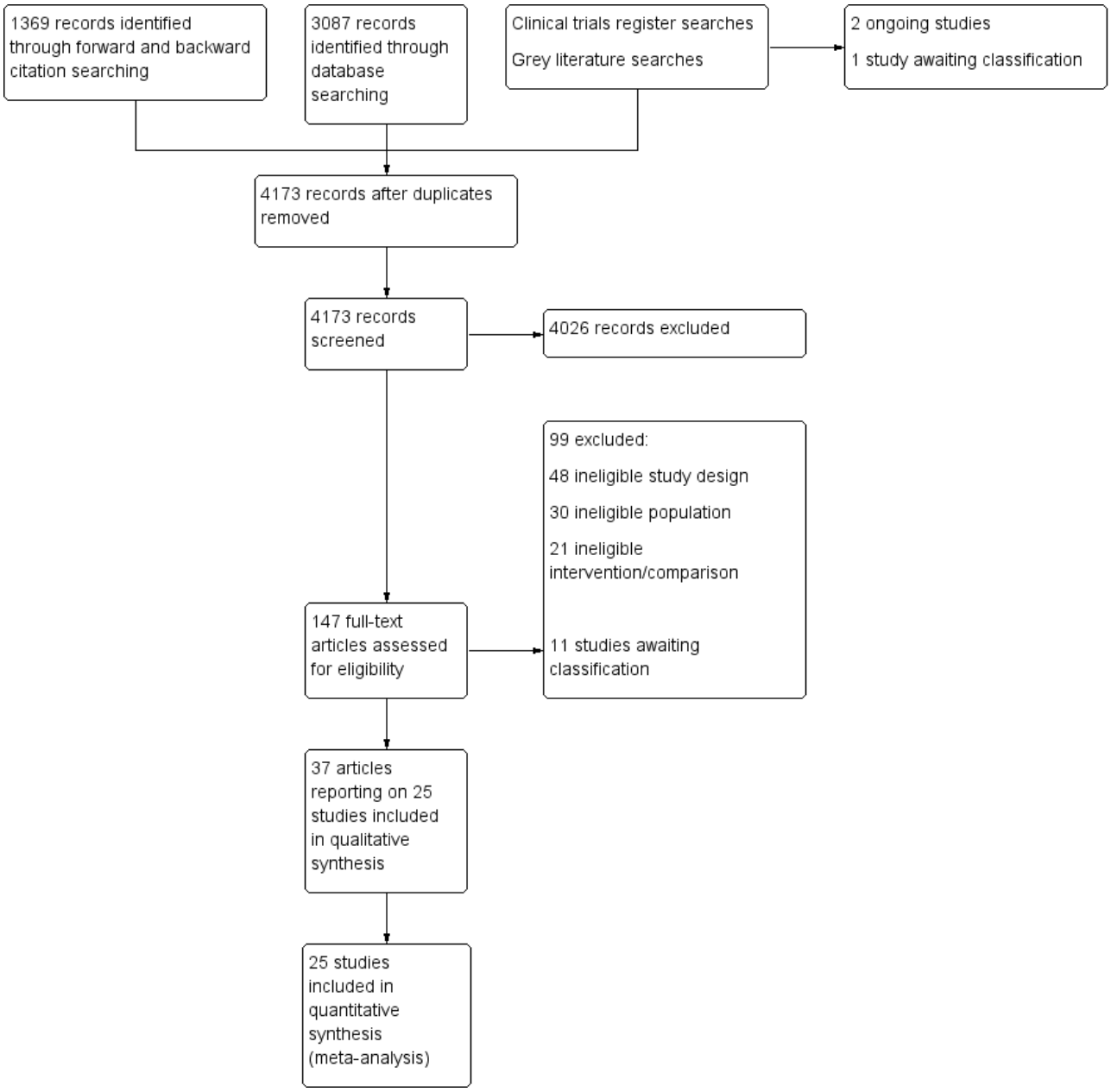
RESULTS

Description of studies

Results of the search

We screened 4173 titles and abstracts, of which we identified 1369 through forward and backward citation searches. We screened titles from clinical trials registers and grey literature searches. We assessed 147 full texts for eligibility. See Figure 1.

Figure 1. Flow diagram of search strategy.



Included studies

See Characteristics of included studies table.

We included 25 studies (37 publications), with 8816 participants (Abdulmeguid 2007; Abrishami 2010; Adams 1986; Altintas 2011; Bauer 2000; Bertolini 2003; Borzotta 1994; Casaer 2011; Cerra 1988; Chiarelli 1996; Dunham 1994; Engel 1997; Fan 2016; Gencer 2010; Hadfield 1995; Harvey 2014; Heidegger 2013; Justo Meirelles 2011; Kudsk 1992; Peterson 1988; Radrizzani 2006; Rapp 1983; Xi 2014; Young 1987). Two studies were quasi-randomized (Altintas 2011; Fan 2016), and the remaining studies were RCTs. We found no cluster-randomized studies. Reports for Bertolini 2003 and Radrizzani 2006 were for the same study, but participants were divided according to criteria for sepsis (severe sepsis in Bertolini 2003; and non-severe sepsis in Radrizzani 2006), and we included them as separate studies for the purpose of this review. We included one study for which we could only source the abstract (Abdulmeguid 2007); we sourced the full text of all remaining studies.

Study population

Participants had a wide variety of primary diagnoses but all were critically ill. Sixteen studies reported that participants were mechanically ventilated (Abdulmeguid 2007; Adams 1986; Altintas 2011; Bertolini 2003; Borzotta 1994; Cerra 1988; Chiarelli 1996; Dunham 1994; Harvey 2014; Heidegger 2013; Justo Meirelles 2011; Kudsk 1992; Radrizzani 2006; Rapp 1983; Wischmeyer 2017; Xi 2014); nine studies did not describe mechanical ventilation status as part of the inclusion or exclusion criteria (Abrishami 2010; Bauer

2000; Casaer 2011; Engel 1997; Fan 2016; Gencer 2010; Hadfield 1995; Peterson 1988; Young 1987).

Study setting

All studies were conducted in the ICU (Abdulmeguid 2007; Abrishami 2010; Adams 1986; Altintas 2011; Bauer 2000; Bertolini 2003; Casaer 2011; Cerra 1988; Chiarelli 1996; Dunham 1994; Fan 2016; Gencer 2010; Hadfield 1995; Harvey 2014; Heidegger 2013; Justo Meirelles 2011; Kudsk 1992; Peterson 1988; Radrizzani 2006; Rapp 1983; Wischmeyer 2017; Xi 2014), or assumed to be in the ICU (Borzotta 1994; Engel 1997; Young 1987). Eight studies were undertaken in the USA (Adams 1986; Borzotta 1994; Cerra 1988; Dunham 1994; Kudsk 1992; Peterson 1988; Rapp 1983; Young 1987); three were in Italy (Bertolini 2003; Chiarelli 1996; Radrizzani 2006); two were in the UK (Hadfield 1995; Harvey 2014); two were in Turkey (Altintas 2011; Gencer 2010); two were in China (Fan 2016; Xi 2014); and one each in Iran (Abrishami 2010); France (Bauer 2000); Belgium (Casaer 2011); Germany (Engel 1997); Switzerland (Heidegger 2013); and Brazil (Justo Meirelles 2011). One international study was undertaken in Belgium, Canada, France, and the USA (Wischmeyer 2017). One study did not report the country in which it was conducted (Abdulmeguid 2007).

Intervention and comparisons

Seventeen studies compared an EN feeding protocol to a PN feeding protocol (Abdulmeguid 2007; Adams 1986; Altintas 2011; Bertolini 2003; Borzotta 1994; Cerra 1988; Engel 1997; Gencer 2010; Hadfield 1995; Harvey 2014; Justo Meirelles 2011; Kudsk 1992; Peterson 1988; Radrizzani 2006; Rapp 1983; Xi 2014; Young 1987); Engel 1997 was a multi-arm study with two EN groups (one standard EN formula and one formula supplemented with arginine, omega-3 fatty acid, nucleotide, and selenium). Six studies compared an EN feeding protocol to a protocol in which EN was supplemented with PN (Abrishami 2010; Bauer 2000; Casaer 2011; Chiarelli 1996; Heidegger 2013; Wischmeyer 2017). Two studies compared EN versus PN and versus combined EN and PN (Dunham 1994; Fan 2016).

Study authors reported initiation of both EN and PN within 48 hours of ICU admission in 13 studies (Adams 1986; Altintas 2011; Bauer 2000; Bertolini 2003; Dunham 1994; Engel 1997; Fan 2016; Harvey 2014; Justo Meirelles 2011; Kudsk 1992; Peterson 1988; Radrizzani 2006; Wischmeyer 2017). One study reported that all participants were given PN within 24 to 36 hours and that EN was initiated in one group at four days (Chiarelli 1996). One study reported that initiation of EN in one group was after at least 14 days of fasting, and study authors did not state at which time point PN was initiated (Xi 2014). Two studies initiated supplemental PN after all participants had been given EN for three days (Casaer 2011; Heidegger 2013). The remaining five study authors did not report time of initiation of feeding (Abdulmeguid 2007; Abrishami 2010; Gencer 2010; Hadfield 1995; Young 1987).

Outcomes

All studies, except Engel 1997, reported participant deaths; some studies did not clearly report time points and some studies reported deaths as participant losses with mortality as a reason for withdrawal from the study. No studies reported data for number of ICU-free days up to day 28, and one study reported data for number of ventilator-free days up to day 28 (Harvey 2014). Study authors reported adverse events which were: mechanical (Borzotta 1994; Casaer 2011; Harvey 2014); metabolic (Borzotta 1994; Fan 2016; Harvey 2014); gastrointestinal (Adams 1986; Altintas 2011; Bauer 2000; Borzotta 1994; Casaer 2011; Cerra 1988; Chiarelli 1996; Fan 2016; Harvey 2014); and infective (Abdulmeguid 2007; Adams 1986; Altintas 2011; Borzotta 1994; Casaer 2011; Engel 1997; Fan 2016; Gencer 2010; Justo Meirelles 2011; Heidegger 2013; Kudsk 1992; Rapp 1983; Wischmeyer 2017; Xi 2014; Young 1987).

Funding sources

Study authors reported funding sources in 11 studies (Abrishami 2010; Adams 1986; Bertolini 2003; Borzotta 1994; Casaer 2011; Hadfield 1995; Harvey 2014; Heidegger 2013; Radrizzani 2006; Rapp 1983; Wischmeyer 2017). Three studies noted no involvement in trial management from funders (Casaer 2011; Heidegger 2013; Radrizzani 2006); remaining studies reported no details of funders' involvement.

Excluded studies

We excluded 99 articles after reading the full text. We reported details of 32 of these studies in Characteristics of excluded studies. Of these 32 studies, we excluded studies in which the setting was not reported and we could not assume it was the ICU (Arefian 2007; Baigrie 1996; Braga 1996; Braga 1998; Braga 2001; Chen 2004; DiCarlo 1999; Dong 2010; Hermann 2004; Kim 2012; Klek 2008; Klek 2011; Malhotra 2004; McArdle 1981; Moore 1989; Reynolds 1997; Ryu 2009; Sand 1997; Suchner 1996; Van Barneveld 2016; Xiao-Bo 2014; Yu 2009; Zhang 2016; Zhu 2012), or too few participants were in the ICU (Woodcock 2001). We excluded two studies of participants with acute pancreatitis (Abou-Assi 2002; Pupelis 2001). One study compared EN versus PN in people in the ICU (Zhang 2005), but reported that participants in the EN group were also given PN as required for the first three to four days and it was therefore ineligible for our review, and one study was described as an RCT but not all participants randomized to the control group received EN (Doig 2013). We excluded one study that compared early-goal directed nutrition (EGDN) versus EN in people in the ICU; the EGDN group were given EN supplemented with PN; however, the supplemented PN was only given if required to meet feeding goals and study authors did not report which participants had and did not have PN (Allingstrup 2017). One study compared EN versus PN but feeding took place for only one day in the ICU and feeding was continued for an additional six days on the ward (Fujita 2012). We excluded one abstract that had not been published as a full report (Zanello 1992); the abstract included no outcomes of interest and was published in 1992.

Studies awaiting classification

We were unable to assess eligibility in 11 studies (Braga 1995; Cao 2014; Chen 2011; NCT00522730; NCT01802099; Ridley 2015; Soliani 2001; Theodorakopoulou 2016; Xiang 2006; Xiu 2015; Yi 2015). We identified one study in clinical trials registers that was completed without published results (NCT00522730). From database searches we identified one protocol for a terminated study (NCT01802099), and one study that had been completed but not published (Ridley 2015). We were unable to source full texts for three trials and could not assess eligibility from abstracts (Braga 1995; Chen 2011; Soliani 2001). Four trials were published only as abstracts with insufficient information to assess eligibility (Cao 2014; Theodorakopoulou 2016; Xiu 2015; Yi 2015), and one study report requires translation before we assess eligibility (Xiang 2006). See Characteristics of studies awaiting classification table.

Ongoing studies

We identified two ongoing studies from clinical trials registers (NCT00512122; NCT02022813). See Characteristics of ongoing studies table.

Risk of bias in included studies

We have included a summary of risk of bias assessments in Figure 2 and Figure 3. Blank spaces in the risk bias summary figures indicate that study authors did not report the review outcome.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies. Blank spaces in tables indicated that study authors did not report the review outcome.

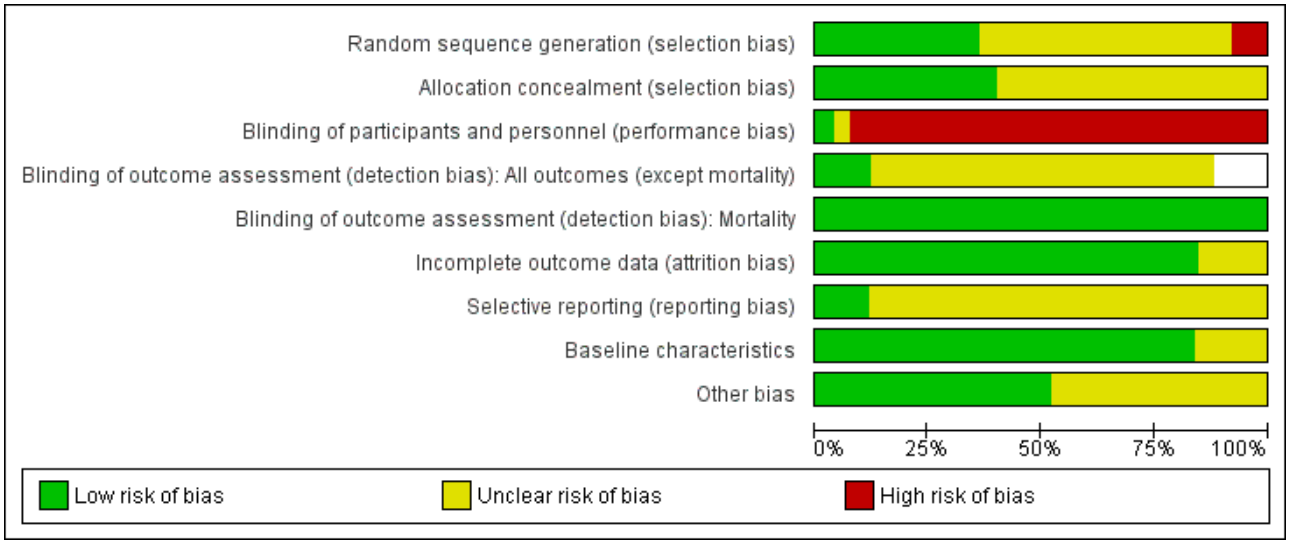


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study. Blank spaces in tables indicate that study authors did not report the review outcome.

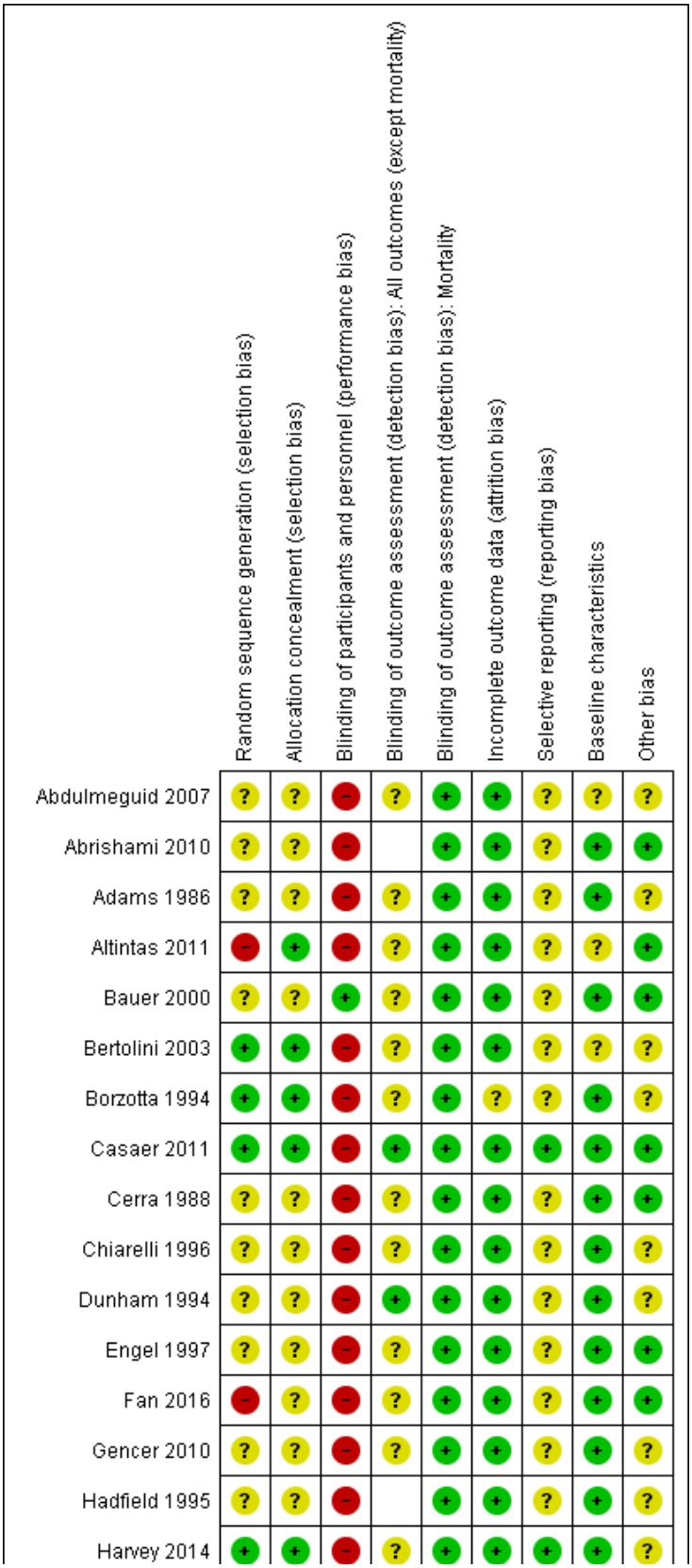
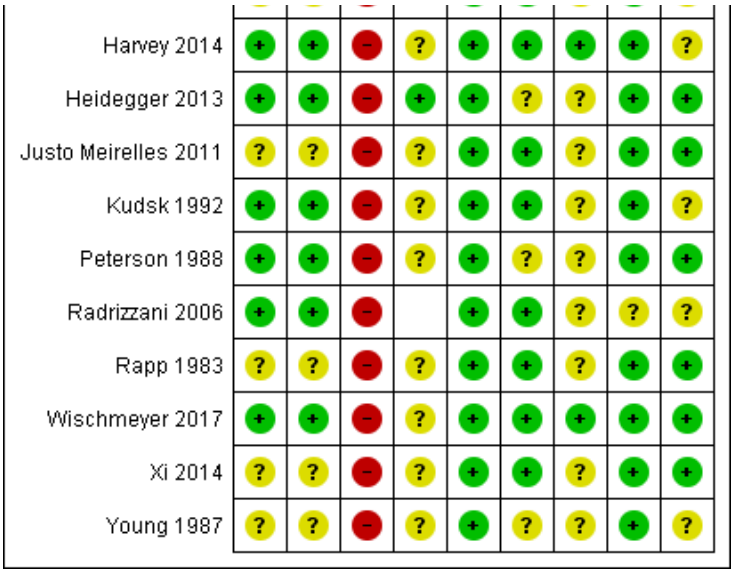


Figure 3. (Continued)



Allocation

All studies were described as randomized and nine studies provided sufficient information on the method of randomization (Bertolini 2003; Borzotta 1994; Casaer 2011; Harvey 2014; Heidegger 2013; Kudsk 1992; Peterson 1988; Radrizzani 2006; Wischmeyer 2017). Two studies randomized participants according to hospital record number (Altintas 2011; Fan 2016), and we judged these to have high risk of bias. The remaining 14 studies reported insufficient information on method of randomization and we recorded these as having unclear risk of bias (Abdulmeguid 2007; Abrishami 2010; Adams 1986; Bauer 2000; Cerra 1988; Chiarelli 1996; Dunham 1994; Engel 1997; Gencer 2010; Hadfield 1995; Justo Meirelles 2011; Rapp 1983; Xi 2014; Young 1987).

Ten studies described adequate allocation concealment methods, and we judged these to have low risk of selection bias (Altintas 2011; Bertolini 2003; Borzotta 1994; Casaer 2011; Harvey 2014; Heidegger 2013; Kudsk 1992; Peterson 1988; Radrizzani 2006; Wischmeyer 2017) The remaining 15 studies reported no description of methods to conceal allocation and we recorded these as having unclear risk of bias (Abdulmeguid 2007; Abrishami 2010; Adams 1986; Bauer 2000; Cerra 1988; Chiarelli 1996; Dunham 1994; Engel 1997; Fan 2016; Gencer 2010; Hadfield 1995; Justo Meirelles 2011; Rapp 1983; Xi 2014; Young 1987).

Blinding

One study reported that participants in the enteral group were given a placebo parenteral solution and we judged this study to have low risk of performance bias (Bauer 2000). One study reported that personnel were not blinded to the intervention group (Heidegger 2013). The remaining studies did not report whether attempts had been made to blind personnel; adequate blinding would involve intrusive procedures (e.g. central line placement or nasogastric tube placement) and if these procedures were not described we assumed that blinding had not occurred (Abdulmeguid 2007; Abrishami 2010; Adams 1986; Altintas 2011; Bertolini 2003; Borzotta 1994; Casaer 2011; Cerra 1988; Chiarelli 1996; Dunham 1994; Engel 1997; Fan 2016; Gencer 2010; Hadfield 1995; Harvey 2014; Justo Meirelles 2011; Kudsk 1992; Peterson 1988; Radrizzani 2006; Rapp 1983; Wischmeyer 2017; Xi 2014; Young 1987). We judged these studies, and Heidegger 2013, to have high risk of performance bias.

We did not believe that lack of blinding of outcome assessors would influence data for the mortality outcome and we judged all studies to have low risk of detection bias for mortality, regardless of whether study authors reported blinding of outcome assessors. Three studies adequately reported blinding of outcome assessors for the remaining review outcomes and we judged these to have low risk of detection bias (Casaer 2011; Dunham 1994; Heidegger 2013). Nineteen studies reported insufficient details of outcome assessor blinding and we judged these to have unclear risk of detection bias (Abdulmeguid 2007; Adams 1986; Altintas 2011; Bauer 2000; Bertolini 2003; Borzotta 1994; Cerra 1988; Chiarelli 1996; Engel 1997; Fan 2016; Gencer 2010; Harvey 2014; Justo Meirelles 2011; Kudsk 1992; Peterson 1988; Rapp 1983; Wischmeyer 2017; Xi 2014; Young 1987). Three studies included data only for mortality and our assessment of detection bias was limited to this outcome (Abrishami 2010; Hadfield 1995; Radrizzani 2006). We noted whether studies had included criteria for diagnoses of outcomes and we were not concerned that lack of information or type of measurement tools had introduced risk of clinician bias.

Incomplete outcome data

We judged 21 studies to have low risk of attrition bias, as there appeared to be no reported losses (Abdulmeguid 2007; Adams 1986; Altintas 2011; Bertolini 2003; Chiarelli 1996; Engel 1997; Fan 2016; Gencer 2010; Hadfield 1995; Justo Meirelles 2011; Rapp 1983; Wischmeyer 2017; Xi 2014), or losses were few and adequately explained by study authors (Abrishami 2010; Bauer 2000; Casaer 2011; Cerra 1988; Dunham 1994; Harvey 2014; Kudsk 1992; Radrizzani 2006). Four studies had a large number of losses or losses were unevenly distributed between groups and we were unclear whether these losses could influence outcome data (Borzotta 1994; Heidegger 2013; Peterson 1988; Young 1987).

Selective reporting

We were able to source prospective clinical trials registration reports for four studies, of which we judged three studies to have low risk of reporting bias (Casaer 2011; Harvey 2014; Wischmeyer 2017). We noted changes to the clinical trials registration documents after completion of the study with regard to data collection time points and we could not be certain whether these changes may have introduced bias to the results; we judged this study to have an unclear risk of selective reporting bias (Heidegger 2013). We were unable to judge reporting bias for the remaining 21 studies because study authors did not report clinical trials registration reports or published protocols (Abdulmeguid 2007; Abrishami 2010; Adams 1986; Altintas 2011; Bauer 2000; Bertolini 2003; Borzotta 1994; Cerra 1988; Chiarelli 1996; Dunham 1994; Engel 1997; Fan 2016; Gencer 2010; Hadfield 1995; Justo Meirelles 2011; Kudsk 1992; Peterson 1988; Radrizzani 2006; Rapp 1983; Xi 2014; Young 1987).

Baseline characteristics

Three studies reported some baseline imbalances between groups and we did not know if these differences could influence outcome data (Altintas 2011; Bertolini 2003; Radrizzani 2006). One study was an abstract and did not provide sufficient detail on baseline characteristics (Abdulmeguid 2007). We judged 21 studies to have low risk of bias for baseline characteristics because data for characteristics were comparable between groups (Abrishami 2010; Adams 1986; Bauer 2000; Borzotta 1994; Casaer 2011; Cerra 1988; Chiarelli 1996; Dunham 1994; Engel 1997; Fan 2016; Gencer 2010; Hadfield 1995; Harvey 2014; Heidegger 2013; Justo Meirelles 2011; Kudsk 1992; Peterson 1988; Rapp 1983; Wischmeyer 2017; Xi 2014; Young 1987).

Other potential sources of bias

We considered whether differences between intervention and comparison groups could have introduced bias; in particular we considered nutritional protocols, patient management and use of concomitant medication, and glycaemic controls. We noted some differences in 12 studies (Abdulmeguid 2007; Adams 1986; Bertolini 2003; Borzotta 1994; Chiarelli 1996; Dunham 1994; Gencer 2010; Hadfield 1995; Harvey 2014; Kudsk 1992; Radrizzani 2006; Young 1987). We were not able to judge if these differences influenced study outcome data and we reported these as having unclear risk of bias. We identified no other sources of bias in the remaining studies.

Effects of interventions

See: **Summary of findings for the main comparison** Enteral versus parenteral nutrition for adults in the intensive care unit; **Summary of findings 2** Enteral versus enteral and parenteral nutrition for adults in the intensive care unit

Enteral nutrition versus parenteral nutrition

Primary outcome

1. Mortality

We noted that some studies reported loss of randomized participants from analysis due to death (Borzotta 1994; Dunham 1994; Kudsk 1992; Peterson 1988; Young 1987). We included participants from three of these studies (Borzotta 1994; Dunham 1994; Kudsk 1992), as data for our primary analysis; we did not include mortality data from Young 1987 or Peterson 1988 because study authors did not report to which intervention group these participants belonged. Data were grouped according to time point.

In hospital

Deaths were reported in Abrishami 2010 during the seven-day study period, at various time points up to day 18 in Borzotta 1994, and at four days in Kudsk 1992 and we assumed that these occurred in hospital. Three studies reported ICU mortality and did not report hospital mortality (Bertolini 2003; Cerra 1988; Heidegger 2013); in this instance, we included data for ICU mortality in this analysis.

One feeding route rather than the other may make little or no difference to in-hospital mortality (RR 1.19, 95% CI 0.80 to 1.77; 361 participants; 6 studies; I^2 = 3%; low-certainty evidence; Analysis 1.1). We used GRADE to downgrade by two levels; we were concerned by study limitations and indirectness. See Summary of findings for the main comparison.

Within 30 days

Six studies did not specify time points and we reported outcome data for these studies with mortality at 30 days (Abdulmeguid 2007; Chiarelli 1996; Fan 2016; Gencer 2010; Hadfield 1995; Justo Meirelles 2011).

One feeding route rather than the other may make little or no difference to mortality within 30 days (RR 1.02, 95% CI 0.92 to 1.13; 3148 participants; I^2 = 32%; low-certainty evidence; Analysis 1.2). We used GRADE to downgrade by two levels; we were concerned by study limitations and indirectness. See Summary of findings for the main comparison.

Within 90 days

Three studies reported mortality within 90 days (Harvey 2014; Rapp 1983; Young 1987). It is uncertain whether one feeding route rather than another reduces mortality within 90 days because the certainty of the evidence is very low (RR 1.06, 95% CI 0.95 to 1.17; 2461 participants; I^2 = 55%; Analysis 1.3). We used GRADE to downgrade by three levels; we were concerned by study limitations, indirectness, and imprecision. See Summary of findings for the main comparison.

Within 180 days

One study comparing EN versus PN reported mortality from one to four months; we assumed that there were no earlier deaths and we included it as mortality data within 180 days (Adams 1986). Study authors reported one death in the EN group (23 participants) and three deaths in the PN group (23 participants). We used the Review Manager 5 calculator to calculate an effect estimate (RR 0.33, 95% CI 0.04 to 2.97) (Review Manager 2014). It is uncertain whether either feeding route affects number of people who die within 180 days because the certainty of this evidence is very low; we were concerned by study limitations and imprecision. See Summary of findings for the main comparison.

Secondary outcomes

1. Number of intensive care unit-free days up to day 28

No studies reported data for number of ICU-free days.

2. Number of ventilator-free days up to day 28

One study (2388 participants included in the analysis) reported data for number of ventilator-free days up to day 28 (Harvey 2014). Study authors reported little or no difference in number of days free of respiratory support (EN group: mean 14.2 (standard deviation (SD) ± 12.2) days versus PN group: mean 14.2 (SD ± 12.1) days; P = 0.94). It is uncertain whether either feeding route affected the number of ventilator-free days up to day 28 because the certainty of the evidence is very low; we were concerned by study limitations and imprecision. See Summary of findings for the main comparison.

3. Adverse events as reported by study authors

Study authors did not always describe outcomes as 'adverse events.' We collected outcomes as described by study authors, which we categorized as mechanical events, metabolic events, gastrointestinal events, and infective events. We combined data when more than one study reported an event, and when data were reported as 'number of participants' with an event rather than number of events. We reported single study data of adverse events in Table 1.

Mechanical events

Two studies comparing EN versus PN reported data for aspiration (Borzotta 1994; Harvey 2014). It is uncertain whether one feeding route rather than another reduces aspiration because the certainty of this evidence is very low (RR 1.53, 95% CI 0.46 to 5.03; 2437 participants; I^2 = 0%; Analysis 1.4). We used GRADE to downgrade by three levels; we were concerned by study limitations, indirectness, and imprecision. See Summary of findings for the main comparison.

Two studies comparing EN versus PN reported data for pneumothorax, with little or no difference in incidences of pneumothorax according to feeding group (RR 1.46, 95% CI 0.19 to 11.22; 2437 participants; I^2 = 0%; Analysis 1.5) (Borzotta 1994; Harvey 2014).

Single studies reported data for malfunctioned line, clogged jejunostomy tube, accidental disconnected line, and eroded line (Adams 1986), and one study reported data for transpyloric tube occlusion, failure to intubate, and withdrawal of tube by participant (Dunham 1994). See Table 1.

Metabolic events

Two studies comparing EN versus PN reported data for hyperglycaemia (Borzotta 1994; Harvey 2014). We found fewer people had hyperglycaemia who were given EN (RR 0.57, 95% CI 0.35 to 0.93; 2437 participants; I^2 = 0%; Analysis 1.6). We noted that very few people in either group had hyperglycaemia in one large study (Harvey 2014).

Single studies reported data for hepatic failure, acute renal failure, and pancreatitis (Adams 1986), electrolyte disturbance (Harvey 2014), and hypoproteinaemia (Fan 2016). See Table 1.

Gastrointestinal events

Three studies comparing EN versus PN reported data for vomiting (Altintas 2011; Cerra 1988; Harvey 2014). It is uncertain whether PN leads to a reduction in vomiting because the certainty of this evidence is very low (RR 3.42, 95% CI 1.15 to 10.16; 2525 participants; I^2 = 0%; Analysis 1.7). We used GRADE to downgrade by three levels; we were concerned by study limitations, indirectness, and imprecision. See Summary of findings for the main comparison.

Six studies comparing EN versus PN reported data for diarrhoea (Adams 1986; Altintas 2011; Borzotta 1994; Cerra 1988; Fan 2016; Young 1987). We found that fewer people had diarrhoea when given PN (RR 2.17, 95% CI 1.72 to 2.75; 363 participants; I^2 = 57%; Analysis 1.8).

Three studies comparing EN versus PN reported data for abdominal distension, with little or no difference in incidence of abdominal distension according to feeding regimen (RR 1.53, 95% CI 0.34 to 6.96; 2505 participants; I^2 = 0%; Analysis 1.9) (Altintas 2011; Harvey 2014; Peterson 1988).

Single studies also reported data for nausea, bloating or cramps, and gastrointestinal bleeding (Adams 1986); gastric reflux, ileus, and small bowel ileus (Dunham 1994); stress ulcer (Fan 2016); jaundice, ischaemic bowel, and elevated liver enzymes (Harvey 2014); and anastomotic leak (Xi 2014). See Table 1.

Infective events

Seven studies comparing EN versus PN reported data for sepsis (Altintas 2011; Engel 1997; Justo Meirelles 2011; Kudsk 1992; Peterson 1988; Xi 2014; Young 1987). EN may reduce incidences of sepsis (RR 0.59, 95% CI 0.37 to 0.95; 361 participants; I^2 = 27%; low-certainty evidence; Analysis 1.10). We used GRADE to downgrade by two levels; we were concerned by study limitations and indirectness. See Summary of findings for the main comparison.

Seven studies comparing EN versus PN reported data for pneumonia, or aspiration pneumonia, or ventilator-acquired pneumonia (Adams 1986; Altintas 2011; Borzotta 1994; Fan 2016; Justo Meirelles 2011; Kudsk 1992; Young 1987). One study reported data for pneumonia and aspiration pneumonia and we included only data for pneumonia in the analysis (Young 1987). One feeding regimen rather than another may make little or no difference to pneumonia (RR 1.10, 95% CI 0.82 to 1.48; 415 participants; I^2 = 55%; low-certainty evidence; Analysis 1.11). We used GRADE and downgraded by two levels; we were concerned by study limitations and indirectness. See Summary of findings for the main comparison.

Three studies comparing EN versus PN reported data for intra-abdominal infection or intra-abdominal abscess (Adams 1986; Gencer 2010; Kudsk 1992). We found fewer intra-abdominal infections when EN was given (RR 0.26, 95% CI 0.07 to 0.89; 202 participants; I^2 = 0%; Analysis 1.12).

Three studies reported data for wound infection (Adams 1986; Borzotta 1994; Gencer 2010). We found little or no difference between groups in number of participants with a wound infection (RR 1.45, 95% CI 0.55 to 3.82; 155 participants; I^2 = 55%; Analysis 1.13).

Three studies reported data for urinary tract infection (Borzotta 1994; Gencer 2010; Young 1987). We found little or no difference between groups in number of participants with a urinary tract infection (RR 1.48, 95% CI 0.65 to 3.40; 160 participants; I^2 = 49%; Analysis 1.14).

Single studies also reported data for: persistent fever without obvious cause (Adams 1986); catheter infections (Altintas 2011); meningitis, sinusitis, bronchitis, *Clostridium difficile*, and peritonitis (Borzotta 1994); intracranial infection and pyaemia (Fan 2016); pulmonary infection (Gencer 2010); empyema (Kudsk 1992); and aspiration pneumonia and infection (type of infection not described) (Young 1987). See Table 1.

Bertolini 2003 reported that there were no severe adverse events related to the intervention or comparison and Radrizzani 2006 reported no severe adverse events related to the intervention. Hadfield 1995 did not report adverse events. Abdulmeguid 2007 collected data for nosocomial bloodstream infections and septic morbidity but these were not clearly reported in the abstract. Rapp 1983 reported data for some participants who had sepsis but this was not clearly reported.

Subgroup analysis

1. Early initiation of feeding (less than 48 hours) versus late initiation of feeding (48 hours or greater)

Eleven studies comparing EN versus PN initiated feeding within 48 hours (Adams 1986; Altintas 2011; Bertolini 2003; Dunham 1994; Engel 1997; Fan 2016; Harvey 2014; Justo Meirelles 2011; Kudsk 1992; Peterson 1988; Radrizzani 2006). No studies reported late initiation of EN and late initiation of PN, therefore we could not conduct subgroup analysis for this comparison.

2. Normocaloric intake (to match 80% to 100% of energy expenditure) versus hypocaloric intake (less than 70% of energy expenditure)

We considered possible subgroup analysis based on terms used by study authors to describe whether intake was formulated to be normocaloric or hypocaloric; we did not make judgements based on other information such as target rates (measured as kilocalories/kilogram). No studies described intake as normocaloric or hypocaloric, therefore, we did not conduct subgroup analysis.

3. 'Frail elderly' versus other participants

We identified no studies that specified inclusion of frail elderly participants, or subdivided participant characteristics by this description.

4. Gastrointestinal medical or surgical participants versus non-gastrointestinal medical or surgical participants

Three studies comparing EN versus PN included participants with only abdominal injury or who had gastrointestinal surgery (Gencer 2010; Kudsk 1992; Peterson 1988). For the relevant outcomes, we compared these with studies in which participants did not have a primary diagnosis of gastrointestinal medical or surgical conditions. We could not be certain of primary diagnoses in Abdulmeguid 2007, and did not include this study in subgroup analysis.

Subgroup analysis showed little or no difference in rates of in-hospital mortality (Chi^2 = 0.05, degrees of freedom (df) = 1 (P = 0.83), I^2 = 0%) based on whether participants were gastrointestinal surgical or medical participants (RR 0.88, 95% CI 0.06 to 13.74; 98 participants; 1 study), or participants who did not have a primary diagnosis of a gastrointestinal surgical or medical condition (RR 1.19, 95% CI 0.80 to 1.77; 361 participants; 6 studies; I^2 = 22%; Analysis 1.15).

Subgroup analysis showed no difference in rates of mortality at 30 days (Chi^2 = 0.25, df = 1 (P = 0.62), I^2 = 0%) based on whether participants were gastrointestinal surgical or medical participants (RR 0.67, 95% CI 0.12 to 3.71; 60 participants; 1 study), or participants who did not have a primary diagnosis of a gastrointestinal surgical or medical condition (RR 1.03, 95% CI 0.93 to 1.15; 3008 participants; 9 studies; I^2 = 41%; Analysis 1.16).

Sensitivity analysis

1. Selection bias

We assessed six studies as having low risk of selection bias for both sequence generation and allocation concealment (Bertolini 2003; Borzotta 1994; Harvey 2014; Kudsk 1992; Peterson 1988; Radrizzani 2006). In sensitivity analysis, we excluded studies that had high or unclear risk of both sequence generation and allocation concealment. For in-hospital mortality, this altered the effect estimate with fewer deaths for participants given PN (RR 2.66, 95% CI 1.04 to 6.85; 196 participants; 3 studies; I^2 = 0%). There was no difference in effect estimates for mortality within 30 days, and within 90 days.

2. Attrition bias

We judged two studies to have unclear risk of attrition bias and performed sensitivity analysis by excluding them from appropriate analyses (Borzotta 1994; Young 1987). For the comparison EN versus PN, we noted no change in effect for in-hospital mortality, mortality at 30 days, and mortality at 90 days.

3. Effects model

We reanalysed our mortality data using a random-effects model; this did not change the effect.

Enteral nutrition versus enteral nutrition and parenteral nutrition

Primary outcome

1. Mortality

One study reported loss of randomized participants from analysis due to death (Dunham 1994), and we included these participants for our primary analysis.

In hospital

Five studies comparing EN versus EN and PN reported data for in-hospital mortality (Abrishami 2010; Casaer 2011; Dunham 1994; Heidegger 2013; Wischmeyer 2017). One feeding regimen rather than the other may make little or no difference to in-hospital mortality (RR 0.99, 95% CI 0.84 to 1.16; 5111 participants; I^2 = 0%; low-certainty evidence; Analysis 2.1). We used GRADE to downgrade by two levels; we were concerned by study limitations and indirectness. See Summary of findings 2.

Within 30 days

One study did not report the time point for mortality and we included this study in the analysis as mortality within 30 days (Fan 2016). We included three studies in the analysis comparing EN versus EN and PN (Chiarelli 1996; Fan 2016; Heidegger 2013). It is uncertain whether combined EN and PN reduced mortality at 30 days because the certainty of the evidence is very low (RR 1.64, 95% CI 1.06 to 2.54; 409 participants; I^2 = 0%; Analysis 2.2). We used GRADE to downgrade by three levels; we were concerned by

study limitations, indirectness, and imprecision. See Summary of findings 2.

Within 90 days

Two studies comparing EN versus EN and PN reported data for mortality within 90 days (Bauer 2000; Casaer 2011). One feeding regimen rather than the other may make little or no difference to mortality at 90 days (RR 1.00, 95% CI 0.86 to 1.18; 4760 participants; I^2 = 0%; low-certainty evidence; Analysis 2.3). We used GRADE to downgrade the evidence by two levels; we were concerned by study limitations and indirectness. See Summary of findings 2.

Within 180 days

One study (120 participants) comparing EN versus EN and PN reported mortality at two years; interpretation of a figure of cumulative survival over time reported by study authors showed that all deaths were within 180 days (Bauer 2000). Study authors reported 24 deaths in each group (60 participants per group). We used the Review Manager 5 calculator to obtain the effect estimate (RR 1.00, 95% CI 0.65 to 1.55) (Review Manager 2014). It is uncertain whether one feeding regimen rather than another reduces mortality within 180 days because the certainty of this evidence is very low. We used GRADE to downgrade by three levels; we were concerned by study limitations (one level) and imprecision (two levels). See Summary of findings 2.

Secondary outcomes

1. Number of intensive care unit-free days up to day 28

No studies reported data for number of ICU-free days.

2. Number of ventilator-free days up to day 28

No studies reported data for number of ventilator-free days.

3. Adverse events as reported by study authors

Study authors did not always describe outcomes as 'adverse events.' We collected outcomes as described by study authors, which we categorized as mechanical events, metabolic events, gastrointestinal events, and infective events. We combined data when more than one study reported an event. We reported single study data of adverse events in Table 2. Abrishami 2010 did not report adverse event outcomes.

Mechanical events

Two studies comparing EN versus EN and PN reported data for feeding tube obstruction (Casaer 2011; Dunham 1994). There was little or no difference in events between groups (RR 0.96, 95% CI 0.70 to 1.32; 4662 participants; I^2 = 0%; Analysis 2.4).

One study reported data for failure to intubate, and withdrawal of tube by participant (Dunham 1994), and one study reported data for nasal bleeding, central venous catheter obstruction, pneumohaemothorax, and subclavian artery puncture (Casaer 2011). See Table 2.

Metabolic events

One study comparing EN versus EN and PN reported data for hypoproteinaemia (Fan 2016). See Table 2.

Gastrointestinal events

Four studies comparing EN versus EN and PN reported data for diarrhoea (Bauer 2000; Casaer 2011; Chiarelli 1996; Fan 2016). We noted substantial statistical heterogeneity between studies (I^2 = 88%) and did not pool data (Analysis 2.5).

Single studies reported data for vomiting or aspiration (Casaer 2011), gastric reflux (Dunham 1994), and stress ulcer (Fan 2016). See Table 2.

Infective events

Two studies reported pneumonia (aspirated pneumonia in Fan 2016; pneumonia in the ICU in Wischmeyer 2017). It is uncertain whether one feeding regimen rather than another reduced pneumonia because the certainty of this evidence is very low (RR 1.40, 95% CI 0.91 to 2.15; 205 participants; I^2 = 31%; Analysis 2.6). We used GRADE to downgrade the evidence by three levels; we were concerned by study limitations (one level) and imprecision (two levels). See Summary of findings 2.

Two studies reported wound infections (Casaer 2011; Wischmeyer 2017); we used data for skin/soft tissue wounds in Wischmeyer 2017. We found little or no difference in events between groups (RR 0.67, 95% CI 0.50 to 0.92; 4765 participants; I^2 = 46%; Analysis 2.7).

Two studies reported bloodstream infections (Casaer 2011; Wischmeyer 2017); we used data for primary bloodstream infections in Wischmeyer 2017. We found little or no difference in events between groups (RR 0.81, 95% CI 0.66 to 1.01; 4765 participants; I^2 = 0%; Analysis 2.8).

Three studies reported urinary tract infections (Bauer 2000; Casaer 2011; Wischmeyer 2017); we used data for 'lower urinary tract infections' in Wischmeyer 2017. We found little or no difference in events between groups (RR 0.87, 95% CI 0.65 to 1.17; 4885 participants; I^2 = 52%; Analysis 2.9).

Three studies reported airway infections (Bauer 2000; Casaer 2011; Wischmeyer 2017); we used data for 'lower respiratory tract infection' in Wischmeyer 2017, and 'respiratory infection' in Bauer 2000. We noted substantial statistical heterogeneity between studies (I^2 = 78%) and did not pool data (Analysis 2.10).

Single studies reported data for pyaemia and intracranial infection (Fan 2016); and surgical deep infections, catheter bloodstream infections, upper urinary tract infections, and intra-abdominal infections (Wischmeyer 2017). See Table 2. One study reported number of infections after day nine and reported this as number of events rather than by participant; we did not include these data because we could not be certain whether participants had more than one infection (Heidegger 2013).

Subgroup analysis

1. Early initiation of feeding (less than 48 hours) versus late initiation of feeding (48 hours or greater)

Four studies comparing EN versus EN and PN initiated feeding with 48 hours (Bauer 2000; Dunham 1994; Fan 2016; Wischmeyer 2017). One study comparing EN versus EN and PN initiated a late feeding protocol for the EN group after four days of all participants being given PN (Chiarelli 1996); PN was initiated early and weaning to EN was initiated late. Two studies comparing EN versus EN and PN initiated a late feeding protocol for the PN group after three days of

all participants being given EN (Casaer 2011; Heidegger 2013); EN was initiated early and supplemental PN was initiated late. We did not conduct subgroup analysis for this comparison because there were few studies.

2. Normocaloric intake (to match 80% to 100% of energy expenditure) versus hypocaloric intake (less than 70% of energy expenditure)

We considered possible subgroup analysis based on terms used by study authors to describe whether intake was formulated to be normocaloric or hypocaloric; we did not make judgements based on other information such as target rates (measured as kilocalories/kilogram). No studies described intake as normocaloric or hypocaloric and we did not conduct a subgroup analysis.

3. 'Frail elderly' versus other participants

We identified no studies that specified inclusion of frail elderly participants, or subdivided participant characteristics by this description.

4. Gastrointestinal medical or surgical participants versus non-gastrointestinal medical or surgical participants

Two studies comparing EN versus EN and PN included participants who were only non-gastrointestinal surgical or medical participants (Abrishami 2010; Heidegger 2013). Two studies included participants with a mix of primary diagnoses which included gastrointestinal medical or surgical conditions (Casaer 2011; Wischmeyer 2017). One study did not report whether participants had gastrointestinal medical or surgical conditions (Fan 2016). We did not conduct a subgroup analysis because there were few studies.

Sensitivity analysis

1. Selection bias

We assessed five studies as having high or unclear risk of sequence generation (Abrishami 2010; Bauer 2000; Chiarelli 1996; Dunham 1994; Fan 2016). We excluded these studies from the analysis and found no difference in interpretation of effect estimates for in-hospital mortality. It was not feasible to conduct sensitivity analysis for mortality at 30 days and mortality at 90 days because only one study remained.

2. Attrition bias

We judged one study to have unclear risk of attrition bias and performed sensitivity analyses by excluding it from appropriate analyses (Heidegger 2013). There was no difference in effect for mortality in hospital and at 30 days.

3. Effects model

We reanalysed our mortality data using a random-effects model; this did not change the effect.

DISCUSSION

Summary of main results

We included 25 studies comparing EN versus PN or versus EN and PN given to critically ill adults in the ICU. In addition, we identified nine studies awaiting classification (three completed or terminated studies without publication of full report, two studies published only as abstracts with insufficient information, three studies for which we were unable to access full reports, one study requires translation), and two ongoing studies.

We found low- and very low-certainty evidence showing no difference between EN versus PN in mortality in hospital, within 30 days, within 90 days, and within 180 days. No studies reported number of ICU-free days up to day 28. One study reported number of ventilator-free days up to day 28 and it is uncertain whether one feeding route rather than another altered the number of ventilator-free days because certainty of the evidence is very low. We found low- and very low-certainty evidence showing no difference between EN versus combined EN and PN in mortality in hospital, within 90 days, and within 180 days. It is uncertain whether combined EN and PN reduces mortality at 30 days because certainty of the evidence is very low.

Studies reported adverse events, these were: mechanical (aspiration, pneumothorax, nasal bleeding, subclavian artery puncture, tube or line obstruction, line malfunctions, failure to intubate); metabolic (hyperglycaemia, hypoproteinaemia, and electrolyte disturbance); gastrointestinal (diarrhoea, vomiting, abdominal distension, nausea, bloating or cramps, jaundice, stress ulcer, elevated liver enzymes, and gastric reflux); and infective (sepsis, pneumonia, catheter infections, pulmonary infection, intracranial infection, primary bloodstream infections, wound infections, intra-abdominal infection, urinary tract infections, surgical infections, airway infection, pyaemia, empyema, and line sepsis).

We found low- and very low-certainty evidence showing no difference between EN versus PN in participants with aspiration or pneumonia. We found that EN may reduce sepsis (low-certainty evidence) and it is uncertain whether PN reduces vomiting because certainty of the evidence is very low. In addition, we found no evidence of a difference between EN versus PN in: incidences of pneumothorax, abdominal distension, wound infections, and urinary tract infections. We found fewer people who were given EN had hyperglycaemia and had intra-abdominal infections, and fewer people who were given PN had diarrhoea. We did not use GRADE to assess the certainty of the evidence for these additional adverse events, and noted that evidence was from few studies.

It is uncertain whether combined EN and PN compared to PN reduces pneumonia because the certainty of the evidence is very low. In addition, we found little or no difference between EN versus combined EN and PN in participants with wound infections, bloodstream infections, urinary tract infections, or feeding tube occlusion.

Overall completeness and applicability of evidence

We identified 25 studies including 8816 participants who were admitted to the ICU with a wide range of diagnoses. Whilst we noted limited statistical heterogeneity in most of the review outcome analyses, it is possible that the range of primary diagnoses may have introduced heterogeneity and reduced the applicability of these findings, and we used GRADE assessment to reduce our certainty in the estimates of effect. Despite the number of included studies, we were unable to conduct subgroup analyses on some of our proposed subgroups, and this limited exploration of differences between included studies. We also noted that studies ranged in date of publication from 1983 to 2017, and, whilst we did not assess the potential influence of date on our results, it is possible that

changes in management of people in the ICU may mean that some study data may not be generalizable to the current ICU context.

Quality of the evidence

Enteral nutrition versus parenteral nutrition

We noted that all personnel were aware of the type of feeding regimen for each group of participants and for all outcomes; we believed that this introduced a high risk of performance bias. Using the GRADE approach, we downgraded the certainty of the evidence for mortality at each time point, for the number of ventilator-free days up to day 28, and each adverse event (aspiration, sepsis, pneumonia, and vomiting) by one level for study limitations.

Studies included participants with varied primary diagnoses (e.g. gastrointestinal or non-gastrointestinal medical or surgical patients, and whether participants were being mechanically ventilated). We believed that this reduced the directness of the evidence for some outcomes; it was possible that participants with some diagnoses may have responded differently to each feeding. Using the GRADE approach, we downgraded the certainty of evidence for in-hospital mortality, mortality within 30 days and 90 days, and adverse events by one level for indirectness.

We noted that most studies included a small number of participants, and two studies included large sample sizes (Casaer 2011; Harvey 2014); these studies introduced a larger weighting to the effect estimates across some analyses, and was particularly noticeable in the analyses of aspiration and vomiting in which only two studies reported data for several adverse event outcomes. We considered the effect of these large studies on our results and, using the GRADE approach, we downgraded the certainty of the evidence of aspiration and vomiting by one level for imprecision. For mortality at 180 days, we found only one small study and we believed that this result alone gave an imprecise effect and we downgraded the certainty of the evidence for this outcome by one level for imprecision.

Enteral nutrition versus enteral nutrition and parenteral nutrition

We noted that all personnel were aware of the type of feeding regimen for each group of participants and for all outcomes, we believed that this introduced a high risk of performance bias. Using the GRADE approach, we downgraded the certainty of the evidence for mortality (at each time point) and for pneumonia by one level for study limitations.

Studies included participants with varied primary diagnoses (e.g. gastrointestinal or non-gastrointestinal medical or surgical patients, and whether participants were being mechanically ventilated). We believed that this reduced the directness of the evidence for some outcomes; it is possible that participants with some diagnoses may have responded differently to each feeding. Using the GRADE approach, we downgraded the certainty of evidence for in-hospital mortality, and mortality within 30 days and 90 days, by one level for indirectness.

For mortality at 180 days, we found only one small study, and for pneumonia we found two small studies. We believed that these results alone gave an imprecise effect and downgraded the certainty of evidence for these outcomes by one level for imprecision.

Potential biases in the review process

We conducted a thorough search and used two review authors to assess study eligibility, extract data, and assess risk of bias in included studies, and, therefore, we reduced potential bias in the review process. However, we reached some decisions on eligibility based on information presented only in study reports and we did not contact study authors for clarification; we excluded some studies that did not state clearly that participants were in the ICU. We followed a protocol decision to include outcome data reported as number of ICU-free days, and number of ventilator-free days, up to day 28 (Lewis 2016). Many of the included studies had reported length of stay in ICU, or duration of mechanical ventilation, and we did not include this outcome data in the review.

Agreements and disagreements with other studies or reviews

We noted that reviews by other review authors used different criteria for deciding whether participants were critically ill and, therefore, these reviews did not include all the same studies (Elke 2016; Simpson 2005). Simpson 2005 reported reduced mortality with PN, however this contradicted the more recent review by Elke 2016 whose findings were consistent with our review findings of no effect on mortality for EN versus PN.

We found no evidence of a difference in number of participants with adverse events. Reviews by Elke 2016 and Simpson 2005 reported reduced infectious complications when PN was given. Whilst these reviews included some different studies to our review, review authors presented composite data for number of infections as reported by study authors. We reported data for infections by the number of participants who had particular types of infection, rather than a composite figure, and therefore our review differed in the type of data reported for infections.

AUTHORS' CONCLUSIONS

Implications for practice

Comparing enteral nutrition (EN) versus parenteral nutrition (PN), we found that one feeding regimen rather than another may make little or no difference to mortality in hospital or within 30 days. We are uncertain whether either of these feeding regimens reduces mortality within 90 days or within 180 days because the certainty of the evidence is very low. We are uncertain whether either of these feeding regimens reduces the number of ventilator-free days up to 28 days, or reduces the incidence of aspiration, because the certainty of the evidence is very low. We found low-certainty evidence that using either feeding regimen may make little or no difference to pneumonia. We found low-certainty evidence that EN may reduce sepsis, and we are uncertain whether PN reduces vomiting because the certainty of the evidence is very low.

Comparing EN versus EN and PN, we found that one feeding regimen rather than another may make little or no difference to mortality in hospital or within 90 days. We are uncertain whether either of these feeding regimens reduces mortality within 30 days or within 180 days, or reduces incidences of pneumonia, because the certainty of the evidence is very low.

Evidence is from 25 studies with 8816 participants with a wide range of diagnoses; all participants were critically ill in the intensive care unit (ICU). The 11 studies in the Characteristics of studies awaiting

classification table may alter the conclusions of the review once assessed.

Implications for research

Research continues in the field of ICU nutrition and we have included two ongoing studies, and 11 studies that are awaiting classification, which may contribute to future updates of this review. We acknowledge the difficulty in reducing performance bias in future studies, but propose that studies should introduce methods to reduce detection bias, and improve methods of allocation concealment. Large studies with a mixed ICU population would increase generalizability to the intensive care setting. We propose that future studies consider measure of outcomes in terms of number of ICU-free days, and number of ventilator-free days, up to day 28 because these measures reflect the expected loss of participants in this setting due to death. Also, we propose that future studies assess the impact of nutrition on long-term functional outcomes.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Abdulmeguid 2007

Methods	RCT, 2-arm, parallel design
Participants	**Total number of randomized participants:** 80 **Inclusion criteria** 1. Critically ill, mechanically ventilated people in the ICU **Exclusion criteria** 1. Not reported in abstract

Abdulmeguid 2007 *(Continued)*

	Baseline characteristics No details reported in abstract **Country:** not reported (published in Croatian journal) **Setting:** ICU
Interventions	**EN group** n = 40 **Details:** nutritional requirements based on Harris-Benedict equation. Formula consisted of fat, carbohydrate, and protein. Identical to PN group **PN group** n = 40 **Details:** nutritional requirements based on Harris-Benedict equation. Formula consisted of fat, carbohydrate, and protein. Identical to EN group
Outcomes	1. Serum glucose levels 2. Nosocomial bloodstream infections 3. Septic morbidity 4. LOS in ICU and hospital 5. Duration of mechanical ventilation 6. Mortality
Notes	**Funding/declarations of interest:** not reported **Study dates:** not reported We were unable to source the full-text of this study, and did not have the study authors' contact details to attempt contact.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details. Abstract only
Allocation concealment (selection bias)	Unclear risk	No details. Abstract only
Blinding of participants and personnel (performance bias) All outcomes	High risk	No details. Abstract only. We assumed investigators made no attempts to blind personnel
Blinding of outcome assessment (detection bias) All outcomes (except mortality)	Unclear risk	No details. Abstract only
Blinding of outcome assessment (detection bias) Mortality	Low risk	No details. Abstract only. Lack of blinding unlikely to influence outcome data for mortality

Abdulmeguid 2007 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No details. Abstract only. Outcome data were well reported and we assumed there were no losses
Selective reporting (reporting bias)	Unclear risk	No details. Abstract only
Baseline characteristics	Unclear risk	Study authors described participants as matched on SAPS II, age, and primary diagnoses. No baseline characteristics tables or additional detail available
Other bias	Unclear risk	Study authors described nutritional formula of both groups as identical. Insufficient detail in abstract to make judgement on other sources of bias

Abrishami 2010

Methods	RCT, single-centre, 2-arm, parallel design
Participants	**Total number of randomized participants:** 20 **Inclusion criteria** 1. > 18 years of age, recent ICU admission (< 24 hours), having SIRS, APACHE II > 10, expected not to feed via oral route for ≥ 5 days **Exclusion criteria** 1. People with high probability of death in next 7 days of admission 2. Pregnant or lactating 3. Having contraindications to EN **Primary diagnoses** 1. SIRS **Baseline characteristics** **EN group** 1. Age, mean (SD): 58.4 (± 5.07) years 2. Gender: not reported 3. APACHE II, median: 17.0 4. SOFA, median: 9.0 **EN + PN group** 1. Age, mean (SD): 54.9 (± 5.16) years 2. Gender: not reported 3. APACHE II, median: 18.5 4. SOFA, median: 7.0 **Country:** Iran **Setting:** ICU
Interventions	**EN group** n = 10; 0 losses

Abrishami 2010 *(Continued)*

	Details: nasogastric tube feeding for 7 days. Feeding formula was Fresubin Original (Fresenius Kabi, Germany) given in solution as 1 kcal/mL. Average 70 kg participant initially received 50 mL every 3 hours, increased with 50 mL increments to maximum 300 mL every 3 hours at rate of 100 mL/h. GRV threshold at 300 mL with delay of feeding for 3 hours if threshold was reached. Glycaemic management not reported. **EN + PN group** n = 10; loss of 1 participant on day 3 (move to different hospital); number analysed assumed to be 9. **Details:** EN as above. PN consisted of 500 mL of 10% AA solutions (B Braun, Germany), 500 mL of 50% dextrose, infused over 24 hours. Equivalent management of GRV. Duration of feeding for 7 days
Outcomes	1. Mortality (within 7 days) 2. Analysis of inflammatory markers 3. Length of ICU and hospital stay
Notes	**Funding/declarations of interest:** partly supported by grant from Tehran University of Medical Sciences **Study dates:** November 2007 to May 2009

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomized but no additional details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	No details and we assumed investigators made no attempts to blind personnel
Blinding of outcome assessment (detection bias) Mortality	Low risk	No details. Lack of blinding unlikely to influence outcome data for mortality
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant moved to another hospital after 3 days, not clear whether data for this participant were sourced but small loss unlikely to influence outcome data
Selective reporting (reporting bias)	Unclear risk	No protocol or clinical trials registration reported. Therefore, not feasible to make judgement on selective outcome reporting bias
Baseline characteristics	Low risk	Appeared to be equivalent between groups
Other bias	Low risk	Glycaemic management equivalent for each group. No other sources of bias identified

Adams 1986

Methods	RCT, single-centre, 2-arm, parallel design
Participants	**Total number of randomized participants:** 46 **Inclusion criteria** 1. 18 to 60 years of age 2. 80% to 130% of desirable bodyweight 3. Significant injuries to ≥ 2 body systems **Exclusion criteria** 1. History of hepatic or renal failure **Primary diagnoses** 1. People with trauma injuries to include: head injury, spinal fracture, severe facial fractures, severe thoracic injury, major intra-abdominal injury, pelvic fracture, long bone fractures, or other major soft-tissue injury **Baseline characteristics** **EN group** 1. Age, mean (SD): 30 (± 9) years 2. Gender M/F: 15/8 3. APACHE II: not reported **PN group** 1. Age, mean (SD): 29 (± 10) years 2. Gender M/F: 16/7 3. APACHE II: not reported **Country:** USA **Setting:** medical centre
Interventions	**EN group** n = 23; 0 losses; 4 participants required conversion to PN; assume ITT analysis **Details:** jejunostomy tube placement. Feeding started on first postoperative day. Feeding assumed to be for duration of study period (14 days). Target rate changed during study as participants in both groups appeared to have insufficient nitrogen balance; Phase 1: target rate calculated as Harris-Benedict BEE x 1.68, Phase 2: target rate calculated as Harris-Benedict BEE x 2.0 plus an additional 20%. Formula consisted of polymeric feeding solution (5 participants received Isocal HCN: 15% protein calories, 45% carbohydrate calories, 49% lipid calories. 18 participants received Traumacal: 22% protein calories, 40% carbohydrate calories, 48% lipid calories) (Mead Johnson Nutritional Division, Evansville, IN, USA). Participants given insulin to manage blood glucose levels. Metabolic or gastrointestinal intolerances were treated by physician as required. **Caloric intake received, mean:** Phase 1: 2088 calories; Phase 2: 2678 calories **PN group** n = 23; 0 losses **Details:** subclavian line placement. Feeding started on first postoperative day, assumed duration of study period (14 days). Phase 1: target rate calculated as Harris-Benedict BEE x 1.68, Phase 2: target rate calculated as Harris-Benedict BEE x 2.0. Formula consisted of 25% dextrose, 4.25% crystalline AAs (Travasol: Baxter Healthcare Corporation, Deerfield, IL, USA). Additional caloric prescriptions of 500 mL

Adams 1986 *(Continued)*

	of 10% lipid, twice weekly, were optional. 50 mL per hour for first 24 hours, then advanced as tolerated at physician's discretion. **Caloric intake received, mean:** Phase I: 2572 calories; Phase 2: 2876
Outcomes	1. Length of hospital stay 2. Length of ICU stay 3. Length of time on the surgical service 4. Number of ventilator days 5. Number and type of operations 6. Total number of days receiving EN or PN 7. First day of oral intake 8. Weight at time nutritional support was discontinued 9. Medical complications (wound infection, pneumonia, intra-abdominal infection, persistent fever, gastrointestinal bleeding, hepatic failure, acute renal failure, pancreatitis) 10. Complications (bloating, cramps, nausea; diarrhoea (diagnosed by 3 to 6 loose or liquid stools per day, or > 6 loose stools for severe diarrhoea) 11. Catheter sepsis (not clearly reported) 12. Mortality 13. Costs of nutritional support
Notes	**Funding/declarations of interest:** supported, in part, by a grant from Mead Johnson Nutritional Division, Evansville, IN, USA **Study dates:** January 1982 to June 1984

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomized by surgical team in operating theatre. No additional information provided
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	No details and we assumed that investigators made no attempts to blind personnel
Blinding of outcome assessment (detection bias) All outcomes (except mortality)	Unclear risk	No details
Blinding of outcome assessment (detection bias) Mortality	Low risk	No evidence of blinding. Lack of blinding unlikely to influence outcome data for mortality
Incomplete outcome data (attrition bias) All outcomes	Low risk	No apparent losses
Selective reporting (reporting bias)	Unclear risk	Clinical trial registration or prospectively written protocol not reported. Not feasible to judge selective outcome reporting bias

Adams 1986 *(Continued)*

Baseline characteristics	Low risk	Appeared comparable
Other bias	Unclear risk	Changes to feeding protocol during study, but target rates were comparable between groups. No other sources of bias identified

Altintas 2011

Methods	RCT, single-centre, 2-arm, parallel design
Participants	**Total number of randomized participants:** 71 **Inclusion criteria** 1. Needed invasive mechanical ventilation in the ICU **Exclusion criteria** 1. Informed consent could not be obtained 2. Participant received > 48 hours of mechanical ventilation in another unit 3. Participant required < 72 hours of mechanical ventilation in the ICU or died within the first 72 hours 4. Randomized route of nutrition support was medically contraindicated 5. Nutrition support could not be started because of severe metabolic/haemodynamic instability during the first 48 hours of ventilation, or the participant was already receiving nutrition support at the time of intubation **Primary diagnoses** 1. Acute respiratory failure 2. Acute neurological pathology 3. Severe metabolic/renal disease 4. Intoxication 5. Postoperative complications, or other diagnoses **Baseline characteristics** **EN group** 1. Age, mean (SD): 57.77 (± 19.88) years 2. Gender M/F: 15/15 3. APACHE II, mean (SD): 20.03 (± 7.43) **PN group** 1. Age, mean (SD): 57.95 (± 18.00) years 2. Gender M/F: 23/18 3. APACHE II, mean: 22.66 (± 7.47) **Country:** Turkey **Setting:** university hospital, medical ICU
Interventions	**EN group** n = 30; 0 losses; ITT analysis **Details:** preference for postpyloric tube placement, otherwise gastric feeding, feeding initiated within 48 hours, at target rate of 25 to 30 kcal/kg/day using ideal bodyweight, formula with proteins, carbohy-

Altintas 2011 *(Continued)*

	drates, and lipids. 20 mL/hour of standard solution, increased every 4 to 6 hours by 20 mL/hour if GRV < 150 mL. Continuous infusion of insulin as needed with target level of 100-140 mg/kL. **Caloric intake received, reported as mean (SD) percentage of target calories given:** 46.48 (± 19.34) **PN group** n = 41; 0 losses; deviations from protocol for 3 participants who were changed to EN feeding due to clinical needs; ITT analysis **Details:** preference for central or venous route, according to participant condition and contraindications to central venous line insertion, otherwise peripheral route. Target rate of delivery and glycaemic management same as EN group. Feeding started at full dose, unless participant at risk of refeeding syndrome, or severely malnourished and already had electrolyte disturbance. **Caloric intake received, reported as mean (SD) percentage of target calories given:** percentage of target calories given 66.78 (SD ± 18.85)
Outcomes	1. Mortality (in hospital and ICU) 2. Pneumonia (diagnosed according to ACCP consensus statement) 3. Sepsis 4. Catheter infections 5. Diarrhoea (diagnosed by an increase in stool amount > 1 L and frequency > 3/day with loss of consistency) 6. Vomiting 7. Hypervolaemia 8. Severe shock 9. Length of ICU stay 10. Length of mechanical ventilation 11. Achievement of feeding goals 12. Interruption of feeding
Notes	**Funding/declarations of interest:** no details **Study dates:** February 2004 to January 2006

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quasi-randomized method of sequence generation. Quote: "Patients were randomized to receive either EN or PN according to the last digit of their assigned hospital record number: odd numbers received PN, and even numbers received EN"
Allocation concealment (selection bias)	Low risk	Adequate concealment despite inadequate sequence generation. Hospital record numbers were assigned by staff independent of the ICU team
Blinding of participants and personnel (performance bias) All outcomes	High risk	No details and we assumed investigators made no attempts to blind personnel
Blinding of outcome assessment (detection bias) All outcomes (except mortality)	Unclear risk	No details

Altintas 2011 *(Continued)*

Blinding of outcome assessment (detection bias) Mortality	Low risk	No details. Lack of blinding unlikely to influence assessment of outcomes for mortality
Incomplete outcome data (attrition bias) All outcomes	Low risk	No apparent losses but deviations from protocol in 3 participants in PN group. ITT analysis used
Selective reporting (reporting bias)	Unclear risk	Clinical trials registration not reported. Not possible to make assessment of selective outcome reporting bias
Baseline characteristics	Unclear risk	More sepsis and acute pathology in PN group; not reported as statistically significant. Unclear if these differences could influence outcome data. Also, we noted that number of participants in each group was not equivalent (41 in PN group; 30 in EN group) and this was not explained
Other bias	Low risk	Glycaemic controls equivalent between groups. Nutritional goals appeared to be equivalent. No other sources of bias identified

Bauer 2000

Methods	RCT, single-centre, 2-arm, parallel design
Participants	**Total number of randomized participants:** 120 **Inclusion criteria** 1. > 18 years of age, admitted to the ICU for > 2 days, expected to stay alive > 2 days. Expected to eat < 20 kcal/kg/day for > 2 days, and EN to be progressively administered for > 2 days **Exclusion criteria** 1. Postelective surgery patients 2. People with contraindication to enteral or parenteral feeding 3. History of allergy to vitamins **Primary diagnoses** 1. Multiple trauma 2. Respiratory failure 3. Stroke 4. Sepsis 5. Coronary artery disease 6. Poisoning 7. Renal failure 8. Gastrointestinal bleeding **Baseline characteristics** **EN group** 1. Age, mean (SD): 55 (± 18) years 2. Gender, M/F: 42/18 3. SAPS II, mean (SD): 41 (± 13) **EN + PN group**

Bauer 2000 *(Continued)*

1. Age, mean (SD): 53 (± 18) years
2. Gender, M/F: 40/20
3. SAPS II, mean (SD): 43 (± 14)

Country: France

Setting: 2 ICUs (medical and surgical) at same hospital

Interventions	**EN group** n = 60; 7 losses; ITT analysis **Details:** feeding for 4 to 7 days with target rate of delivery 25 kcal/kg bodyweight/day = 100 kcal carbohydrates-fat per gram of nitrogen. Typical 70 kg person received 100 mL initially, with an increased amount in 50 mL steps to a maximum of 350 mL every 4 hours. Feeding solution consisted of protein (20%), polyunsaturated fats (30%), carbohydrates (50%), non-soluble fibres, sodium chloride, potassium chloride, hydrosoluble and liposoluble vitamins. All participants in the EN group also received placebo PN formula, consisting of: sodium chloride, Intravit, Soluvit (Pharmacia and Upjohn, St Quentin-Yvelines, France). GRV measured before each feed; delayed feeding if > 300 mL and cisapride added. Glucose level checked every 4 hours and maintained around 1.6 to 2 g/L with insulin using a sliding scale **Caloric intake received, mean (SD):** EN: 9.9 (± 3.9) kcal/kg/day; PN: 1.4 (± 0.3) kcal/kg/day **EN + PN group** n = 60; 6 losses; ITT analysis **Details:** EN composition as above. PN feeding through central line access. Feeding solution consisted of EN: protein (20%), polyunsaturated fats (30%), carbohydrates (50%), non-soluble fibres, sodium chloride, potassium chloride, hydrosoluble and liposoluble vitamins. PN: 3-in-1 solution of carbohydrates, lipids, and protein; Vitrimix (Fresenius Kabi); hydrosoluble vitamins; Soluvit (Pharmacia and Upjohn, St Quentin-Yvelines, France). **Caloric intake received, mean (SD):** EN: 11 (± 3.3) kcal/kg/day; PN: 13.9 (± 2.5) kcal/kg/day **Note:** study authors reported that increases in EN were the same. PN increases were the same in theory, but not in actuality due to the lack of fat content in the EN group placebo feed
Outcomes	1. Mortality (reported at 90 days, ≤ 2 years) 2. Diarrhoea 3. Need for ventilator support 4. Circulatory, neurological, renal support 5. LOS (ICU and hospital) 6. Nosocomial infections 7. Number of days of ventilator support
Notes	**Funding/declarations of interest:** no reported details **Study dates:** August 1996 to May 1997

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization carried out at central pharmacy but methods were not adequately described
Allocation concealment (selection bias)	Unclear risk	Use of sealed envelopes; no additional details

Bauer 2000 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both participants and personnel were blind to the intervention. Quote: "The bags were prepared under the label A or B. Neither the health care providers nor the patients were aware of their content. Both types of bags were opalescent by the adjunction of small amount of fat and vitamins."
Blinding of outcome assessment (detection bias) All outcomes (except mortality)	Unclear risk	No details. Statistician was blinded
Blinding of outcome assessment (detection bias) Mortality	Low risk	No details; lack of blinding unlikely to influence outcome data for mortality
Incomplete outcome data (attrition bias) All outcomes	Low risk	Some participants received sufficient nutrition by day 4, and some died by day 4 but no difference in these losses between groups and participants included in analysis as ITT
Selective reporting (reporting bias)	Unclear risk	Clinical trials registration not reported. Not possible to make assessment on selective outcome reporting bias
Baseline characteristics	Low risk	Baseline characteristics were very similar between groups
Other bias	Low risk	Protocol for glycaemic management was the same for both groups. Other differences in nutritional protocol are due to study design (EN vs EN + PN). No other sources of bias identified

Bertolini 2003

Methods	RCT, multi-centre, 2-arm, parallel design
Participants	**Total number of randomized participants:** 36 **Inclusion criteria** 1. > 18 years of age, in high level care, in need of artificial ventilation and nutrition for ≥ 4 days **Exclusion criteria** 1. Motor GCS < 4 2. Pure cerebral disease 3. Spinal trauma 4. Referral from ICUs in which participants stayed > 24 hours **Primary diagnoses** 1. All had severe sepsis or septic shock; some participants had respiratory failure, or respiratory plus cardiovascular failure **Baseline characteristics** **EN group** 1. Age, mean (SD): 59.3 (± 17.6) years 2. Gender, M/F: 11/7 3. SAPS II, median (IQR): 41 (39 to 46) 4. SOFA, median (IQR): 7 (5 to 8)

Bertolini 2003 *(Continued)*

	PN group 1. Age, mean (SD): 59.0 (± 21.4) years 2. Gender, M/F: 10/11 3. SAPS II, median (IQR): 43 (35 to 51) 4. SOFA, median (IQR): 7 (6 to 8) **Country:** Italy **Setting:** 33 ICUs
Interventions	**EN group** n = 17; note 1 participant wrongly randomized to non-septic group (see Radrizzani 2006) and then analysed in this report; ITT analysis. 18 participants analysed. **Details:** feeding initiated within 48 hours of ICU admission. Feeding started at 10 kcal/kg/day, rising to 25 to 28 kcal/kg/day by 4th day. Nutritional formula consisted of 55% carbohydrates, 25% fat, 21% protein, 1.3 kcal/mL, containing per 100 mL: L-arginine 0.8 g, omega-3 fatty acids 0.15 g, omega-6 fatty acids 0.7 g, vitamin E 2.9 mg, β-carotene 0.75 mg, zinc 2.2 mg, and selenium 7 µg (Perative Abbott). **Caloric intake received, mean (SD):** 19.1 (± 7.6) kcal/kg/day over the first 6 days **PN group** n = 19; note 2 participants wrongly randomized to non-septic group (see Radrizzani 2006) and then analysed in this report; ITT analysis. 21 participants analysed **Details:** feeding protocol as for EN group. Nutritional formula consists of equivalent carbohydrates, fats, and proteins (59% carbohydrates, 23% fat, 18% protein) but does not appear to include additional vitamins/minerals **Caloric intake received, mean (SD):** 25.9 (± 6.4) kcal/kg/day over the first 6 days
Outcomes	1. Mortality at 28 days and in the ICU 2. Length of ICU stay
Notes	**Funding/declarations of interest:** Abbott Italia **Study dates:** November 1999 to April 2001 **Note:** study was described as an interim analysis. It is the same study as Radrizzani 2006 but data included were for a subgroup of participants with sepsis only. Also, study authors considered the difference in caloric intake and differences in some baseline characteristics to be significant, and conducted an adjusted analysis after which they concluded that these factors were potentially confounding and subsequently ceased randomization into this study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate sequence generation. Use of computer-generated randomization code
Allocation concealment (selection bias)	Low risk	Adequate concealment. Quote: "The randomisation code was generated by a computer programme at the co-ordinating centre and was revealed to investigators by telephone at the moment of randomisation, once baseline data collection was completed."

Bertolini 2003 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	No details and we assumed investigators made no attempts to blind personnel
Blinding of outcome assessment (detection bias) All outcomes (except mortality)	Unclear risk	Study authors reported that outcome data analysts were not blinded; study authors did not report whether outcome assessors were blinded
Blinding of outcome assessment (detection bias) Mortality	Low risk	Lack of blinding unlikely to influence outcome data for mortality
Incomplete outcome data (attrition bias) All outcomes	Low risk	No apparent losses
Selective reporting (reporting bias)	Unclear risk	Clinical trials registration or prospectively published protocol not reported. Not possible to make assessment on reporting bias
Baseline characteristics	Unclear risk	Study authors noted an imbalance in baseline characteristics (PN group had more women, more participants aged > 60 years, more participants with cardiovascular and respiratory failure) and completed adjusted analysis for these variables. We were unclear whether these differences may affect results for our outcomes
Other bias	Unclear risk	Participants in PN group were given more calories in first 3 days because of study design and study authors completed adjusted analysis for this variable. Participants in EN group given additional supplements of minerals/vitamins which are not included in PN formula. We were unclear whether these differences may affect results for our outcomes

Borzotta 1994

Methods	RCT, single-centre, 2-arm, parallel design
Participants	**Total number of randomized participants:** 59 **Inclusion criteria** 1. Adults, 18 to 60 years of age, with head injuries and a GCS ≤ 8, coma persisting > 24 hours **Exclusion criteria** 1. Spinal cord injury 2. Pre-existing metabolic disorders 3. Renal failure 4. Inflammatory bowel disease 5. Neurological prognosis of rapidly fatal injury **Primary diagnosis** 1. Severe head injury **Baseline characteristics** **EN group**

Borzotta 1994 *(Continued)*

1. Age, mean (SD): 26.2 (± 10.4) years
2. Gender, M/F: 21/7
3. APACHE II, mean (SD): 15.7 (± 3.5)

PN group

1. Age, mean (SD): 28.9 (± 10) years
2. Gender, M/F: 19/2
3. APACHE II, mean (SD): 14.9 (± 3.9)

Country: USA

Setting: level 1 trauma centre

Interventions	**EN group** n = 36; 8 losses; 28 analysed. Per-protocol analysis (except for mortality) **Details:** jejunal tube placement, and gastrotomy tubes placed to drain stomach. Feeding started within 24 hours of randomization. Target rates calculated with Harris Benedict formula BEE + 50%. Initiated at 20% of target rate for 12 hours; 40% for 12 hours; 60% for 12 hours; 80% for 12 hours; then target rate. Formula was a Vivonex solution TEN (Norwich Eaton Pharmaceuticals, Inc, Norwich, NY, USA) consisting of 4.9 g/L glutamine, carbohydrates, fat, AAs, other minerals, and Travasol solution (Baxter Healthcare Corp, Deerfield, IL, USA) consisting of 3.21 g/L glutamine, carbohydrates, fat, AAs, other minerals. If extra protein was required then Travasol 10% was given to EN solution. At day 9 to 11, EN group converted from Vivonex TEN to Isotein HN via jejunal tube ("thus keeping both groups identical except for route") **PN group** n = 23; 2 losses; 21 analysed. Per-protocol analysis (except for mortality) **Details:** central venous catheter placement. Feeding continued for 5 days and then attempts to convert to gastric feeding by any routes at the discretion of the clinician. Target rates calculated with Harris Benedict formula BEE + 50%. Feeding initiated 40% target rate of 24 hours; 60% for 12 hours, 80% for 12 hours, then target rate. Formula was an Isotein HN solution (Sandoz Nutrition Corp: Minneapolis, MN, USA) consisting of carbohydrates, fat, AAs, and other minerals. If extra protein was required then Travasol 10% was given to PN solution
Outcomes	1. Infections 2. Nutrition-related complications including hyperglycaemia (diagnosed by blood glucose level of > 180 mg/dL) and diarrhoea 3. Mortality
Notes	**Funding/declarations of interest:** financial support from Norwich Eaton Pharmaceuticals, NY, USA. **Study dates:** July 1990 to December 1991

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate sequence generation. Computer-generated random number tables
Allocation concealment (selection bias)	Low risk	Computer-generated numbers and we assumed that allocation was concealed from investigators
Blinding of participants and personnel (performance bias)	High risk	No details and we assumed investigators made no attempts to blind personnel

Borzotta 1994 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes (except mortality)	Unclear risk	No details
Blinding of outcome assessment (detection bias) Mortality	Low risk	No details. Lack of blinding unlikely to influence outcome data for mortality
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Some loss of participant data: 2 participants in EN group, 8 participants in PN group. Reasons for losses were explained and mortality data included these (death was one of reasons for loss)
Selective reporting (reporting bias)	Unclear risk	Clinical trials registration or prospectively published protocol was not reported. Therefore, not feasible to make judgement on selective outcome reporting bias
Baseline characteristics	Low risk	Appeared comparable, although we noted a large difference in sample size between groups which was unexplained
Other bias	Unclear risk	Some possible differences in nutritional formula. Unclear if this was likely to influence data

Casaer 2011

Methods	RCT, multi-centre, 2-arm, parallel design
Participants	**Total number of randomized participants:** 4640 **Inclusion criteria** 1. Adults admitted to participating ICUs, scored ≥ 3 on NRS, did not meet any of exclusion criteria **Exclusion criteria** 1. < 18 years of age 2. Moribund or coded DNR 3. Enrolled in another trial 4. Had short-bowel syndrome 5. Had home ventilation 6. In a diabetic coma 7. Referred with nutritional regimen 8. Pregnant or lactating 9. No central catheter 10. Taking oral nutrition 11. Readmitted to ICU 12. NRS score < 3 13. Other reason (not described by study authors) 14. Did not give consent 15. People with chronic malnourishment (BMI < 17 kg/m^2) before admission to ICU 16. Referral from another ICU with an established regimen of EN or PN **Primary diagnoses**

Casaer 2011 *(Continued)*

1. Cardiac surgery
2. Complicated abdominal or pelvic surgery
3. Transplantation
4. Trauma
5. Burns
6. Reconstructive surgery
7. Complicated pulmonary or oesophageal surgery
8. Respiratory disease
9. Complicated vascular surgery
10. Gastroenterological or hepatic disease
11. Complicated neurosurgery
12. Haematological or oncological disease
13. Neurological disease
14. Cardiovascular disease
15. Renal disease
16. Neurological presentation of medical disease
17. Metabolic disorder
18. Other (not described by study authors)

Baseline characteristics

EN group

1. Age, mean (SD): 64 (± 15) years
2. Gender, M/F: 1486/842
3. APACHE II, mean (SD): 23 (± 10)

EN + PN group

1. Age, mean (SD): 64 (± 14)
2. Gender, M/F: 1486/826
3. APACHE II, mean (SD): 23 (± 11)

Country: Belgium

Setting: 7 ICUs

Interventions	**EN group** (study authors referred to this group as "late-initiation group") n = 2328; 15 discontinued intervention owing to protocol violation (inadvertent administration of ≥ 1 L/day PN for ≥ 2 days during intervention period); 2328 analysed as ITT **Details:** IV 20% glucose solution (target for total energy intake was 400 kcal/day on 1st ICU day, and 800 kcal/day on 2nd ICU day), and EN via duodenal feeding tube. If EN was insufficient after 7 days, PN was initiated on day 8 to reach caloric goal. Continuous insulin infusion adjusted to obtain blood glucose level 80 to 100 mg/dL **EN + PN group** (study authors referred to this group as "early-initiation group") n = 2312; 0 losses; 2312 analysed **Details:** IV 20% glucose solution (target for total energy intake was 400 kcal/day on first ICU day, and 800 kcal/day on second ICU day). On day 3, PN initiated with dose targeted to 100% of caloric goal through combined EN + PN (except when clinicians predicted that participant would tolerate sufficient EN or oral feeding on day 3). Amount of PN was calculated as amount that was not effectively delivered by EN. Calculations of caloric goal included protein energy and based on ideal bodyweight, age, and gender. PN was reduced and eventually stopped if participant was able to meet > 80% caloric goal with EN or able to resume normal oral feeding. Continuous insulin infusion adjusted to obtain blood glucose level 80 to 100 mg/dL

Casaer 2011 *(Continued)*

Outcomes	1. Death (number of participants alive at discharge from ICU in ≤ 8 days, death in the ICU and in hospital, survival up to 90 days) 2. Rates of complications, and hypoglycaemia 3. Number of ICU days and time to discharge from the ICU 4. Number of participants with new infections (airways, lungs, bloodstream, urinary tract, wounds) 5. Duration of antibiotic therapy 6. Inflammation 7. Time to weaning from mechanical ventilation and need for tracheostomy 8. Acute kidney injury (using RIFLE) 9. Renal replacement therapy 10. Need for and duration of pharmacological or mechanical haemodynamic support 11. Liver dysfunction 12. Duration of hospital stay 13. Functional status at discharge (6-minute walk test and participants who were independent in ADL) 14. Healthcare costs
Notes	**Funding/declarations of interest:** supported by Methusalem programme of the Flemish government, Research Fund of the Catholic University of Leuven, Belgium; the Research Foundation Flanders, Belgium; and the Clinical Research Fund of the University Hospitals Leuven, Belgium. In addition, the Catholic University of Leuven received unrestricted research grant from Baxter Healthcare for less than one-third of study costs. Baxter Healthcare were not involved in the design of study, collection, analysis, or interpretation of data, in preparation of manuscript for publication. **Study dates:** August 2007 to November 2010

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Use of a digital system to prepare order of envelopes
Allocation concealment (selection bias)	Low risk	Use of sequentially numbered, sealed, opaque envelopes, and block size was concealed from treating physicians and nurses
Blinding of participants and personnel (performance bias) All outcomes	High risk	No details and we assumed that investigators made no attempts to blind personnel
Blinding of outcome assessment (detection bias) All outcomes (except mortality)	Low risk	All outcome assessors were blinded to group allocation
Blinding of outcome assessment (detection bias) Mortality	Low risk	All outcome assessors were blinded to group allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Small number of losses in 1 group, unlikely to influence outcome data
Selective reporting (reporting bias)	Low risk	Prospective clinical trials registration (NCT00512122). Outcomes reported same as clinical trials registration documents. We noted that duration of ICU

Casaer 2011 *(Continued)*

		was reported but not listed in the registration documents, but primary outcomes were generally all reported
Baseline characteristics	Low risk	Appeared comparable
Other bias	Low risk	Protocol for glycaemic management was the same for both groups. No other sources of bias identified

Cerra 1988

Methods	RCT, single-centre, 2-arm, parallel design
Participants	**Total number of randomized participants:** 70 **Inclusion criteria** 1. Adults, phase of persistent hypermetabolism 4 to 6 days after sepsis and surgery **Exclusion criteria** 1. Known cirrhosis 2. Severe malnutrition 3. Known diabetes mellitus requiring insulin 4. Receiving steroids 5. Undergoing chemotherapy **Primary diagnosis** 1. Persistent hypermetabolism after sepsis **Baseline characteristics** **EN group** 1. Age, mean (SD): 56 (± 15) years 2. Gender, M/F: 20/13 3. APACHE II: not reported **PN group** 1. Age, mean (SD): 55 (± 11) years 2. Gender, M/F: 22/15 3. APACHE II: not reported **Country:** USA **Setting:** surgical ICU
Interventions	**EN group** n = 33; 2 losses; ITT analysis = 31 analysed **Details:** nasoduodenal feeding, started 4 to 6 days after sepsis and surgery, target rate of 1.5 g protein/kg/day. 30 NPC/kg/day, carbohydrates, protein, fats, salts, minerals etc. Duration of feeding assumed to be for 8 to10 days **Note:** 10 participants given PN during period prior to randomization **Caloric intake received, mean (SD):** protein: 80 (± 26) g/day. Non-protein: 1684 (± 573) kcal/day

Cerra 1988 *(Continued)*

	PN group n = 37; 2 losses: ITT analysis = 35 analysed **Details:** feeding formula described as "identical composition" to EN group, with same target rate of delivery **Note:** 10 participants given PN during period prior to randomization **Caloric intake received, mean (SD):** protein: 88 (± 20) g/day. Non-protein: 2000 (± 20) kcal/day
Outcomes	1. Mortality (during ICU stay) 2. Multiple organ failure 3. Diarrhoea and vomiting
Notes	**Funding/declarations of interest:** no details reported **Study dates:** not reported **Note:** participants in study were a subgroup of a larger epidemiological study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomized but no additional details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	No details and we assumed investigators made no attempts to blind personnel
Blinding of outcome assessment (detection bias) All outcomes (except mortality)	Unclear risk	No details
Blinding of outcome assessment (detection bias) Mortality	Low risk	No details. Lack of blinding unlikely to influence outcome data for mortality
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss of 4 participants, with reasons reported by study authors; small number of losses unlikely to influence data
Selective reporting (reporting bias)	Unclear risk	Clinical trials registration not reported. Not feasible to judge risk of reporting bias
Baseline characteristics	Low risk	Appeared comparable
Other bias	Low risk	No details of glycaemic controls, limited detail in paper but nutritional composition is described as identical. We noted more calories in PN group, but study authors reported "no statistical difference."

Chiarelli 1996

Methods	RCT, single-centre, 2-arm, parallel design
Participants	**Number of randomized participants:** 24 **Inclusion criteria** 1. People requiring artificial nutrition and able to use gastrointestinal tract for the purpose **Exclusion criteria** 1. Not reported **Primary diagnosis** 1. Multiple trauma 2. Guillain-Barré syndrome 3. Intracerebral/subarachnoid bleed 4. Gastric carcinoma 5. Intestinal carcinoma 6. Hypoxic coma **Baseline characteristics** **EN group** 1. Age, mean (range): 52 (17 to 78) years 2. Gender: not reported 3. SAPS II, mean (SD): 10 (± 4) **EN + PN group** 1. Age, mean (range): 49 (18 to 77) years 2. Gender: not reported 3. SAPS II, mean (SD): 11 (± 4) **Country:** Italy **Setting:** ICU
Interventions	**EN group** n = 12: no apparent losses **Details:** nutrition initiated 24 to 36 hours after admission. All participants fed with PN for 4 days, then 'weaned' to EN. Nasogastric tube placement, duration of feeding for 7 days, with formula consisting of high protein content with high ratio of calories/nitrogen. **Caloric intake received, mean (SD):** 33 (± 9) kcal/kg **EN with PN group** n = 12; no apparent losses **Details:** nutrition initiated 24 to 36 hours after admission. All participants given PN for 4 days, then given mixed feeding of 50% PN and 50% EN **Caloric intake received, mean (SD):** 31 (± 6) kcal/kg
Outcomes	1. Metabolic indices 2. Incidence of diarrhoea (diagnosed by faecal mass of > 700 g/day) 3. Nitrogen balance

Chiarelli 1996 *(Continued)*

4. Infection (measured by blood cultures, chest x-ray, and bronchoaspirates)
5. Duration of mechanical ventilation
6. LOS, mortality (time point not reported)

Notes	**Funding/declarations of interest:** not reported **Study dates:** not reported Study report published in Italian

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants randomly assigned to groups but no additional details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	No details and we assumed investigators made no attempts to blind personnel
Blinding of outcome assessment (detection bias) All outcomes (except mortality)	Unclear risk	No details
Blinding of outcome assessment (detection bias) Mortality	Low risk	No details. Lack of blinding unlikely to influence outcome data for mortality
Incomplete outcome data (attrition bias) All outcomes	Low risk	No apparent losses
Selective reporting (reporting bias)	Unclear risk	Clinical trial registration or publication of prospective protocol not reported; not feasible to judge risk of reporting bias
Baseline characteristics	Low risk	Study authors reported that baseline characteristics were comparable
Other bias	Unclear risk	No other sources of bias identified

Dunham 1994

Methods	RCT, single-centre, 3-arm, parallel design
Participants	**Total number of randomized participants:** 38 **Inclusion criteria** 1. Blunt traumatic event, GCS ≥ 5, ISS ≥ 15 2. No spinal neuropathy above 8th thoracic spinal level 3. No major fluid restriction requirement

Dunham 1994 *(Continued)*

4. Aged 18 to 60 years
5. Able to undergo upper gastrointestinal endoscopy
6. Respiratory insufficiency that mandated need for mechanical ventilation for ≥ 48 hours

Excluded criteria

1. If randomization did not take place within 30 hours after admission or admission did not occur within 12 hours after injury

Primary diagnoses

1. Blunt trauma injuries

Baseline characteristics

EN group

1. Age: not reported
2. Gender: not reported
3. APACHE II: not reported
4. GCS, mean (SD): 11 (± 5)
5. ISS, mean (SD): 34 (± 18)

PN group

1. Age: not reported
2. Gender: not reported
3. APACHE II: not reported
4. GCS, mean (SD): 12 (± 3)
5. ISS, mean (SD): 38 (± 12)

EN + PN group

1. Age: not reported
2. Gender: not reported
3. APACHE II: not reported
4. GCS, mean (SD): 11 (± 4)
5. ISS, mean (SD): 37 (± 15)

Country: USA

Setting: trauma centre

Interventions

EN group

n = 12; 0 losses

Details: transpyloric tube placement, feeding started within 24 hours of randomization and continued for 7 days. Investigators used Harris Benedict formula BEE x 1.3 to calculate caloric intake. Aimed to provide 50% projected calories by 24 hours after randomization; and 100% by 48 hours. Formula was Traumacal (Mead-Johnson), NPC given in form of lipids (30%) and carbohydrates (70%). Ratio of NPC to nitrogen was 105:1. Protein load was 1.75 g/kg/day.

Mean caloric intake: 1789 calories/day for 7 days

PN group

n = 16; 1 participant died on 4th study day, not included in study analysis but we have included in review outcome data.

Details: feeding started within 24 hours of randomization and continued for 7 days. Investigators used Harris Benedict formula BEE x 1.3 to calculate caloric intake. Aim to provide 50% projected calories by

Dunham 1994 *(Continued)*

	24 hours after randomization; and 100% by 48 hours. Formula consisted of dextrose-lipid-AA mixture; soybean solution, multi-vitamin mixture. Mixture was 6.7% AA and 23.1% dextrose, soybean solution provided 30% of the NPC. **Mean caloric intake:** 1961 calories/day for 7 days **EN + PN group** n = 10; 0 losses **Details:** feeding started within 24 hours of randomization and continued for 7 days. Investigators used Harris Benedict formula BEE x 1.3 to calculate caloric intake. Aim to provide 50% projected calories by 24 hours after randomization; and 100% by 48 hours. EN formula provided 50% of calories and PN formula provided 50% of calories. EN consisted of Traumacal (Mead-Johnson), NPC given in form of lipids (30%) and carbohydrates (70%). PN formula consisted of dextrose-lipid-AA mixture; soybean solution, multi-vitamin mixture. **Mean caloric intake:** 2030 calories/day for 7 days
Outcomes	1. Number of ventilator days 2. Number of ICU days 3. Total hospital stay 4. Presence of ARDS 5. Respiratory infection 6. Any infection 7. Renal failure 8. Icterus 9. Death 10. Hospital and professional charges
Notes	**Funding/declarations of interest:** not reported **Study dates:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomized but no additional details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	No details and we assumed investigators made no attempts to blind personnel
Blinding of outcome assessment (detection bias) All outcomes (except mortality)	Low risk	Most outcome data were taken from the trauma registry. Quote: "All data from the trauma registry and the finance officers were blinded, since these sources had no knowledge of the patient's status relative to the research arm assigned."
Blinding of outcome assessment (detection bias) Mortality	Low risk	Outcome assessors were blinded

Dunham 1994 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant was not included in data for PN group due to death during 7-day intervention period; we have included this event in review analysis. No other loss of data
Selective reporting (reporting bias)	Unclear risk	Clinical trials registration or prospectively published protocol not reported; not feasible to judge risk of selective outcome reporting bias
Baseline characteristics	Low risk	Some usual baseline characteristics not reported (age, gender) but other characteristics all appeared comparable
Other bias	Unclear risk	Target rate of nutrition the same. Unclear if differences in formula were equivalent

Engel 1997

Methods	RCT, single-centre, 3-arm, parallel design
Participants	**Number of randomized participants:** 20 **Inclusion criteria** 1. APACHE II score > 10, requiring ≥ 7 days of nutritional support, 18 to 65 years of age **Exclusion criteria** 1. Abdominal injury 2. Gastrointestinal stenosis 3. Liver or renal insufficiency 4. High catecholamine requirement 5. Acute or severe pancreatitis 6. Post-transplantation surgery 7. Taking cortisone medication 8. Immunosuppressant therapy and autoimmune illnesses **Primary diagnoses** 1. Multiple trauma **Baseline characteristics** **EN group (standard)** 1. Age, mean (SD): 41 (± 16) years 2. Gender, M/F: 10/0 3. APACHE II, mean (SD): 16.3 (± 4.5) **EN group (supplemented)** 1. Age, mean (SD): 33 (± 13) years 2. Gender M/F: 8/2 3. APACHE II, mean (SD): 15.7 (± 4.4) **PN group** 1. Mean age: 32 (SD ± 10) years 2. Gender M/F: 7/3 3. Mean APACHE II: 16.3 (SD ± 3.1)

Engel 1997 *(Continued)*

	Country: Germany **Setting:** ICU
Interventions	**EN group (standard)** n = 10; 0 losses **Details:** nasojejunal tube with feeding pump, feeding started within 24 hours of trauma, "Oligopeptide standard diet" (Survimed OPD, Frensenius). Target energy of 25 kcal/kg/day. Initial rate of 25 mL/hour. Infusion rate increased at rate of 25 mL/hour up to the 4th day and a minimum of 75 mL/hour. **Caloric intake received:** not reported **EN group (supplemented)** n = 10; 0 losses **Details:** nasojejunal tube with feeding pump, feeding started within 24 hours of trauma. Formula consisted of Impact (Fa. Sandoz), supplemented with arginine, omega-3 fatty acids, nucleotide, and selenium. Target energy of 25 kcal/kg/day. Initial rate of 25 mL/hour. Infusion rate increased at rate of 25 mL/hour up to the 4th day and a minimum of 75 mL/hour. **Caloric intake received:** not reported **PN group** n = 10; 0 losses **Details:** isocaloric and isonitrogenous total PN **Caloric intake received:** not reported
Outcomes	1. Septic complications (diagnosed according to the ACCP/SCCM definitions) 2. Immunological measurements
Notes	**Funding/declarations of interest:** not reported **Study dates:** not reported **Note:** for the purpose of review analysis, we combined data for the 2 EN groups.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomized but no additional details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	No details and we assumed investigators made no attempts to blind personnel
Blinding of outcome assessment (detection bias) All outcomes (except mortality)	Unclear risk	No details

Engel 1997 *(Continued)*

Blinding of outcome assessment (detection bias) Mortality	Low risk	No details. Lack of blinding unlikely to influence outcome data for mortality
Incomplete outcome data (attrition bias) All outcomes	Low risk	No apparent losses
Selective reporting (reporting bias)	Unclear risk	Clinical trials registration of prospectively published protocol not reported; not feasible to assess risk of reporting bias
Baseline characteristics	Low risk	Appear comparable
Other bias	Low risk	No other sources of bias identified

Fan 2016

Methods	RCT, single-centre, 3-arm, parallel design
Participants	**Total number of randomized participants:** 120 **Inclusion criteria** 1. Admitted to the NICU, with diagnosis of severe TBI, GCS score 6 to 8, NRS ≥ 3 **Exclusion criteria** 1. Glucocorticoid and blood products were used during the study 2. Haemodynamic instability 3. Immunosuppressive drug used in the past 6 months 4. Received radiotherapy or chemotherapy in the past year 5. Injured > 12 hours before admission 6. Died within 3 weeks 7. Previous history of metabolic diseases such as diabetes mellitus **Primary diagnosis** 1. Severe TBI **Baseline characteristics** **EN group** 1. Age, mean (SD): 40.12 (± 11.25) years 2. Gender, M/F: 18/22 3. APACHE II: not reported **PN group** 1. Age, mean (SD): 41.56 (± 15.10) years 2. Gender, M/F: 21/19 3. APACHE II: not reported **EN + PN group** 1. Age, mean (SD): 42.31 (± 14.18) years 2. Gender, M/F: 23/17 3. APACHE II: not reported

Fan 2016 *(Continued)*

	Country: China **Setting:** NICU
Interventions	**EN group** n = 40; 0 losses **Details:** all participants had nasogastric tube intubation and central venous catheterization within 48 hours of admission. EN given via nasogastric tube accompanied by suctioning gastric tube, within 48 hours of admission. Increasing dose to a maximum of 1500 mL/day in 7 days, with a pumping speed < 75 mL/hour. Normal sodium, glucose, and saline given IV. Energy as 105 to 126 kJ/kg/day. Supplements of vitamins, micro-elements, natrium, and kalium given if required **PN group** n = 40; 0 losses **Details:** all participants had nasogastric tube intubation and central venous catheterization within 48 hours of admission. Participants given PN through central venous catheter within 48 hours. Ratio of 2:1 for carbohydrates to lipids, and ratio of 100:1 for calorie nitrogen ratio. Energy as 105 to 126 kJ/kg/day. Supplements of vitamins, micro-elements, natrium, and kalium given if required **EN + PN group** n = 40; 0 losses **Details:** all participants had nasogastric tube intubation and central venous catheterization within 48 hours of admission. EN given via nasogastric tube accompanied by suctioning gastric tube, within 48 hours of admission. Increasing dose to a maximum of 1000 mL/day in 7 days, with a pumping speed < 50 mL/hour. Insufficient energy was given by PN. Energy as 105 to 126 kJ/kg/day. Supplements of vitamins, micro-elements, natrium, and kalium given if required
Outcomes	1. Nutritional status measurements (serum total protein, serum albumin, serum prealbumin, haemoglobin) 2. Immune function (T cells subsets and immunoglobulin) 3. Complications (diarrhoea, stress ulcer, intracranial infection, pyaemia, hypoproteinaemia, aspirated pneumonia) 4. LOS in NICU 5. Mechanical ventilation status and duration 6. Death
Notes	**Funding/declarations of interest:** supported by the Natural Science Foundation of Shandong province, and Technology Supporting Program of Qingdao **Study dates:** January 2009 to May 2012

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quasi-randomized method of sequence generation. Participants were randomly allocated according to hospital record numbers
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	High risk	No details and we assumed investigators made no attempts to blind personnel

Fan 2016 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes (except mortality)	Unclear risk	No details
Blinding of outcome assessment (detection bias) Mortality	Low risk	No details. Lack of blinding unlikely to influence outcome data for mortality
Incomplete outcome data (attrition bias) All outcomes	Low risk	No apparent losses
Selective reporting (reporting bias)	Unclear risk	Clinical trials registration of prospectively published protocol not reported; not feasible to assess risk of reporting bias
Baseline characteristics	Low risk	Appeared comparable
Other bias	Low risk	No other sources of bias identified

Gencer 2010

Methods	RCT, single-centre, 2-arm, parallel design
Participants	**Number of randomized participants:** 60 **Inclusion criteria** 1. Postoperative participants undergoing surgery for abdominal cancer **Exclusion criteria** 1. Not reported **Primary diagnoses** 1. Gastric, colon, and rectal cancer **Baseline characteristics** **EN group** 1. Age, mean (SD): 65.1 (± 12.2) years 2. Gender, M/F: 17/13 3. APACHE II: not reported **PN group** 1. Age, mean (SD): 67.3 (± 11.6) years 2. Gender, M/F: 19/11 3. APACHE II: not reported **Country:** Turkey **Setting:** ICU
Interventions	**EN group**

Gencer 2010 *(Continued)*

	n = 30; no apparent losses **Details:** nasogastric or jejunum feeding, initiated within 12 hours of surgery with target rate of delivery at 35 kcal/kg/day **PN group** n = 30; no apparent losses **Details:** standard formula of TPN (75% carbohydrate, 25% fat), with target rate of delivery at 35 kcal/kg/day
Outcomes	1. Immunology measurements 2. Postoperative complications (including wound, pulmonary, and urinary infections; intra-abdominal abscess) 3. ICU and hospital stay 4. Mortality
Notes	**Funding/declarations of interest:** funding not reported. Study authors declared no conflicts of interest. **Study dates:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomly assigned to groups; no additional details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	We assumed investigators made no attempts to blind personnel
Blinding of outcome assessment (detection bias) All outcomes (except mortality)	Unclear risk	No details
Blinding of outcome assessment (detection bias) Mortality	Low risk	Lack of blinding unlikely to influence outcome data for mortality
Incomplete outcome data (attrition bias) All outcomes	Low risk	No apparent losses
Selective reporting (reporting bias)	Unclear risk	Clinical trials registration not reported; not feasible to assess risk of reporting bias
Baseline characteristics	Low risk	Appeared comparable
Other bias	Unclear risk	No other sources of bias identified

Hadfield 1995

Methods	RCT, single-centre, 2-arm, parallel design
Participants	**Total number of randomized participants:** 24 **Inclusion criteria** 1. > 3 days in ICU **Exclusion criteria** 1. People in ICU for brief period (< 72 hours) 2. Serial measurement of gastrointestinal tract permeability could not be made 3. People with a history of malabsorption or who had undergone bowel surgery, people in renal failure **Primary diagnoses** 1. Surgery for cardiopulmonary bypass 2. Respiratory failure **Baseline characteristics** Overall gender, M/F: 17/7 **EN group** 1. Age, mean (SEM): 66.2 (± 2.0) years 2. APACHE II, mean (SD): 16.9 (± 1.2) **PN group** 1. Age, mean (SEM): 64.6 (± 2.6) years 2. APACHE II, mean (SD): 13.3 (± 1.2) **Country:** UK **Setting:** adult ICU
Interventions	**EN group** n = 13; 0 losses **Details:** nasogastric tube placement, formula used was Alitraq (Abbott Laboratories), supplemented with glutamine, delivered at 30 mL/hour (rate increased to meet nutritional requirements during 24 to 36 hours). Sucralfate (for stress ulcers) also given when required. **PN group** n = 11; 0 losses **Details:** formula described as standard regimen (Kabi 1 or Kabi 2 - Kabi Pharmacia, Ltd, Milton Keynes, UK). Did not include glutamine supplement. Sucralfate (for stress ulcers) also given when required.
Outcomes	1. Mortality 2. Gastrointestinal tract absorption and permeability
Notes	**Funding/declarations of interest:** Abbott Laboratories Ltd **Study dates:** not reported
Risk of bias	

Hadfield 1995 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomized but no additional details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	No details and we assumed investigators made no attempts to blind personnel
Blinding of outcome assessment (detection bias) Mortality	Low risk	Lack of blinding unlikely to influence outcome data for mortality
Incomplete outcome data (attrition bias) All outcomes	Low risk	No apparent losses
Selective reporting (reporting bias)	Unclear risk	Clinical trials registration not reported. Not possible to make judgement on risk of bias for selective outcome reporting
Baseline characteristics	Low risk	Appeared comparable
Other bias	Unclear risk	Glutamine supplement given to EN group but not PN group

Harvey 2014

Methods	RCT, multi-centre, 2-arm, parallel design
Participants	**Total number of participants:** 2400 **Inclusion criteria** 1. ≥ 18 years of age 2. Expected to require nutritional support for ≥ 2 days, within 36 hours of admission to ICU that was expected to last ≥ 3 days **Exclusion criteria** 1. Participants could not be fed through either PN or EN route 2. Received nutritional support in previous 7 days 3. Had a gastrostomy or jejunostomy in situ 4. Were pregnant 5. Not expected to be in the UK for next 6 months **Primary diagnoses** 1. Study authors reported co-existing illnesses as liver, renal, respiratory, cardiovascular, and immunodeficiency **Baseline characteristics** **EN group**

Harvey 2014 *(Continued)*

1. Age, mean (SD): 62.9 (± 15.4) years
2. Gender, M/F: 725/472
3. APACHE II, mean (SD): 19.6 (± 7.0)
4. SOFA, mean (SD): 9.6 (± 3.3)

PN group

1. Age, mean (SD): 63.3 (± 15.1) years
2. Gender, M/F: 689/502
3. APACHE II, mean (SD): 19.6 (± 6.9)
4. SOFA, mean (SD): 9.5 (± 3.4)

Country: UK

Setting: 33 ICUs

Interventions	**EN group** n = 1200; 1195 analysed; participants lost to follow-up were not included in analysis, but protocol deviations were. See note **Details:** nasogastric or nasojejunal tube feeding for 5 days. Time of initiation of feeding: median 22 (IQR 16 to 28) hours. Target rate of 25 kcal/kg bodyweight/day, with goal to reach target within 48 to 72 hours. Prokinetics given for GRV cut-offs at 200 to 500 mL. Use of international guidelines for glycaemic management, plus target level for serum glucose of < 180 mg/dL (10 mmol/L) **Caloric intake received, mean (SD):** 74 (± 44) kcal/kg **PN group** n = 1200; 1188 analysed; participants lost to follow-up were not included in analysis, but protocol deviations were **Details:** central venous catheter placement. Target rate of delivery as for EN. Equivalent nutritional formula as EN, with same glycaemic management. IV feeding for 5 days, then weaned to gastric feeding. Time of initiation of feeding of feeding: median 24 (IQR 17 to 30) hours **Caloric intake received, mean (SD):** 89 (SD ± 44) kcal/kg
Outcomes	1. All-cause mortality at 30 days, discharge, 90 days, and 1 year 2. Length of ICU and hospital stay 3. Infectious and non-infectious complications (including hyperglycaemia, defined as any new episode of hyperglycaemia during study period) 4. Duration of organ support
Notes	**Funding/declarations of interest:** NIHR **Study dates:** June 2011 to March 2014 Protocol deviations: EN: 30 did not receive assigned nutritional support, 26 received no nutritional support, 4 received PN. PN: 36 did not receive assigned nutritional support, 24 received no nutritional support, 12 received EN. All analysed as ITT. Additionally, there was a cross-over of 18 participants in the EN group and 81 participants in the PN group, but these occurred towards the end of feeding and did not constitute protocol deviations.

Risk of bias

Bias	Authors' judgement	Support for judgement

Harvey 2014 *(Continued)*

Random sequence generation (selection bias)	Low risk	Adequate sequence generation. 24-hour telephone randomization system with computer algorithm used to balance groups in ICU
Allocation concealment (selection bias)	Low risk	Telephone randomization system and we assumed that allocation was concealed from investigators
Blinding of participants and personnel (performance bias) All outcomes	High risk	No details and we assumed investigators made no attempts to blind personnel
Blinding of outcome assessment (detection bias) All outcomes (except mortality)	Unclear risk	No details
Blinding of outcome assessment (detection bias) Mortality	Low risk	Lack of blinding unlikely to influence outcome data for mortality
Incomplete outcome data (attrition bias) All outcomes	Low risk	Small number lost to follow-up and not included in ITT analysis. Some protocol deviations but less than 10%; ITT analysis used for these
Selective reporting (reporting bias)	Low risk	Prospective clinical trials registration ISRCTN17386141. Protocol outcomes were consistent with outcomes reported in published study
Baseline characteristics	Low risk	Appear comparable
Other bias	Unclear risk	Not enough information on nutritional formula to make judgement. "Standard stock supply" used. Glycaemic controls appeared the same

Heidegger 2013

Methods	RCT, multi-centre, 2-arm, parallel design
Participants	**Total number of participants:** 305 **Inclusion criteria** 1. People who received < 60% of their energy target from EN at day 3 after admission to the ICU 2. Expected to stay for > 5 days 3. Expected to survive for > 7 days 4. Had a functional gastrointestinal tract. **Exclusion criteria** 1. People who were receiving PN 2. Had persistent gastrointestinal dysfunction and ileus 3. Were pregnant 4. Refused to consent 5. Had been readmitted to the ICU after previous randomization **Primary diagnoses** 1. Shock

Heidegger 2013 *(Continued)*

2. Neurological
3. Cardiac surgery
4. Polytrauma
5. Pneumonia
6. Cardiac arrest
7. Respiratory failure
8. Myocardial infarction
9. Acute pancreatitis
10. Liver failure
11. Other

Baseline characteristics

EN group

1. Age, mean (SD): 60 (± 16) years
2. Gender, M/F: 105/47
3. APACHE II, mean (SD): 23 (± 7)
4. SAPS II, mean (SD): 47 (± 15)

EN + PN group

1. Age, mean (SD): 61 (± 16) years
2. Gender, M/F: 110/43
3. APACHE II, mean (SD): 22 (± 7)
4. SAPS II, mean (SD): 49 (± 17)

Country: Switzerland

Setting: 2 ICUs, medical and surgical

Interventions	**EN group** n = 152; 10 participants discontinued study due to protocol violations; ITT analysis **Details:** nasogastric tube feeding (preferable). All participants fed EN until day 3. Participants in EN group continued with EN feeding for 5 days as part of intervention period, then remained on EN for 28 days as required. Target rate of delivery for women 25 kcal/kg of ideal bodyweight/day, for men 30 kcal/kg of ideal bodyweight/day. Protein delivery at 1.2 g/kg of ideal bodyweight/day, formula consisted of polymeric, fibre-enriched formulas, routinely prescribed in both hospitals, containing 1.05 to 1.62 kcal/mL of energy (18% proteins, 29% lipids (8% medium-chain triglycerides), 53% carbohydrates). Prokinetics given if GRV ≥ 300 mL. Continuous IV insulin therapy to maintain blood glucose at lower than 8.5 mmol/L. **Caloric intake received, mean (SD):** 20 (± 7) kcal/kg/day for days 4 to 8 **EN + PN group** n = 153; 20 participants discontinued study due to protocol violations; ITT analysis **Details:** central or peripheral catheter placement. All participants fed with EN formula until day 3. Participants in EN + PN group supplemented with PN feeding for 5 days, then resumed with only EN for 28 days as required. Target rate of delivery as for EN. EN formula as above. Formula for PN consisted of 0.62-1.37 kcal/mL of energy (20% proteins, 29% lipids (15% medium-chain triglycerides), and 51% carbohydrates). **Caloric intake received, mean (SD):** 28 (± 5) kcal/kg/day for days 4 to 8
Outcomes	1. Nosocomial infections after day 8 until day 28 2. LOS in the ICU and hospital until day 28

Heidegger 2013 *(Continued)*

3. Mortality in the ICU
4. General mortality
5. Duration of invasive mechanical ventilation

Notes	**Funding/declarations of interest:** Foundation Nutrition 2000Plus, ICU Quality Funds, Baxter, and Fresenius Kabi. Study authors reported that, "sponsors of study had no role in study design, data collection, data analysis, data interpretation, or writing of the report." **Study dates:** December 2008 to December 2010 **Note:** study authors reported number of infections, rather than number of participants with an infection, and we could not report this data because we did not know if a participant had more than 1 infection

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate sequence generation. Computer-generated randomization sequence
Allocation concealment (selection bias)	Low risk	Adequate allocation concealment. Sequentially numbered, sealed, opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Some attempts to reduce risk of bias; study investigators involved in decisions regarding caloric goal were blinded. However, other investigators, personnel, and participants were not blinded
Blinding of outcome assessment (detection bias) All outcomes (except mortality)	Low risk	Quote: "The senior site investigator from each university hospital prospectively obtained information about infectious episodes in study patients from the other centre, and was unaware of the treatment groups assigned to patients." Attempts to reduce outcome assessor and statistician blinding sufficient for our review outcomes
Blinding of outcome assessment (detection bias) Mortality	Low risk	Assume blinding of outcome assessors for blinding; and lack of blinding unlikely to influence outcome data for mortality
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	20 participants in EN + PN group, and 10 participants in EN group discontinued study mostly due to protocol violation. Study authors used an ITT analysis. We noted an uneven number of losses between groups, with > 10% loss in the EN + PN group, and that death before 9 days was classed as protocol violation. We assumed that participants who died were included in mortality data for this study
Selective reporting (reporting bias)	Unclear risk	Quote: "registered with ClinicalTrials.gov, number NCT00802503" Prospective registration. All outcomes reported in trial register documents were consistent with reported outcomes. However, we noted changes to the trial registration documents after completion of the trial to state time point for data collection of infections between day 9 to day 28. We could not be certain whether this change affected the data reported in the published study
Baseline characteristics	Low risk	Appeared comparable
Other bias	Low risk	No other sources of bias identified. No evidence of differences in glycaemic controls or nutritional protocol

Justo Meirelles 2011

Methods	RCT, single-centre, 2-arm, parallel design
Participants	**Total number of randomized participants:** 22 **Inclusion criteria** 1. 18 to 60 years of age, admitted to the ICU, diagnosed with TBI (GCS 9 to 12) **Exclusion criteria** 1. Chronic renal failure 2. History of COPD 3. Hepatic dysfunction or cirrhosis or bilirubin > 3 mg% 4. Insulin-dependent diabetes mellitis 5. Morbid obesity 6. Pre-existing malnutrition 7. Pregnancy 8. Immune depressive conditions 9. Associated abdominal trauma 10. Participants excluded if not able to receive treatment for 2 consecutive days **Primary diagnoses** 1. TBI **Baseline characteristics** **EN group** 1. Age, mean (SD): 31 (± 13) years 2. Gender, M/F: 11/1 3. APACHE II, mean (range): 14 (8 to 22) **PN group** 1. Age, mean (SD): 31 (± 10) years 2. Gender, M/F: 9/1 3. APACHE II, mean (range): 13 (7 to 21) **Country:** Brazil **Setting:** ICU
Interventions	**EN group** n = 12: 0 losses **Details:** oro- or naso-feeding tube in gastric position with pump infusion. Feeding initiated as soon as participant was haemodynamically stable. Duration of feeding for 5 days, with target rate of delivery of 25 to 30 kcal/kg/day with 1.5 g/kg/day of protein. Composition of feeding solution per 100 mL: protein 3.6 g (70% soy protein), carbohydrate 14 g, lipids 3.5 g added with casein to reach 1.5 g/kg/day **Caloric intake received, mean (SD):** total during 5 days: 5958 (± 3619) kcal **PN group** n = 10; 0 losses

Justo Meirelles 2011 *(Continued)*

	Details: central venous access, with equivalent target rate of delivery as EN group. Composition of feeding solution per 100 mL: 3.8 g of AAs, 14 g of glucose and 3.3 g or lipids **Caloric intake received, mean (SD):** total during 5 days: 6586 (± 1052) kcal
Outcomes	1. Mortality 2. Morbidity 3. Length of ICU stay 4. Days of mechanical ventilation 5. Pneumonia 6. Sepsis
Notes	**Funding/declarations of interest:** not reported **Study dates:** August 2008 to June 2009

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	No details and we assumed investigators made no attempts to blind personnel
Blinding of outcome assessment (detection bias) All outcomes (except mortality)	Unclear risk	No details
Blinding of outcome assessment (detection bias) Mortality	Low risk	Lack of blinding unlikely to influence assessment of mortality
Incomplete outcome data (attrition bias) All outcomes	Low risk	No apparent losses
Selective reporting (reporting bias)	Unclear risk	Details of clinical trial registration not reported. Not possible to make assessment of selective outcome reporting bias
Baseline characteristics	Low risk	All comparable
Other bias	Low risk	Glycaemic controls not reported. We noted no differences in nutritional protocol. No other sources of bias identified

Kudsk 1992

Methods	RCT, single-centre, 2-arm, parallel design

Kudsk 1992 *(Continued)*

Participants	**Total number of randomized participants:** 98 **Inclusion criteria** 1. 18 years of age, intra-abdominal injury requiring laparotomy, with ATI ≥ 15 **Exclusion criteria** 1. Not reported **Primary diagnoses** 1. Abdominal trauma **Baseline characteristics** **EN group** 1. Age, mean (SEM): 30.4 (± 1.7) years 2. Gender, M/F: not reported 3. APACHE II: not reported **PN group** 1. Age, mean (SEM): 30.6 (± 1.4) years 2. Gender, M/F: not reported 3. APACHE II: not reported **Country:** USA **Setting:** trauma ICU
Interventions	**EN group** n = 52; 1 death within 4 days, excluded from study analysis but we included in the review analysis; 2 participants were switched to PN group at 1 week, included in ITT analysis **Details:** feeding tube placement in jejunum. Target rate of delivery 1.5 to 2.0 g/kg/day of protein/AAs and 30 to 35 kcal/kg/day of NPC. Participants randomized within 8 hours of surgery, mean (SD) time until initiation of feeding was 24 (± 1.7) hours. Feeding formula was Vital HN (Ross Laboratories, Columbus, OH, USA), and consisted of protein (16.7%), branched-chain AAs (18.2%), carbohydrates (73.9%), and fat (9.4%) **Caloric intake received, mean (SEM):** 30.2 (± 1.2) NPC/kg/day (maximum rate). Participants in the EN group received significantly less total nutrition per day than participants in the PN group. **PN group** n = 46; 1 death within 4 days, excluded from study analysis but we included in the review analysis; of 40 participants, people with infections were transferred to EN group, but kept in analysis as ITT **Details:** central venous access. Target rate of delivery as for EN group. Mean (SD) time until initiation of feeding was 22.9 (± 1.6) hours. Pharmacy provided formula with similar concentrations of protein, carbohydrate, and fat. **Caloric intake received, mean (SEM):** 29.9 (± 15) NPC/kg/day
Outcomes	1. Length of hospital stay 2. Number of ventilator days 3. Septic morbidity (to include pneumonia (diagnosed by symptoms of fever, leukocytosis, positive sputum/bronchoalveolar lavage specimens, purulent sputum, development of new pulmonary infiltrates) 4. Intra-abdominal abscess

Kudsk 1992 *(Continued)*

	5. Emphysema 6. Line sepsis (diagnosed by symptoms of purulence of exit site of catheter, positive catheter cultures in association with positive blood cultures)
Notes	**Funding/declarations of interest:** not reported **Study dates:** December 1989 to August 1991 **Note:** 8 participants (did not state from which groups) required return to surgery within 24 to 48 hours, then randomized to receive EN or PN. Assumed that analysis and baseline characteristics were from point of new randomization (i.e. participants were removed and then re-introduced into the study. 2 participants were switched from EN to PN because of failure to tolerate ≥ 50% or nutritional goal; use of ITT analysis for these participants. Protocol broken for 6 participants who had candida infections (4 in PN group, 2 in EN group)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization table
Allocation concealment (selection bias)	Low risk	Computer randomization and we assumed that allocation was concealed from investigators
Blinding of participants and personnel (performance bias) All outcomes	High risk	No details and we assumed investigators made no attempts to blind personnel.
Blinding of outcome assessment (detection bias) All outcomes (except mortality)	Unclear risk	Principal investigator, who we assumed was not blinded, was involved in data analysis (review of charts at hospital discharge). However, attempts were made to reduce bias by using a 2nd blinded surgeon to resolve discrepancies in infections diagnoses
Blinding of outcome assessment (detection bias) Mortality	Low risk	Lack of blinding unlikely to influence outcome data for mortality
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 participants excluded from analysis due to death; included in review analysis
Selective reporting (reporting bias)	Unclear risk	No protocol or clinical trials registration reported, therefore, not feasible to make judgement on risk of selective reporting bias
Baseline characteristics	Low risk	Appeared comparable
Other bias	Unclear risk	Some changes to feeding protocols that were deemed clinically appropriate. Use of ITT analysis

Peterson 1988

Methods	RCT, single-centre, 2-arm, parallel design
Participants	**Total number of randomized participants:** 59

Peterson 1988 *(Continued)*

	Inclusion criteria 1. Adults undergoing emergency celiotomy, ATI > 15 and < 40 **Exclusion criteria** 1. Pelvic fractures that required > 6 units of blood in first 12 hours of hospital admission 2. Total blood loss > 25 units in the first 24 hours 3. Repeat laparotomy within 72 hours 4. Treatment with steroids or chemotherapy **Primary diagnosis** 1. Abdominal trauma **Baseline characteristics** **EN group** 1. Age, mean (SEM): 28.3 (± 1.9) years 2. Gender, M/F: 17/4 **PN group** 1. Age, mean (SEM): 31.4 (± 2.4) years 2. Gender M/F: 20/5 **Country:** USA **Setting:** ICU
Interventions	**EN group** n = 29; 8 losses, participants withdrawn due to: failure to meet inclusion/exclusion criteria, presence of underlying bowel disease, mechanical failure of EN delivery, early patient transfer, death within 72 hours; 21 analysed **Details:** needle-catheter jejunostomy placed at initial laparotomy. BEE calculated by Harris-Benedict equation at 1.5 x BEE. Feeding initiated within 12 hours of surgery. Formula consisted of Vivonex TEN (Norwich Eaton Pharmaceuticals, Inc, Norwich, NY, USA); provided 2.5% fat and approximately 33% branched chain AAs with NPC to grams nitrogen ratio of 150:1 **Caloric intake received, mean (SEM):** day 5: 2203.7 (± 172.8) kcal/kg **PN group** n = 30; 5 losses, participants withdrawn due to: failure to meet inclusion/exclusion criteria, presence of underlying bowel disease, early patient transfer, death within 72 hours; 25 analysed **Details:** central venous catheter placed at initial laparotomy. BEE calculated by Harris-Benedict equation at 1.5 x BEE. Feeding initiated within 12 hours of surgery, except 2 participants for which feeding was initiated within 24 to 36 hours after laparotomy. Formula consisted of a mixture of FraAmine HBC 6.9% (Kendall-McGaw Laboratories, Irvine, CA, USA) and TrophAmine 6% (Kendall-McGaw Laboratories, Irvine, CA, USA); provided 2.5% fat and approximately 33% branched chain AAs with NPC to grams nitrogen ratio of 150:1 **Caloric intake received, mean (SEM):** day 5: 2548.1 (± 85.3) kcal/kg
Outcomes	1. Serum and protein levels 2. LOS in ICU 3. LOS in hospital 4. Septic complications

Peterson 1988 *(Continued)*

	5. Adverse events (abdominal distension, cramping, increased residual volumes; intolerance to feedings secondary to prolonged ileus secondary to mesenteric trauma)
Notes	**Funding/declarations:** not reported **Study dates:** February 1985 to September 1987

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomized by computer assignment"
Allocation concealment (selection bias)	Low risk	Computer randomization and we assumed that allocation was concealed from investigators.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No details and we assumed investigators made no attempts to blind personnel
Blinding of outcome assessment (detection bias) All outcomes (except mortality)	Unclear risk	No details
Blinding of outcome assessment (detection bias) Mortality	Low risk	Lack of blinding unlikely to influence outcome data for mortality
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Large number of losses after randomization. Explanations given, but it was unclear if the number of losses was balanced between groups
Selective reporting (reporting bias)	Unclear risk	Details of clinical trial registration not reported. Not possible to make assessment of selective outcome reporting bias
Baseline characteristics	Low risk	Appeared comparable
Other bias	Low risk	No other sources of bias identified

Radrizzani 2006

Methods	RCT, multi-centre, 2-arm, parallel design
Participants	**Total number of randomized participants:** 290 **Inclusion criteria** 1. > 18 years of age 2. Judged by attending physicians to need artificial ventilation and nutrition for ≥ 4 days **Exclusion criteria** 1. Contraindication to PN or EN 2. Motor GCS < 4

Radrizzani 2006 *(Continued)*

3. Pure cerebral disease
4. Spinal trauma
5. Referral from ICUs in which participants had spent > 24 hours

Primary diagnoses

1. Respiratory failure
2. Cardiovascular failure
3. Neurological failure
4. Multiple organ failure

Baseline characteristics

EN group

1. Age, mean (SD): 51.5 (± 22.9) years; number of participants aged > 60 years were 68/142
2. Gender, M/F: 101/41
3. SAPS II, median (IQR): 35.5 (27 to 45)
4. SOFA, median (IQR): 6 (4 to 6)

PN group

1. Age, mean (SD): 49.2 (± 26.0) years; number of participants aged > 60 years were 63/145
2. Gender, M/F: 112/33
3. SAPS II, median (IQR): 37 (26 to 45)
4. SOFA, median (IQR): 6 (4 to 8)

Country: Italy

Setting: 33 adult ICUs

Interventions	**EN group** n = 143; 1 participant met criteria for sepsis and not analysed (baseline characteristics excluded this participant), ITT was used for remaining participants. 142 participants analysed **Details:** no details of feeding tube placement. Duration of feeding assumed to be 6 days, with mean (SD) time to initiation of feeding 30.1 (± 13.8) hours, started at 10 kcal/kg/day, rising to 25 to 28 kcal/kg/day by the 4th day. Nutritional formula consisted of 55% carbohydrates, 25% fat, 21% protein, 1.3 kcal/mL, containing per 100 mL: L-arginine 0.8 g, omega-3 fatty acids, omega-6 fatty acids 0.7 g, vitamin E 2.9 mg, β-carotene 0.75 mg, zinc 2.2 mg, and selenium 7 µg. Blood glucose kept < 180 mg/dL **Caloric intake received, mean (SD):** 20.0 (± 8.3) kcal/kg/day **PN group** n = 147; 2 participants met criteria for sepsis and not analysed (baseline characteristics excluded this participant), ITT was used for remaining participants. 145 participants analysed **Details:** mean (SD) time to initiation of feeding 32.0 (± 12.2) hours. Nutrition supplied by pump 24 hours/day, with target of 25 to 28 kcal/kg bodyweight/day. PN not supplemented with EN before day 6. Nutritional formula consisted of 59% carbohydrate, 23% fat, 18% protein, 1.2 kcal/mL **Caloric intake received, mean (SD):** 23.7 (± 8.6) kcal/kg Authors conducted an adjusted analysis for caloric differences and baseline differences; concluded that differences were not significant
Outcomes	1. 28-day mortality (non-severe septic and severe septic) 2. Sepsis or septic shock (septic shock participants only) 3. LOS

Radrizzani 2006 *(Continued)*

4. Organ failure
5. Ventilator days (non-severe septic shock participants only)

Notes	**Funding/declarations of interest:** partially funded by Abbott Italia. Also unrestricted educational grant from AstraZeneca Italy **Study dates:** November 1999 to December 2001 Participants stratified to severely septic and non-severely septic. Early stopping of recruitment, initially of severely septic participants who had increased mortality in EN group, then of non-severely septic due to low accrual rate

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate sequence generation, computer-generated randomization
Allocation concealment (selection bias)	Low risk	Adequate allocation concealment, randomization code generated externally and communicated via telephone to ICUs
Blinding of participants and personnel (performance bias) All outcomes	High risk	No details and we assumed investigators made no attempts to blind personnel
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Lack of blinding unlikely to influence outcome data for mortality
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 participants excluded from analysis and included in the analysis of associated study (Bertolini 2003) due to misdiagnosis. Not included in review analysis
Selective reporting (reporting bias)	Unclear risk	Clinical trials registration not reported. Not feasible to assess risk of reporting bias
Baseline characteristics	Unclear risk	Some baseline characteristics imbalance. Quote: "The PN group had more men than the iEN group, more patients coming from wards and fewer from emergency rooms, and more with multiple organ failure. Other baseline characteristics were similar in the two arms." According to the adjusted analysis, these baseline differences did not confound the results
Other bias	Unclear risk	Blood glucose protocols equivalent between groups. Overall nutritional protocols were not comparable for the first 4 days of the study; an adjusted analysis was planned for this. No other sources of bias identified

Rapp 1983

Methods	RCT, single-centre, 2-arm, parallel design
Participants	**Total number of randomized participants:** 38 **Inclusion criteria** 1. People with head injury: penetrating missile wounds or blunt head trauma causing intracranial haematomas 2. A major focal neurological deficit or unconsciousness, or both **Exclusion criteria** 1. Severe extracranial injuries that were expected to alter metabolic demands or to delay use of standard EN, such as abdominal-organ injury **Primary diagnosis** 1. Head injury **Baseline characteristics** **EN group** 1. Age, mean (SD): 34.9 (± 3.76) years 2. Gender: not reported 3. APACHE II: not reported **PN group** 1. Age, mean (SD): 29.2 (± 4.12) years 2. Gender: not reported 3. APACHE II: not reported **Country:** USA **Setting:** neurosurgical unit
Interventions	**EN group** n = 18; 0 losses **Details:** nasogastric tube placement. Feeding started as soon as possible after randomization, when bowel sounds were present and GRV <100 mL/hour. Study authors did not report target rate of delivery. Formula was Vital (Ross Laboratories, Columbus, Ohio, USA) - 42 g protein, 10.8 g fat, 185 g carbohydrates per litre **Caloric intake received, mean:** 685 calories and 4.0 g nitrogen per day **PN group** n = 20; 0 losses **Details:** percutaneous intraclavicular subclavian vein catheter placement. Feeding started within 48 hours of admission. Study authors did not report target rate of delivery. Formula consisted of synthetic AAs 42.5 g/L, 25% dextrose, electrolytes, vitamins, trace elements. 10% soybean oil emulsion 250 to 500 mL/day. Insulin used to control hyperglycaemia as required **Caloric intake received, mean:** 1750 calories and 10.2 nitrogen per day
Outcomes	1. Fluid intake and output 2. Use of respirator 3. Nosocomial infections (not reported)

Rapp 1983 *(Continued)*

4. Sepsis (not clearly reported)
5. Use of antibiotics
6. Serum glucose levels
7. Daily temperature peak
8. Use of dexamethasone
9. Participant mortality
10. Length of ICU stay
11. Length of Hospital stay

Notes	**Funding/declarations of interest:** supported, in part, by a grant from Baxter-Travenol Laboratories **Study dates:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomized but no additional details
Allocation concealment (selection bias)	Unclear risk	No evidence of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	No details and we assumed investigators made no attempts to blind personnel
Blinding of outcome assessment (detection bias) All outcomes (except mortality)	Unclear risk	No evidence of blinding
Blinding of outcome assessment (detection bias) Mortality	Low risk	Lack of blinding unlikely to influence outcome data for mortality
Incomplete outcome data (attrition bias) All outcomes	Low risk	No apparent losses
Selective reporting (reporting bias)	Unclear risk	Clinical trials registration not reported. Not feasible to assess risk of reporting bias
Baseline characteristics	Low risk	Appeared comparable
Other bias	Low risk	Insulin use to control hyperglycaemia was described for the PN group and we assumed that this was the same for each group. No other sources of bias identified

Wischmeyer 2017

Methods	RCT, multi-centre, 2-arm, parallel design. Pilot study
Participants	**Total number of randomized participants:** 125

Wischmeyer 2017 *(Continued)*

Inclusion criteria

1. Critically ill adults > 18 years of age
2. Mechanically ventilated
3. Had acute respiratory failure
4. Were receiving EN or were to be initiated on EN within 48 hours of ICU admission
5. BMI < 25 kg/m^2 or > 35 kg/m^2, based on pre-ICU actual or estimated dry weight

Exclusion criteria:

1. > 72 hours from ICU admission to consent, not expected to survive an additional 48 hours from screening evaluation
2. Lack of commitment to full aggressive care
3. Contraindication to EN deemed to require PN for the first 7 days of ICU admission
4. Already at goal rate of EN from screening evaluation
5. Already receiving PN on admission to ICU
6. Admitted diabetic ketoacidosis or non-ketotic hyperosmolar coma
7. Pregnant or lactating
8. Clinical fulminant hepatic failure
9. Dedicated port of central line not available
10. Known allergy to study nutrients
11. Enrolment in another study

Primary diagnosis

1. Acute respiratory failure
2. Sepsis
3. Gastrointestinal
4. Neurological
5. Other (not described by study authors)
6. Trauma
7. Metabolic
8. Cardiovascular/vascular
9. Haematological

Baseline characteristics

EN group

1. Age, mean (SD): 55.1 (± 16.2) years
2. Gender, M/F: 39/34
3. APACHE II, mean (SD): 20.8 (± 7.2)
4. SOFA, mean (SD): 5.9 (± 3.6)
5. BMI, mean (SD): 33.2 (± 15.0) kg/m^2
6. BMI < 25 kg/m^2: 38 participants
7. BMI > 35 kg/m^2: 35 participants

EN + PN group

1. Age, mean (SD): 55.8 (± 19.8) years
2. Gender, M/F: 21/31
3. APACHE II, mean (SD): 20.5 (± 6.4)
4. SOFA, mean (SD): 6.2 (± 3.5)
5. BMI, mean (SD): 33.5 (± 14.9) kg/m^2
6. BMI < 25 kg/m^2: 27 participants
7. BMI > 35 kg/m^2: 25 participants

Wischmeyer 2017 *(Continued)*

	Country: Canada, USA, Belgium, France **Setting:** 11 ICUs
Interventions	**EN group** n = 73; 0 losses (for clinical outcomes) **Details:** EN initiated at 20 mL/hour and increased by 20 mL/hour every 4 hours, until goal was reached. A standard polymeric solution with 1.2 (± 0.2) kcal/mL was used to standardize nutrition delivery. Continued for 7 days or until death **EN + PN group** n = 52; 0 losses (for clinical outcomes) **Details:** PN given via central IV access. PN solution had similar caloric density to EN solutions (1.2 kcal/mL providing 0.06 to 0.09 g protein/mL). PN initiated at 20 mL/hour and increased by 20 mL/hour every 4 hours, until goal was reached. Continued for 7 days or until death
Outcomes	1. Amount of calories and protein received 2. Study feasibility assessment 3. ICU, hospital and 6-month mortality 4. Development of infections 5. Duration of ICU stay 6. Multiple organ dysfunction 7. Duration of mechanical ventilation 8. Vital status and quality of life (Barthel Index, SF-36) 9. Duration of hospital stay 10. Muscle function (ultrasounds, CT scans, hand-grip strength, 6-minute walk test)
Notes	**Funding/declarations of interest:** The National Institutes of Health; The Royal Alexandra Hospital Foundation, Edmonton, Canada; PN solutions and funding for assistance with distribution from Baxter Inc **Study dates:** June 2011 to January 2015 **Note:** study specifically recruited participants who were underweight or overweight; BMI status was balanced between groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralized web-based randomization system used to randomize participants to groups
Allocation concealment (selection bias)	Low risk	Centralized randomization system used, which would conceal allocation codes
Blinding of participants and personnel (performance bias) All outcomes	High risk	No details and we assumed investigators made no attempts to blind personnel
Blinding of outcome assessment (detection bias) All outcomes (except mortality)	Unclear risk	No evidence of blinding

Wischmeyer 2017 *(Continued)*

Blinding of outcome assessment (detection bias) Mortality	Low risk	Lack of blinding unlikely to influence outcome data for mortality
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses for clinical outcome data
Selective reporting (reporting bias)	Low risk	Prospective clinical trials registration (NCT01206166). Outcomes were reported according to clinical trials documents
Baseline characteristics	Low risk	Largely comparable
Other bias	Low risk	We identified no other sources of bias.

Xi 2014

Methods	RCT, single-centre, 2-arm, parallel design
Participants	**Total number of randomized participants:** 45 **Inclusion criteria** 1. 18 to 60 years of age 2. Fasting time > 14 days 3. ASA 1 to 3, condition allowed for EN **Exclusion criteria** 1. Chronic renal failure 2. History of COPD 3. Hepatic dysfunction or cirrhosis or a bilirubin value > 3 mg/dL 4. Metabolic diseases 5. Severe anaemia 6. Blood coagulation dysfunction 7. Pregnancy or lactation 8. History of psychiatric illness 9. Underwent immunosuppressive therapy **Primary diagnoses** 1. Severe acute pancreatitis 2. Duodenal distula 3. Pancreatic trauma 4. High intestinal obstruction 5. Biliary tract fistula 6. Inflammatory intestinal obstruction **Baseline characteristics** **EN group** 1. Age, mean (SD): 52.81 (± 11.68) years 2. Gender, M/F: 16/6 3. APACHE II, mean (SD): 7.56 (± 1.60)

Xi 2014 *(Continued)*

	PN group 1. Age, mean (SD): 50.07 (± 13.56) years 2. Gender, M/F: 17/6 3. APACHE II, mean (SD): 6.47 (± 1.39) **Country:** China **Setting:** ICU
Interventions	**EN group** n = 22; 0 losses **Details:** oro- or naso-enteral feeding tube, in gastric position with pump infusion. All participants fed PN until randomization. EN nutrition commenced when condition of participant allowed EN feeding. Duration of feeding assumed to be 7 days. Target rate of delivery at 20 to 25 kcal/kg/day with protein 1.5 g/kg/day. Glucose adjusted to 10 mmol/L. If EN could not meet participant's caloric needs, then PN was used as supplement from 4th day. **PN group** n = 23; 0 losses **Details:** central venous access. All participants fed PN until randomization and then participants in PN continued with feed. Duration of feeding unclearly reported but assumed to be 7 days. Target rate of delivery as for EN group. Study authors reported no significant difference in the administered total calories between groups (P > 0.05)
Outcomes	1. LOS in ICU 2. Days on mechanical ventilation 3. SIRS score 4. Complications (to include cardiac, leakage of anastomosis, sepsis, respiratory, brain, renal, liver cholestasis, bleeding, thromboembolism) 5. Hospital costs 6. Mortality at day 28 7. Specific organ failure after 7 days 8. Inflammatory markers and immunological measurements
Notes	**Funding/declarations of interest:** not reported **Study dates:** February 2010 to February 2012

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomized but no further detail
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	No details and we assumed that investigators made no attempts to blind personnel

Xi 2014 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes (except mortality)	Unclear risk	No details
Blinding of outcome assessment (detection bias) Mortality	Low risk	No details; lack of blinding unlikely to influence outcome data for mortality
Incomplete outcome data (attrition bias) All outcomes	Low risk	No apparent losses
Selective reporting (reporting bias)	Unclear risk	Clinical trials registration or prospectively prepared protocol not reported; not feasible to assess this domain
Baseline characteristics	Low risk	Appear comparable
Other bias	Low risk	Limited information concerning nutritional protocol or glycaemic controls. No other sources of bias identified

Young 1987

Methods	RCT, single-centre, 2-arm, parallel design
Participants	**Total number of randomized participants:** 51 **Inclusion criteria** 1. People with severe head injury: primary site of injury was the brain **Exclusion criteria** 1. Brain-dead within 4 days of entering the study, or whose families decided to withdraw consent within 5 days **Primary diagnosis** 1. Severe head injury **Baseline characteristics** **EN group** 1. Age, mean (SD): 34.0 (± 2.92) years 2. Gender, M/F: 22/6 3. APACHE II: not reported **PN group** 1. Age, mean (SD): 30.3 (± 2.67) years 2. Gender M/F: 20/3 3. APACHE II: not reported **Country:** USA **Setting:** medical centre
Interventions	**EN group**

Young 1987 *(Continued)*

n = 28; some early participant loss but study authors do not report to which group these participants belonged. 11 participants did not tolerate tube feedings and were switched to PN group; used ITT analysis

Details: nasogastric tube feeding, started as soon as feeding tube in place. Feeding assumed to be for duration of study (i.e. 18 days). Target rate of delivery set at 1.75 x Harris Benedict BEE and 1.5 g protein/kg bodyweight/day. Formula consisted of Traumacal (1.5 calories/mL and 22% protein, 40% fat, and 38% carbohydrate) or Ensure Plus (1.5 calories/mL and 14.7% protein, 32% fat, and 53.3% carbohydrate). Participants given metoclopramide 10 mg/6 hours to stimulate gastrointestinal motility. No participant was treated with corticosteroids

Cumulative intake of protein, mean (SEM): 1.35 (± 0.12) g/kg/day

PN group

n = 23; some early participant loss but study authors did not report to which group these participants belonged; use of ITT analysis

Details: feeding commenced within 48 hours of randomization. Feeding assumed to be for duration of study (18 days); however, participants were given EN once bowel sounds were present and GRV < 100 mL every 2 hours. Target rate of delivery set at 1.75 x Harris Benedict BEE and 1.5 g protein/kg bodyweight/day. Formula consisted of sterile AA/dextrose solutions, multi-vitamins, trace elements, and IV lipids. 17% calories as protein, 41% as fat, 42% dextrose. No participant was treated with corticosteroids

Cumulative intake of protein, mean (SEM): 0.91 (± 0.09) g/kg/day

Outcomes

1. Caloric intake and nitrogen balance
2. Serum protein levels
3. Anthropometry
4. Immunity profile
5. Complications (infection, pneumonia (diagnosed by symptoms of elevated WBC count, increased premature cells, elevated temperature, positive sputum culture, visual evidence of infiltrate)
6. Aspiration pneumonia
7. Aspiration pneumonitis
8. Urinary tract infection
9. Septicaemia (diagnosed by symptoms of fever, positive blood cultures, increased WBC count, no hypotension)
10. Septic shock (diagnosed by additional symptoms of increased cardiac output, decreased systemic vascular resistance)
11. Diarrhoea
12. Mortality

Notes

Funding/declarations of interest: not reported

Study dates: not reported

Note: we assumed that study participants were in the ICU, although study authors did not report this in the paper.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomized but no additional details
Allocation concealment (selection bias)	Unclear risk	No details

Young 1987 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	No details and we assumed that there were no attempts to blind personnel
Blinding of outcome assessment (detection bias) All outcomes (except mortality)	Unclear risk	No details
Blinding of outcome assessment (detection bias) Mortality	Low risk	Lack of blinding unlikely to influence outcome data for mortality
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	7 participants were entered into the study but due to exclusion criteria were excluded from analysis, included 5 deaths within 4 days. Study authors did not report to which group these participants belonged
Selective reporting (reporting bias)	Unclear risk	Clinical trials registration or prospectively prepared protocol not reported; not feasible to assess risk of reporting bias
Baseline characteristics	Low risk	Appeared comparable
Other bias	Unclear risk	Participants in PN group received more calories until the 9th day of study, and 11 EN participants required PN

AA: amino acid; ACCP: American College of Chest Physicians; ADL: activities of daily living; APACHE II: Acute Physiology and Chromic Health Evaluation II; ARDS: acute respiratory deficiency syndrome; ASA: American Society of Anesthesiologists; ATI: Abdominal Trauma Index; BEE: basal energy expenditure; BMI: body mass index; COPD: chronic obstructive pulmonary disease; CT: computed tomography; DNR: do not resuscitate; EN: enteral nutrition; F: female; GCS: Glasgow Coma Scale; GRV: gastric residual volume; HCN: high calorie nutrition; ICU: intensive care unit; iEN: immuno-enteral nutrition; ISS: Injury Severity Score; ITT: intention-to-treat; IQR: interquartile range; IV: intravenous; LOS: length of stay; M: male; n: number of participants; NICU: neuro-intensive care unit; NIHR: National Institute of Health Research; NPC: non-protein calorie; NRS: nutritional risk score; PN: parenteral nutrition; RCT: randomized controlled trial; RIFLE: scoring system for acute kidney injury, risk, injury, failure, loss, end-stage renal disease; SAPS: Simplified Acute Physiology Score; SCCM: Society of Critical Care Medicine; SD: standard deviation; SF-36: 36-item Short Form; SEM: standard error of the mean; SIRS: systemic inflammatory response syndrome; SOFA: Sequential Organ Failure Assessment; TBI: traumatic brain injury; TEN: total enteral nutrition; TPN: total parenteral nutrition; VAP: ventilator-acquired pneumonia; WBC: white blood cell.

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

Study	Reason for exclusion
Abou-Assi 2002	RCT. Compared EN vs PN. People with acute pancreatitis
Allingstrup 2017	RCT. Early-goal directed nutrition vs EN. Adults in ICU. Participants in the early-goal directed nutrition group were given EN and PN; however, PN was only given if required and therefore, we excluded this study because some participants in early-goal directed nutrition group may not have had PN, and this information was not reported by study authors.
Arefian 2007	RCT. EN vs PN. People with trauma injuries. Study authors did not report that participants were in the ICU.
Baigrie 1996	RCT. EN vs PN feeding. People undergoing oesophagectomy or gastrectomy. Study did not report that participants were in the ICU.

Study	Reason for exclusion
Braga 1996	RCT. 3 study groups: EN vs enriched EN vs PN. People undergoing curative surgery for gastric or pancreatic cancer. Study did not report that participants were in the ICU.
Braga 1998	RCT. 3 study groups: EN vs enriched EN vs PN. People undergoing curative surgery for gastric or pancreatic cancer. Study did not report that participants were in the ICU.
Braga 2001	RCT. PN vs early EN feeding. People undergoing curative surgery for cancer of the upper gastrointestinal tract. Study did not report that participants were in the ICU.
Chen 2004	RCT. EN vs PN feeding. People in a burns unit not an ICU
DiCarlo 1999	RCT. 3 study groups: EN vs enriched EN vs PN. People undergoing curative surgery for cancer of the pancreatic head. Study did not report that participants were in the ICU.
Doig 2013	RCT. People admitted to the ICU. This trial assessed early PN in people with relative contraindications to EN, not all the participants randomized to the control group received EN.
Dong 2010	RCT. 3 study groups: EN vs PN vs combined EN with Shenmai injection. People with gastric cancer after surgery. Study aimed to assess postoperative fatigue. Decision made from English abstract; study did not report that participants were in the ICU.
Fujita 2012	RCT. EN vs PN. Participants were in the ICU but only for 1 day as part of standard management of participants after thoracic oesophagectomy. Feeding by EN or PN continued on the ward for 6 postoperative days.
Hermann 2004	RCT. Compared EN vs PN. People with acute myeloid leukaemia. Decision made from abstract as we were unable to source the full text; study did not report that participants were in the ICU
Kim 2012	RCT. EN vs PN. People after gastrectomy with gastric cancer. Study authors did not report that participants were in the ICU.
Klek 2008	RCT. 4 study groups: EN vs immuno-modulating EN vs PN vs immuno-modulating PN. Well-nourished people undergoing resection for gastrointestinal cancer. Study did not report that participants were in the ICU.
Klek 2011	RCT. 4 study groups: EN vs immuno-modulating EN vs PN vs immuno-modulating PN. Malnourished people undergoing resection for gastrointestinal cancer. Study did not report that participants were in the ICU.
Malhotra 2004	RCT. Compared enteral nutrition with PN. People undergoing surgical intervention for peritonitis. Study setting was reported as a surgical unit, not an ICU.
McArdle 1981	RCT. Compared EN vs PN. People treated in a surgical clinic. Study did not report that participants were in the ICU.
Moore 1989	RCT. Compared EN vs PN. People with abdominal trauma. Study did not report that participants were in the ICU.
Pupelis 2001	RCT. > 50% of participants had pancreatitis
Reynolds 1997	RCT. Compared EN vs PN. People undergoing upper gastrointestinal surgery. Study did not report that participants were in the ICU.
Ryu 2009	RCT. Compared EN vs PN. People undergoing surgery for laryngeal or pharyngeal cancer. Study did not report that participants were in the ICU.

Study	Reason for exclusion
Sand 1997	RCT. Compared EN vs PN. People undergoing gastrectomy for gastric cancer. Study did not report that participants were in the ICU.
Suchner 1996	RCT. Compared EN vs PN. People with head trauma or need for craniotomy. Study did not report that participants were in the ICU.
Van Barneveld 2016	RCT. Compared EN vs PN. People undergoing surgery for rectal carcinoma. Study did not report that participants were in the ICU.
Woodcock 2001	RCT. Compared EN vs PN. People requiring adjuvant nutritional support but study authors reported that only 37.4% were in the ICU and we excluded the study as this was too few and the data for participants in the ICU were not separate.
Xiao-Bo 2014	RCT. Compared EN vs PN. People undergoing oesophagectomy for oesophageal cancer. Study did not report that participants were in the ICU.
Yu 2009	RCT. Compared EN vs PN. People undergoing surgery for colorectal cancer. Decision made from English abstract only; study did not report that participants were in the ICU.
Zanello 1992	RCT. Compared EN vs PN. People in the ICU with severe trauma or severe postoperative complications. Published only as an abstract; insufficient information on outcomes and not possible to use data. Abstract was from 1992, and unlikely to be published as a full report.
Zhang 2005	RCT. Compared EN vs PN. People in the ICU after pericardial devascularization. We noted that participants in the EN group were all given PN as a supplement for the first 3 days and, therefore, we excluded this study.
Zhang 2016	RCT. Compared EN vs PN. People with burn-induced fungal infection. Study did not report that participants were in the ICU.
Zhu 2012	RCT. Compared EN vs PN. People with acute stroke. Study did not report that participants were in the ICU.

EN: enteral nutrition; ICU: intensive care unit; PN: parenteral nutrition; RCT: randomized controlled trial.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Braga 1995

Methods	RCT
Participants	77 people in a surgical ICU undergoing curative surgery for gastric or pancreatic cancer. Participants randomized into 3 groups: standard EN formula (n = 24), enriched EN formula with arginine, RNA, and omega-3 fatty acids (n = 26), isocoloric TPN formula (n = 27)
Interventions	EN formula vs enriched EN formula vs isonitrogen-isocaloric parenteral formula. EN started 12 hours following surgery. Infusion rate was gradually increased until full amount was achieved on postoperative day 4.
Outcomes	1. Serum level of total iron-binding capacity, albumin, prealbumin, retinal-binding protein, cholinesterase 2. Delayed hypersensitivity response 3. Lymphocyte subsets 4. Monocyte phagocytosis 5. Postoperative infections

Braga 1995 *(Continued)*

	6. Length of stay Measurements were taken on postoperative days 1 and 8
Notes	We were unable to source the full text for this study and the abstract contained insufficient information to decide eligibility.

Cao 2014

Methods	RCT
Participants	61 people in the NICU
Interventions	EN vs early PN and vs supplemental PN
Outcomes	1. Serum level of total protein, albumin, prealbumin, and transferrin
Notes	Abstract only with insufficient information to justify inclusion

Chen 2011

Methods	RCT
Participants	147 elderly people in a RICU
Interventions	EN + PN vs EN vs PN
Outcomes	1. Energy metabolism 2. Respiratory muscle strength 3. Other short-term outcomes: plasma albumin, haemoglobin, creatinine, nitrogen balance, and blood urea nitrogen
Notes	We were unable to source the full text for this study and the abstract contained insufficient information to decide eligibility.

NCT00522730

Methods	RCT
Participants	15 participants in each group
Interventions	Nutrition delivered continuously for 5 days to provide daily energy supply corresponding to current resting energy expenditure as determined by indirect calorimetry. Formula consisted of 35% of total energy requirements as lipids, 15% as proteins (maximum 1.2 g/kg ideal bodyweight/day), and 50% as dextrose. There was a tight glucose control strategy to avoid hyperglycaemia.
Outcomes	1. Change in plasma concentration of triglycerides 2. Total cholesterol 3. HDL-cholesterol 4. Free fatty acids 5. Apolipoproteins

NCT00522730 *(Continued)*

	6. Lipoprotein 7. Incidence of hyperglycaemia 8. Alteration of liver function 9. Gastrointestinal intolerance 10.Gastrointestinal bleeding 11.Septic complications 12.Occurrence of new organ 13.Dysfunction 14.Length of stay in the ICU 15.Mortality
Notes	Trial was listed as completed in clinical trials register. Awaiting full publication of report to assess inclusion

NCT01802099

Methods	RCT
Participants	Adults, ≥ 18 years of age, requiring mechanical ventilation for > 48 hours, treated with a vasoactive drug via a CVC, eligible for nutritional support started within 24 hours after endotracheal intubation (or within 24 hours after ICU admission if intubation occurred before ICU admission)
Interventions	Early EN formula vs PN formula. EN group given EN for 8 days, then supplemental PN if required. PN group given PN for at least 72 hours, then weaned to EN if haemodynamically stable
Outcomes	1. Mortality (28 days) 2. VAP 3. Bacteraemia 4. CVC-related complications 5. Urinary tract infections 6. Soft tissue infections 7. Nosocomial infections 8. Bacteriological data 9. Vomiting or regurgitation 10.Diarrhoea 11.Bowel ischaemia 12.Mean caloric intake 13.Volume of liquid feed 14.SOFA scores 15.ICU mortality 16.90-day mortality 17.Hospital mortality 18.Mean changes in albumin 19.Prealbumin and C-reactive protein 20.Liver dysfunction episode 21.ICU length of stay 22.Hospital length of stay 23.Duration of mechanical ventilation 24.Changes in mean bodyweight
Notes	Clinical trials registration ID: NCT0180299

NCT01802099 *(Continued)*

	Study terminated early due to Data Safety and Monitoring Board recommendation. Report of results prior to termination not yet published

Ridley 2015

Methods	Enrolled participants allocated to supplemental PN (via CVC) for 7 days post randomization or usual care with EN
Participants	Participants admitted to the ICU within 48-72 hours, mechanically ventilated, ≥ 16 years of age, central venous access suitable for PN solution, ≥ 1 organ system failure related to their acute illness, renal dysfunction, intracranial pressure monitor or ventricular drain in situ, currently receiving extracorporeal membrane, currently has a ventricular assist device
Interventions	EN and supplemental PN formula vs standard EN formula
Outcomes	1. Mean energy amount delivered in calories 2. Total protein amount delivered in first 7 days 3. Total energy amount delivered in the ICU stay 4. Total protein amount delivered in the ICU stay 5. Total antibiotic usage 6. SOFA scores 7. Duration of mechanical ventilation 8. Duration of ICU and hospital stay 9. Mortality up to 180 days post randomization 10.Functional and quality of life to 180 days post randomization
Notes	Clinical trials registration ID: NCT01847534

Soliani 2001

Methods	RCT
Participants	171 people undergoing major abdominal and urological surgery for neoplastic pathology. Aim was to assess the effectiveness and clinical outcomes of total PN.
Interventions	Total PN vs early EN vs early immuno-EN
Outcomes	1. Nutritional and immunological markers 2. Septic morbidity 3. Mortality
Notes	We were unable to source the full text of this study, and its abstract contained insufficient information to decide whether participants were in the ICU.

Theodorakopoulou 2016

Methods	RCT
Participants	148 participants in the ICU

Theodorakopoulou 2016 *(Continued)*

Interventions	EN vs PN
Outcomes	1. Duration of mechanical ventilation 2. ICU and hospital length of stay 3. Mortality rate
Notes	Reported as an abstract only. Study authors did not report denominator figures for each group, and, therefore, there were no useable data.

Xiang 2006

Methods	RCT
Participants	42 critically ill people
Interventions	EN vs PN vs control
Outcomes	1. Partial pressure of arterial oxygen 2. Partial pressure of arterial carbon dioxide 3. White blood cell count 4. Serum alanine aminotransferase 5. Blood urea nitrogen 6. Gastrointestinal haemorrhage
Notes	English abstract did not report review outcomes. Requires translation to assess full eligibility

Xiu 2015

Methods	RCT
Participants	335 people who were expected to survive for > 7 days and were admitted to multiple Chinese ICUs
Interventions	Supplemented EN vs supplemented PN
Outcomes	1. Energy targets 2. Gastric retention 3. Hypoglycaemia
Notes	This study was published only as an abstract that contained insufficient information to decide eligibility.

Yi 2015

Methods	RCT
Participants	63 liver transplant recipients
Interventions	Early EN formula vs PN formula. EN started within 48 hours of transplant surgery

Yi 2015 *(Continued)*

Outcomes	1. Aspartate aminotransferase 2. Alanine aminotransferase 3. Total bilirubin 4. Urea nitrogen 5. Proalbumin 6. Length of stay 7. Infection rate
Notes	This study was published only as an abstract that contained insufficient information to decide eligibility

CVC: central venous catheter; EN: enteral nutrition; HDL: high-density lipoprotein; ICU: intensive care unit; n: number of participants; NICU: neuro-intensive care unit; PN: parenteral nutrition; RCT: randomized controlled trial; RICU: respiratory intensive care unit; RNA: ribonucleic acid; SOFA: sequential organ failure assessment; TPN: total parenteral nutrition; VAP: ventilator-associated pneumonia.

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

NCT00512122

Trial name or title	Impact of early parenteral nutrition completing enteral nutrition in adult critically ill patients
Methods	Participants randomly divided into EN or EN and early PN group. Multi-centre study
Participants	**Inclusion criteria** 1. Adults admitted to any 1 of 5 ICUs 2. NRS ≥ 3 at ICU admission **Exclusion criteria** 1. DNR code or moribund at time of ICU admission 2. Already enrolled in another trial 3. Transferred from another ICU with an established nutritional therapy 4. Ketoacidotic or hyperosmolar coma on admission 5. BMI < 17 kg/m^2 6. Short bowel syndrome 7. Known to be pregnant or nursing 8. On mechanical ventilation at home 9. NRS score < 3 10. Readmitted to ICU after randomization to the EPaNIC trial 11. Not critically ill on admission
Interventions	**EN group:** withholding PN during the first week of ICU stay. Participants will receive exclusively EN. If EN is insufficient after 7th day of ICU stay, PN will be started. **EN and early PN:** PN will be started the morning of 3rd day of ICU stay. Amount of PN will be calculated to cover the caloric needs of the participant, based on EN energy intake during the previous 24 hours.
Outcomes	1. Length of stay in ICU 2. Mortality 3. Days to weaning from mechanical ventilation 4. Need for renal replacement therapies 5. Presence or absence of new kidney injury during ICU stay 6. Days of vasopressor or inotropic support

NCT00512122 *(Continued)*

	7. Presence or absence of signs of ICU liver disease 8. Need for tracheotomy 9. Presence or absence of hyperinflammation within 5 days of ICU admission 10. Blood lipid profiles and albumin on days 1, 5, 10, and 15 after admission 11. Presence or absence of bacteraemia, ventilator-associated pneumonia, and wound infections 12. Episodes of hypoglycaemic events 13. Amount and type of calories delivered 14. Muscle strength 15. Rehabilitation/functionality
Starting date	August 2007
Contact information	Greet Van den Berghe, Katholieke Universiteit Leuven
Notes	Clinical trials registration ID: NCT00512122

NCT02022813

Trial name or title	Impact of supplemental parenteral nutrition in ICU patients on metabolic, inflammatory and immune responses (SPN2)
Methods	RCT. Trial aims to investigate the underlying carbohydrate and protein metabolism changes, as well as the immune and inflammatory modulations associated with these interventions.
Participants	**Inclusion criteria** 1. Adults in ICU 2. Estimated duration of ICU stay > 5 days 3. Estimated survival > 7 days 4. Absence of contraindication to EN 5. Need for mechanical ventilation 6. Informed consent obtained from participants, close relative, or referring physician **Exclusion criteria** 1. Refusal of the participant or next of kin 2. < 18 years of age 3. Non-functional digestive tract 4. Already receiving PN before day 3 5. Absence of a central venous catheter 6. Women who are pregnant 7. Admission after cardiac arrest or severe brain injury
Interventions	**EN group:** EN to be progressed as soon as possible to energy target measured on day 3, and verified on day 4, using the usual facilitators (prokinetics) **Supplemental PN group:** addition of supplemental PN to complete the gap between energy delivered by EN feeding and energy target measured on day 4
Outcomes	1. Glucose and leucine turnover 2. Immune and inflammatory impact of optimized target feeding 3. Overall complications and organ failures 4. Length of mechanical ventilation

NCT02022813 *(Continued)*	5. Length of ICU and hospital stay
Starting date	April 2014
Contact information	Mette M Berger, Prof, Centre Hospitalier Universitaire Vaudois
Notes	Clinical trials registration ID: NCT02022813

BMI: body mass index; DNR: do not resuscitate; EN: enteral nutrition; EPaNIC: early parenteral nutrition completing enteral nutrition in adult critically ill patients; ICU: intensive care unit; NRS: nutritional risk screening; PN: parenteral nutrition; SOFA: sequential organ failure assessment; SPN2: supplemental parenteral nutrition 2.

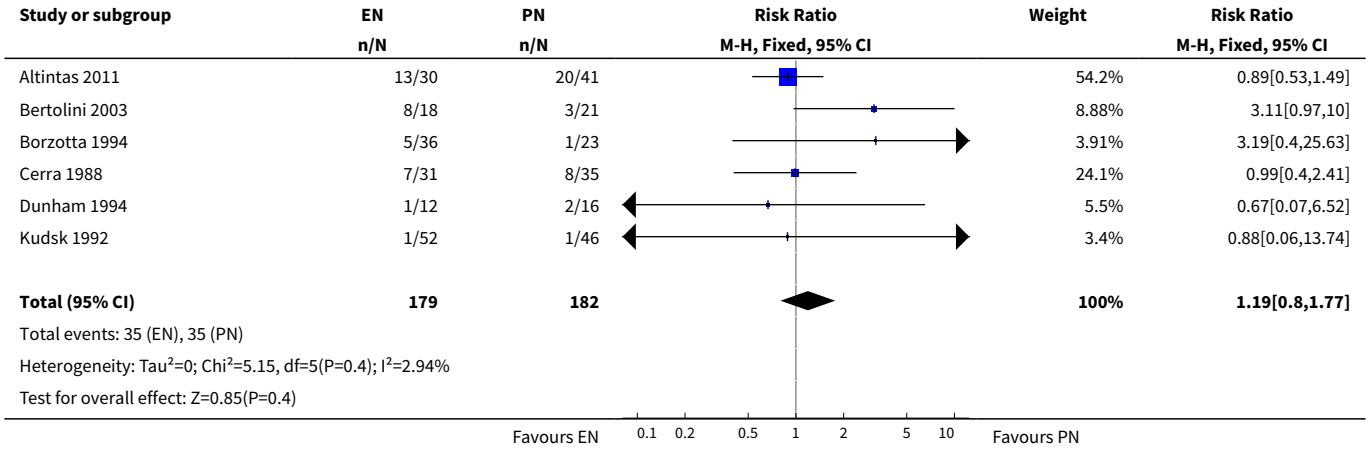
DATA AND ANALYSES

Comparison 1. Enteral (EN) versus parenteral nutrition (PN)

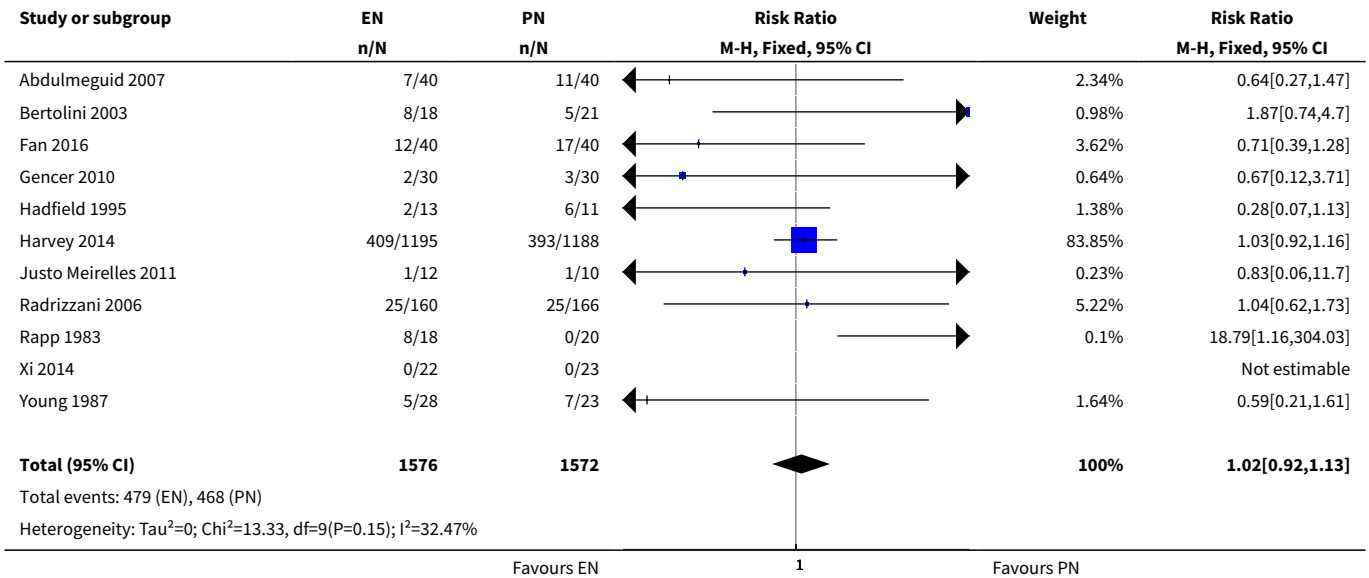
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 In-hospital mortality	6	361	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.80, 1.77]
2 Mortality at 30 days	11	3148	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.92, 1.13]
3 Mortality at 90 days	3	2461	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.95, 1.17]
4 Aspiration	2	2437	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.46, 5.03]
5 Pneumothorax	2	2437	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [0.19, 11.22]
6 Hyperglycaemia	2	2437	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.35, 0.93]
7 Vomiting	3	2525	Risk Ratio (M-H, Fixed, 95% CI)	3.42 [1.15, 10.16]
8 Diarrhoea	6	363	Risk Ratio (M-H, Fixed, 95% CI)	2.17 [1.72, 2.75]
9 Abdominal distension	3	2505	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.34, 6.96]
10 Sepsis	7	361	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.37, 0.95]
11 Pneumonia	7	415	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.82, 1.48]
12 Intra-abdominal infection	3	202	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.07, 0.89]
13 Wound infection	3	155	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.55, 3.82]
14 Urinary tract infection	3	160	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [0.65, 3.40]
15 In-hospital mortality: gastrointestinal (GI) medical/surgical vs non-GI medical/surgical	6	361	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.80, 1.77]
15.1 GI medical/surgical	1	98	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.06, 13.74]

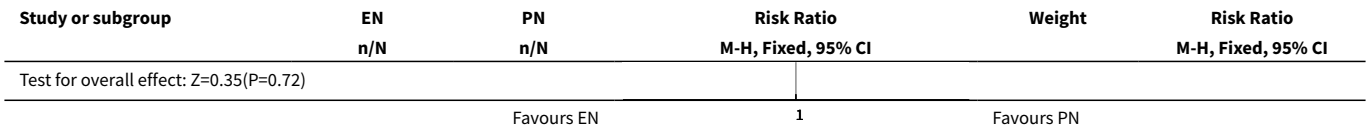
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.2 Non-GI medical/surgical	5	263	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.80, 1.79]
16 Mortality at 30 days: GI medical/surgical vs non-GI medical/surgical	10	3068	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.93, 1.14]
16.1 GI medical/surgical	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.12, 3.71]
16.2 Non-GI medical/surgical	9	3008	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.93, 1.15]

Analysis 1.1. Comparison 1 Enteral (EN) versus parenteral nutrition (PN), Outcome 1 In-hospital mortality.

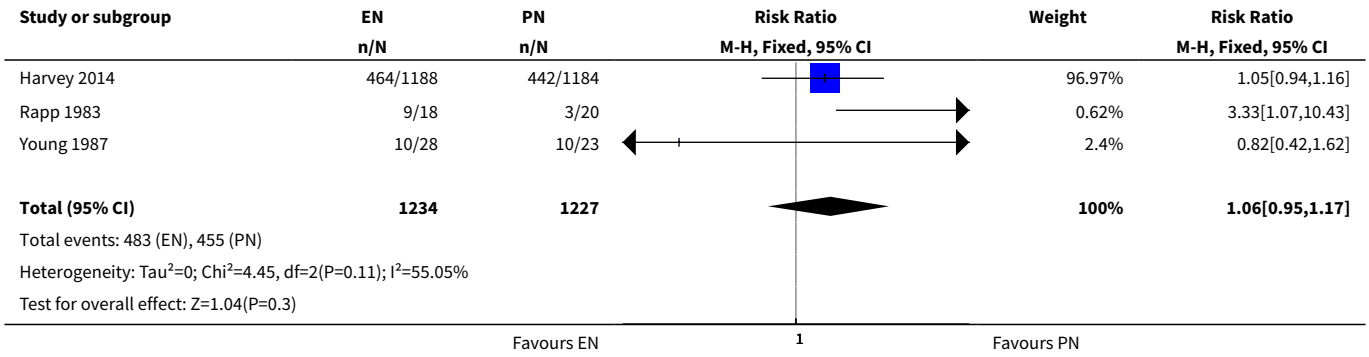


Analysis 1.2. Comparison 1 Enteral (EN) versus parenteral nutrition (PN), Outcome 2 Mortality at 30 days.

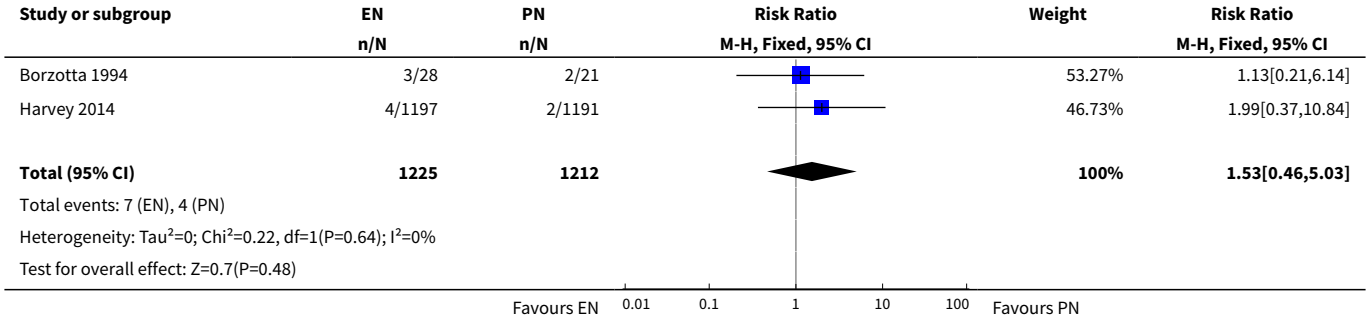




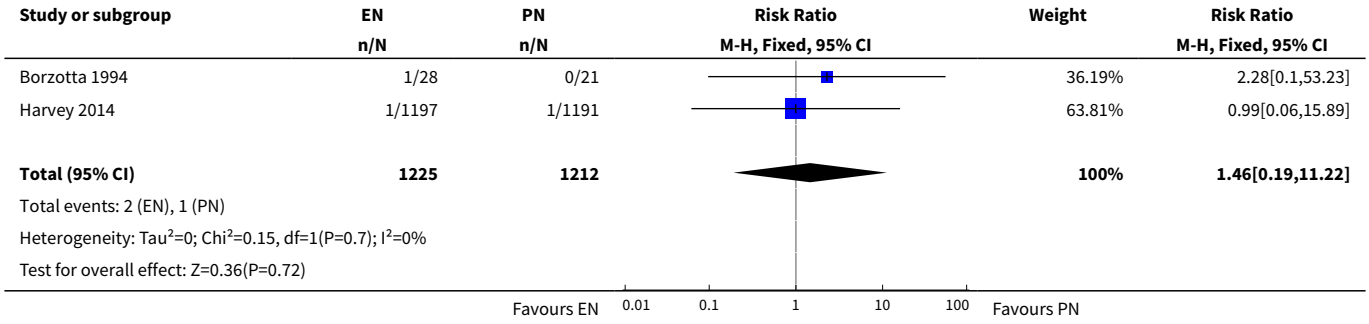
Analysis 1.3. Comparison 1 Enteral (EN) versus parenteral nutrition (PN), Outcome 3 Mortality at 90 days.



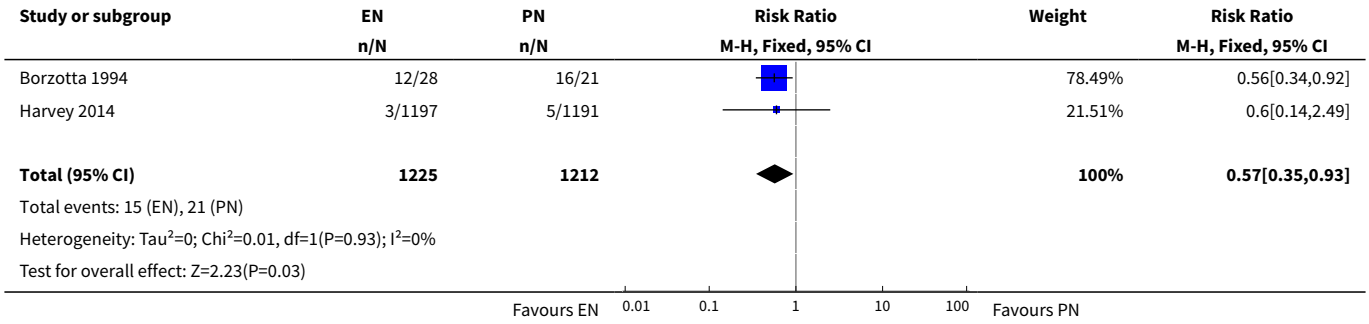
Analysis 1.4. Comparison 1 Enteral (EN) versus parenteral nutrition (PN), Outcome 4 Aspiration.



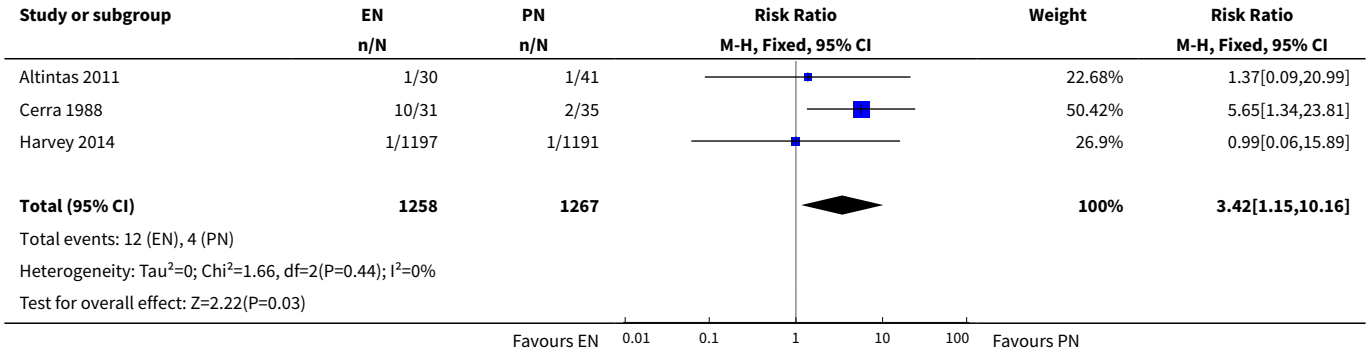
Analysis 1.5. Comparison 1 Enteral (EN) versus parenteral nutrition (PN), Outcome 5 Pneumothorax.



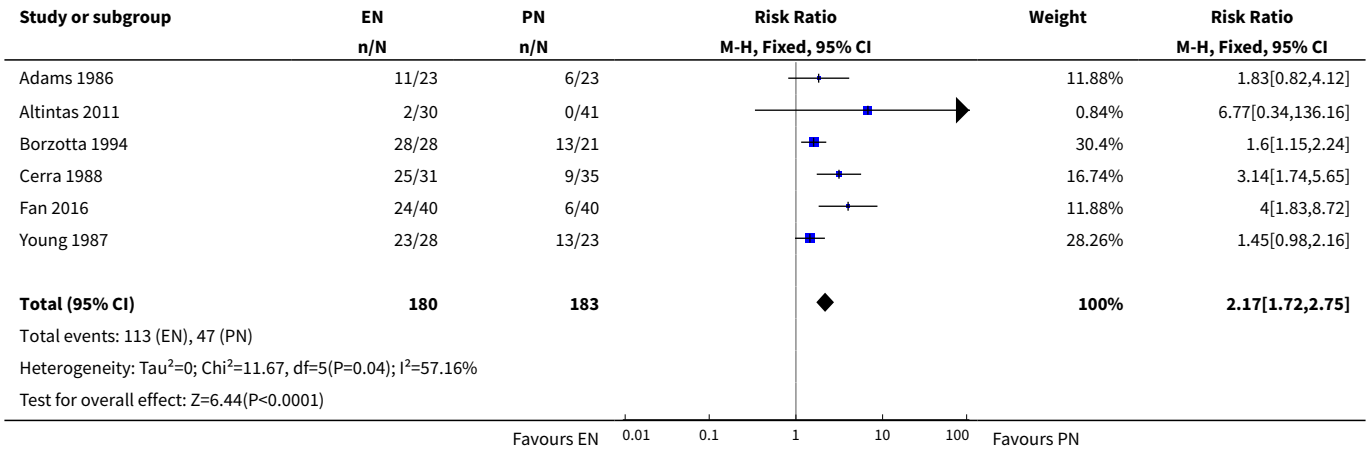
Analysis 1.6. Comparison 1 Enteral (EN) versus parenteral nutrition (PN), Outcome 6 Hyperglycaemia.



Analysis 1.7. Comparison 1 Enteral (EN) versus parenteral nutrition (PN), Outcome 7 Vomiting.

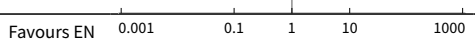


Analysis 1.8. Comparison 1 Enteral (EN) versus parenteral nutrition (PN), Outcome 8 Diarrhoea.



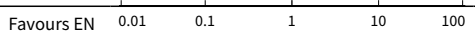
Analysis 1.9. Comparison 1 Enteral (EN) versus parenteral nutrition (PN), Outcome 9 Abdominal distension.

Study or subgroup	EN n/N	PN n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Altintas 2011	0/30	1/41		46.58%	0.45[0.02,10.72]
Harvey 2014	2/1197	1/1191		36.66%	1.99[0.18,21.92]
Peterson 1988	1/21	0/25		16.76%	3.55[0.15,82.72]
Total (95% CI)	**1248**	**1257**		**100%**	**1.53[0.34,6.96]**
Total events: 3 (EN), 2 (PN)					
Heterogeneity: Tau^2=0; Chi^2=0.89, df=2(P=0.64); I^2=0%					
Test for overall effect: Z=0.55(P=0.58)					



Analysis 1.10. Comparison 1 Enteral (EN) versus parenteral nutrition (PN), Outcome 10 Sepsis.

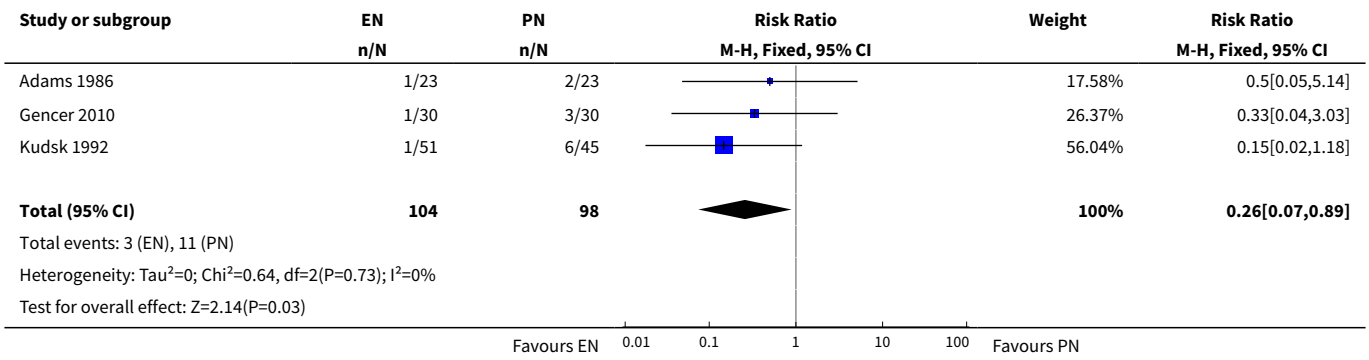
Study or subgroup	EN n/N	PN n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Altintas 2011	7/30	13/41		29.56%	0.74[0.33,1.62]
Engel 1997	3/20	4/10		14.35%	0.38[0.1,1.36]
Justo Meirelles 2011	0/12	2/10		7.29%	0.17[0.01,3.16]
Kudsk 1992	1/51	6/45		17.15%	0.15[0.02,1.18]
Peterson 1988	2/21	8/25		19.65%	0.3[0.07,1.25]
Xi 2014	5/22	4/23		10.52%	1.31[0.4,4.24]
Young 1987	3/28	0/23		1.47%	5.79[0.31,106.71]
Total (95% CI)	**184**	**177**		**100%**	**0.59[0.37,0.95]**
Total events: 21 (EN), 37 (PN)					
Heterogeneity: Tau^2=0; Chi^2=8.17, df=6(P=0.23); I^2=26.6%					
Test for overall effect: Z=2.17(P=0.03)					



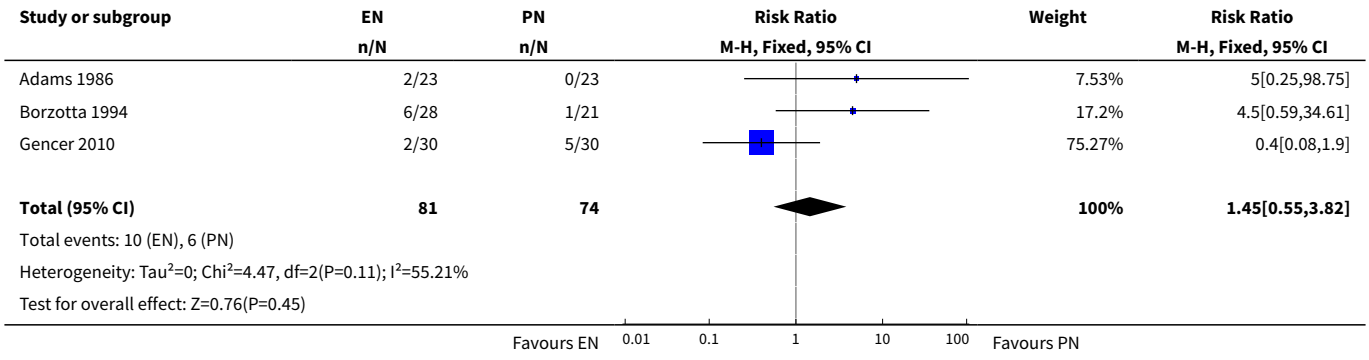
Analysis 1.11. Comparison 1 Enteral (EN) versus parenteral nutrition (PN), Outcome 11 Pneumonia.

Study or subgroup	EN n/N	PN n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Adams 1986	11/23	8/23		13.51%	1.38[0.68,2.78]
Altintas 2011	5/30	11/41		15.7%	0.62[0.24,1.6]
Borzotta 1994	15/28	9/21		17.37%	1.25[0.68,2.28]
Fan 2016	20/40	8/40		13.51%	2.5[1.25,5]
Justo Meirelles 2011	2/12	2/10		3.68%	0.83[0.14,4.9]
Kudsk 1992	6/51	14/45		25.12%	0.38[0.16,0.9]
Young 1987	9/28	6/23		11.12%	1.23[0.51,2.95]
Total (95% CI)	**212**	**203**		**100%**	**1.1[0.82,1.48]**
Total events: 68 (EN), 58 (PN)					
Heterogeneity: Tau^2=0; Chi^2=13.32, df=6(P=0.04); I^2=54.95%					
Test for overall effect: Z=0.64(P=0.52)					

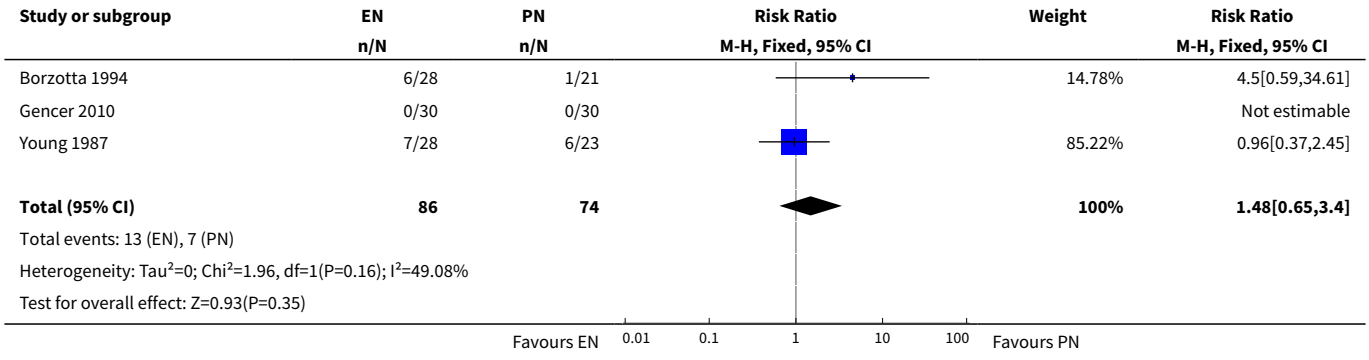
Analysis 1.12. Comparison 1 Enteral (EN) versus parenteral nutrition (PN), Outcome 12 Intra-abdominal infection.



Analysis 1.13. Comparison 1 Enteral (EN) versus parenteral nutrition (PN), Outcome 13 Wound infection.

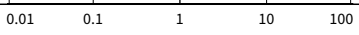


Analysis 1.14. Comparison 1 Enteral (EN) versus parenteral nutrition (PN), Outcome 14 Urinary tract infection.



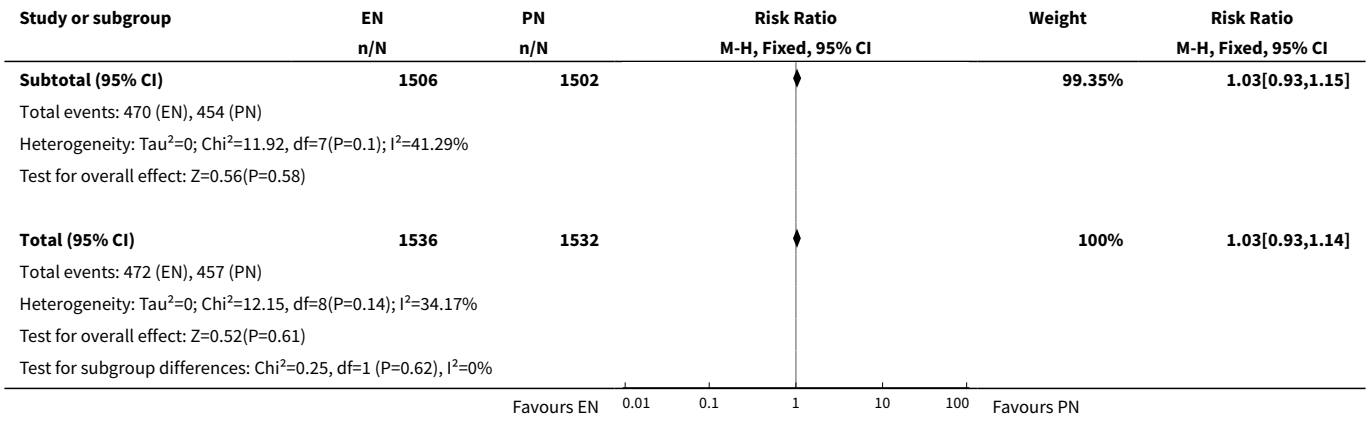
Analysis 1.15. Comparison 1 Enteral (EN) versus parenteral nutrition (PN), Outcome 15 In-hospital mortality: gastrointestinal (GI) medical/surgical vs non-GI medical/surgical.

Study or subgroup	EN n/N	Favours PN n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.15.1 GI medical/surgical					
Kudsk 1992	1/52	1/46		3.4%	0.88[0.06,13.74]
Subtotal (95% CI)	**52**	**46**		**3.4%**	**0.88[0.06,13.74]**
Total events: 1 (EN), 1 (Favours PN)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.09(P=0.93)					
1.15.2 Non-GI medical/surgical					
Altintas 2011	13/30	20/41		54.2%	0.89[0.53,1.49]
Bertolini 2003	8/18	3/21		8.88%	3.11[0.97,10]
Borzotta 1994	5/36	1/23		3.91%	3.19[0.4,25.63]
Cerra 1988	7/31	8/35		24.1%	0.99[0.4,2.41]
Dunham 1994	1/12	2/16		5.5%	0.67[0.07,6.52]
Subtotal (95% CI)	**127**	**136**		**96.6%**	**1.2[0.8,1.79]**
Total events: 34 (EN), 34 (Favours PN)					
Heterogeneity: Tau^2=0; Chi^2=5.14, df=4(P=0.27); I^2=22.23%					
Test for overall effect: Z=0.88(P=0.38)					
Total (95% CI)	**179**	**182**		**100%**	**1.19[0.8,1.77]**
Total events: 35 (EN), 35 (Favours PN)					
Heterogeneity: Tau^2=0; Chi^2=5.15, df=5(P=0.4); I^2=2.94%					
Test for overall effect: Z=0.85(P=0.4)					
Test for subgroup differences: Chi^2=0.05, df=1 (P=0.83), I^2=0%					



Analysis 1.16. Comparison 1 Enteral (EN) versus parenteral nutrition (PN), Outcome 16 Mortality at 30 days: GI medical/surgical vs non-GI medical/surgical.

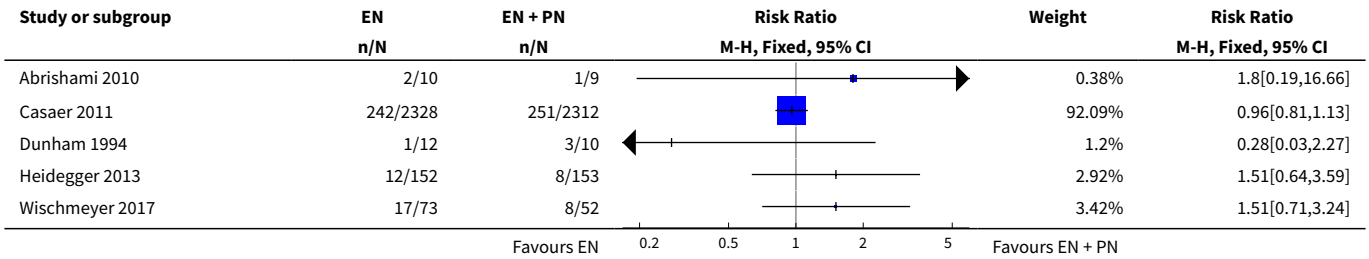
Study or subgroup	EN n/N	PN n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.16.1 GI medical/surgical					
Gencer 2010	2/30	3/30		0.65%	0.67[0.12,3.71]
Subtotal (95% CI)	**30**	**30**		**0.65%**	**0.67[0.12,3.71]**
Total events: 2 (EN), 3 (PN)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.46(P=0.64)					
1.16.2 Non-GI medical/surgical					
Bertolini 2003	8/18	5/21		1.01%	1.87[0.74,4.7]
Fan 2016	12/40	17/40		3.7%	0.71[0.39,1.28]
Hadfield 1995	2/13	6/11		1.42%	0.28[0.07,1.13]
Harvey 2014	409/1195	393/1188		85.86%	1.03[0.92,1.16]
Justo Meirelles 2011	1/12	1/10		0.24%	0.83[0.06,11.7]
Radrizzani 2006	25/160	25/166		5.35%	1.04[0.62,1.73]
Rapp 1983	8/18	0/20		0.1%	18.79[1.16,304.03]
Xi 2014	0/22	0/23			Not estimable
Young 1987	5/28	7/23		1.67%	0.59[0.21,1.61]

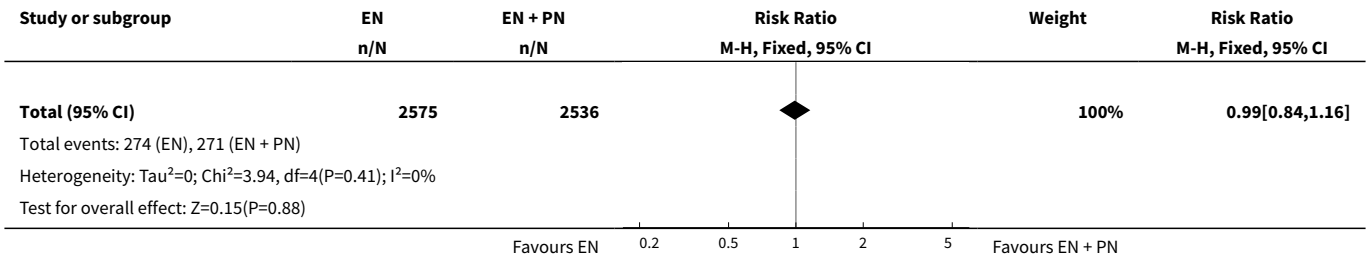


Comparison 2. Enteral (EN) versus combined EN and parenteral nutrition (PN)

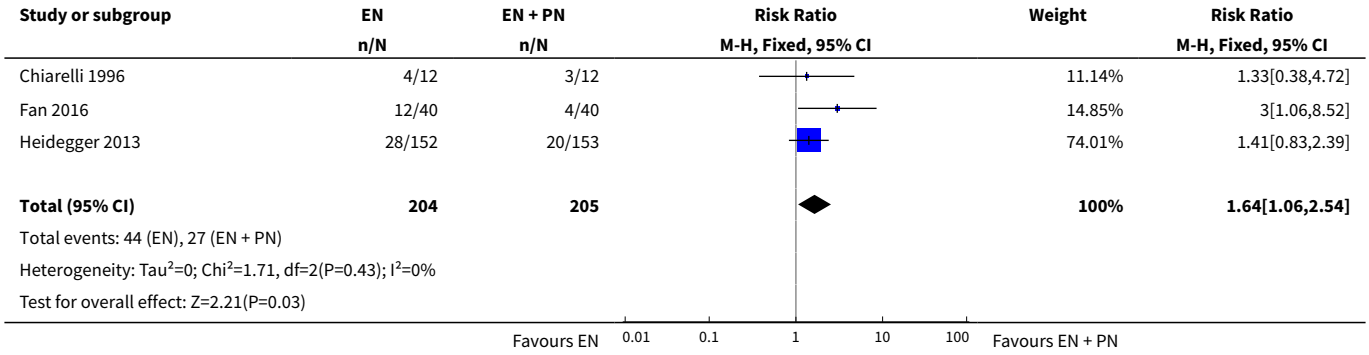
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 In-hospital mortality	5	5111	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.84, 1.16]
2 Mortality at 30 days	3	409	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [1.06, 2.54]
3 Mortality at 90 days	2	4760	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.86, 1.18]
4 Feeding tube obstruction	2	4662	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.70, 1.32]
5 Diarrhoea	4		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Pneumonia	2	205	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.91, 2.15]
7 Wound infection	2	4765	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.50, 0.92]
8 Bloodstream infection	2	4765	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.66, 1.01]
9 Urinary tract infection	3	4885	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.65, 1.17]
10 Airway infection	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 Enteral (EN) versus combined EN and parenteral nutrition (PN), Outcome 1 In-hospital mortality.

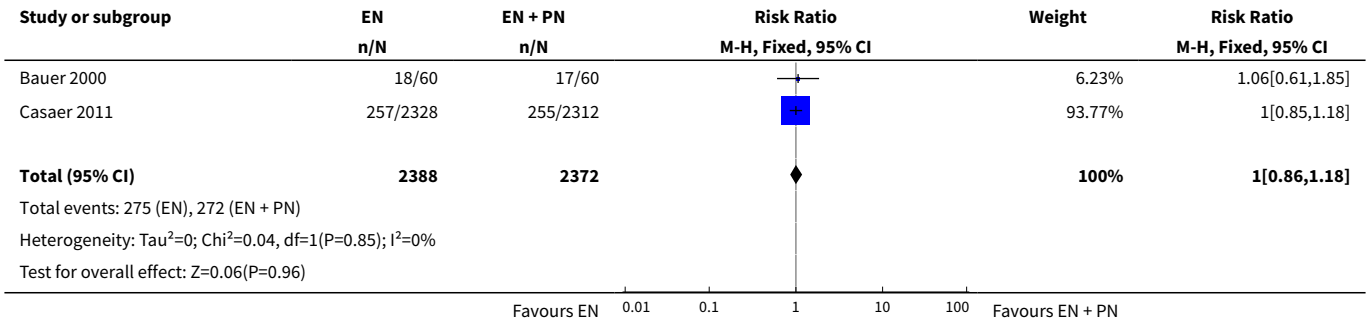




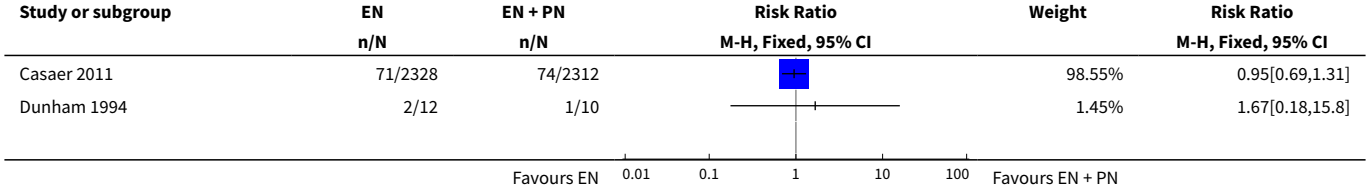
Analysis 2.2. Comparison 2 Enteral (EN) versus combined EN and parenteral nutrition (PN), Outcome 2 Mortality at 30 days.

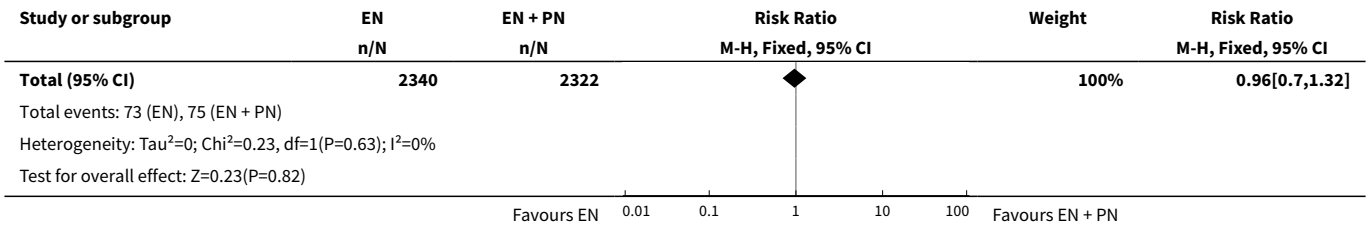


Analysis 2.3. Comparison 2 Enteral (EN) versus combined EN and parenteral nutrition (PN), Outcome 3 Mortality at 90 days.

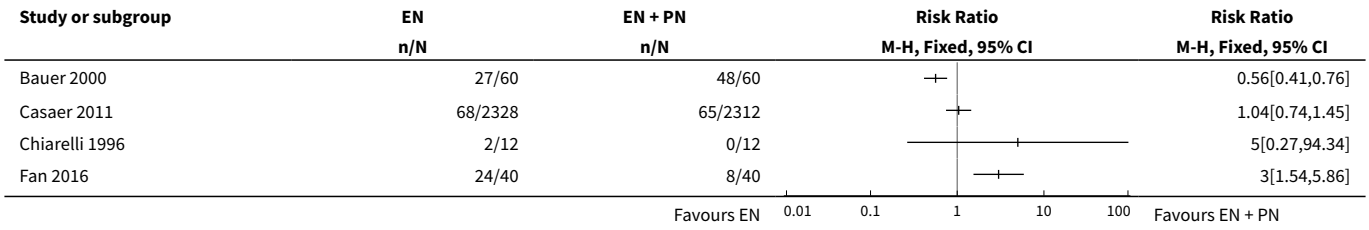


Analysis 2.4. Comparison 2 Enteral (EN) versus combined EN and parenteral nutrition (PN), Outcome 4 Feeding tube obstruction.

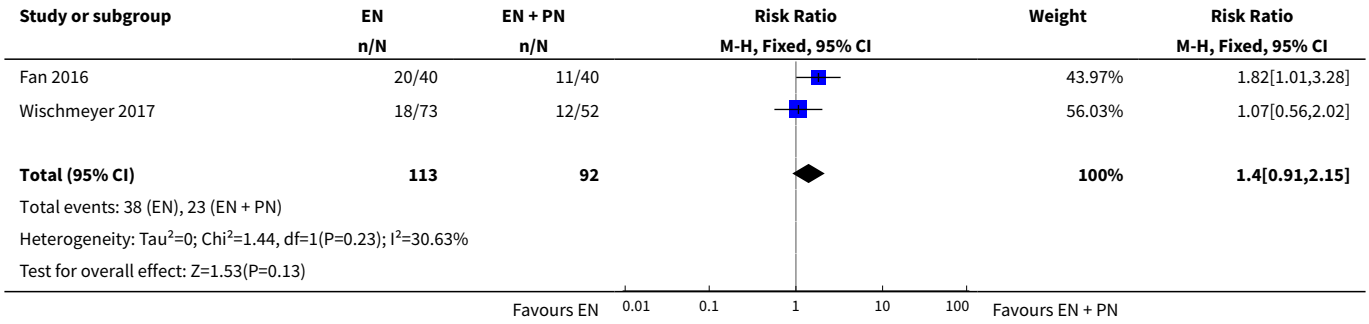




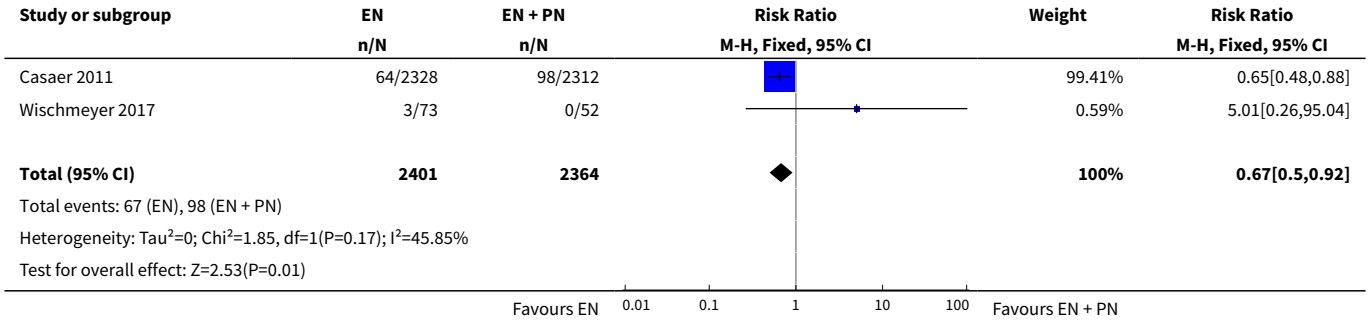
Analysis 2.5. Comparison 2 Enteral (EN) versus combined EN and parenteral nutrition (PN), Outcome 5 Diarrhoea.



Analysis 2.6. Comparison 2 Enteral (EN) versus combined EN and parenteral nutrition (PN), Outcome 6 Pneumonia.



Analysis 2.7. Comparison 2 Enteral (EN) versus combined EN and parenteral nutrition (PN), Outcome 7 Wound infection.



Analysis 2.8. Comparison 2 Enteral (EN) versus combined EN and parenteral nutrition (PN), Outcome 8 Bloodstream infection.

Study or subgroup	EN n/N	EN + PN n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Casaer 2011	142/2328	174/2312		99.67%	0.81[0.65,1]
Wischmeyer 2017	1/73	0/52		0.33%	2.15[0.09,51.73]
Total (95% CI)	**2401**	**2364**		**100%**	**0.81[0.66,1.01]**
Total events: 143 (EN), 174 (EN + PN)					
Heterogeneity: Tau^2=0; Chi^2=0.36, df=1(P=0.55); I^2=0%					
Test for overall effect: Z=1.88(P=0.06)					

Analysis 2.9. Comparison 2 Enteral (EN) versus combined EN and parenteral nutrition (PN), Outcome 9 Urinary tract infection.

Study or subgroup	EN n/N	EN + PN n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bauer 2000	16/60	11/60		12.35%	1.45[0.74,2.87]
Casaer 2011	60/2328	72/2312		81.1%	0.83[0.59,1.16]
Wischmeyer 2017	2/73	5/52		6.56%	0.28[0.06,1.41]
Total (95% CI)	**2461**	**2424**		**100%**	**0.87[0.65,1.17]**
Total events: 78 (EN), 88 (EN + PN)					
Heterogeneity: Tau^2=0; Chi^2=4.15, df=2(P=0.13); I^2=51.84%					
Test for overall effect: Z=0.93(P=0.35)					

Analysis 2.10. Comparison 2 Enteral (EN) versus combined EN and parenteral nutrition (PN), Outcome 10 Airway infection.

Study or subgroup	EN n/N	EN + PN n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Bauer 2000	23/60	28/60		0.82[0.54,1.25]
Casaer 2011	381/2328	605/2312		0.63[0.56,0.7]
Wischmeyer 2017	17/73	5/52		2.42[0.95,6.15]

ADDITIONAL TABLES

Table 1. Adverse events for single studies: enteral nutrition versus parenteral nutrition

Study ID	Description of event	EN group (n/N)	PN group (n/N)
Mechanical events			
Adams 1986	Clogged jejunostomy tube	9/23	N/A

Table 1. Adverse events for single studies: enteral nutrition versus parenteral nutrition *(Continued)*

	Disconnected line	N/A	1/23
	Line eroded into right upper lobe bronchus	N/A	1/23
	Malfunctioned line	N/A	7/23
Dunham 1994	Transpyloric tube occlusion	2/12	0/15
	Failure to intubate	0/12	0/15
	Withdrawal of tube by participant	1/12	N/A
Metabolic events			
Adams 1986	Hepatic failure	1/23	1/23
	Acute renal failure	1/23	1/23
	Pancreatitis	2/23	1/23
Fan 2016	Hypoproteinaemia	22/40	32/40
Harvey 2014	Electrolyte disturbance	5/1197	8/1191
Gastrointestinal events			
Adams 1986	Nausea, cramps, bloating	19/23	16/23
	Gastrointestinal bleeding	0/23	0/23
Dunham 1994	Gastric reflux	0/12	0/15
	Ileus	1/12	0/15
	Small bowel ileus	0/12	1/15
Fan 2016	Stress ulcer	7/40	19/40
Harvey 2014	Elevated liver enzymes	7/1197	3/1191
	Jaundice	1/1197	1/1191
	Ischaemic bowel	0/1197	1/1191
Xi 2014	Anastomotic leak	2/22	6/23
Infective events			
Adams 1986	Persistent fever without obvious cause	1/23	5/23
Altintas 2011	Catheter infection	2/30	4/41
Borzotta 1994	Meningitis	2/28	0/21
	Sinusitis	3/28	6/21

Table 1. Adverse events for single studies: enteral nutrition versus parenteral nutrition *(Continued)*

	Bronchitis	6/28	6/28
	Clostridium difficile	2/28	4/21
	Peritonitis	0/28	1/21
Fan 2016	Intracranial infection	7/40	13/40
	Pyaemia	3/40	19/40
Gencer 2010	Pulmonary infection	2/30	2/30
Kudsk 1992	Empyema	1/51	4/45
Young 1987	Aspiration pneumonia	9/28	3/23
	Infection (type of infection not described)	5/28	4/23

EN: enteral nutrition; n: number of participants with an event; N: total number randomized to group; N/A: not applicable; PN: parenteral nutrition.

Table 2. Adverse events for single studies: enteral nutrition versus enteral nutrition and parenteral nutrition

Study ID	Description of event	EN group (n/N)	EN + PN group (n/N)
Mechanical events			
Casaer 2011	CVC obstruction	9/2328	15/2312
	Nasal bleeding	18/2328	14/2312
	Pneumohaemothorax after CVC placement	0/2328	2/2312
	Subclavian artery puncture	0/2328	2/2312
Dunham 1994	Withdrawal of tube	1/12	0/10
	Failure to intubate	0/12	2/10
Metabolic events			
Fan 2016	Hypoproteinaemia	22/40	7/40
Gastrointestinal events			
Casaer 2011	Vomiting or aspiration	284/2328	295/2312
Dunham 1994	Gastric reflux	0/12	2/10
Fan 2016	Stress ulcer	7/40	9/40
infective events			
Fan 2016	Pyemia	3/40	10/40

Table 2. Adverse events for single studies: enteral nutrition versus enteral nutrition and parenteral nutrition *(Continued)*

	Intracranial infection	7/40	5/40
Wischmeyer 2017	Catheter bloodstream infection	0/73	7/52
	Intra-abdominal infection	0/73	4/52
	Upper urinary tract infection	0/73	1/52
	Surgical deep infection	0/73	1/52

CVC: central venous catheter; EN: enteral nutrition; EN + PN: combined enteral and parenteral nutrition; n: number of participants with an event; N: total number randomized to group.

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Enteral Nutrition] explode all trees
#2 feeding tube* or PEG line* or EN or ((enteral or enteric) near (nutrition or feeding))
#3 #1 or #2
#4 MeSH descriptor: [Parenteral Nutrition] explode all trees
#5 MeSH descriptor: [Plasma Substitutes] explode all trees
#6 (nutrition adj5 venous line*) or PN or ((parenteral or intravenous) near (nutrition or feeding))
#7 #4 or #5 or #6
#8 ICU or (critical* near (ill* or care)) or septic* or sepsis or feeding therap* or plasma substitute*
#9 MeSH descriptor: [Sepsis] explode all trees
#10 MeSH descriptor: [Shock, Septic] explode all trees
#11 MeSH descriptor: [Intensive Care Units] explode all trees
#12 MeSH descriptor: [Multiple Organ Failure] explode all trees
#13 MeSH descriptor: [Systemic Inflammatory Response Syndrome] explode all trees
#14 MeSH descriptor: [Critical Illness] explode all trees
#15 MeSH descriptor: [Critical Care] explode all trees
#16 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15
#17 #3 and #7 and #16 in Trials

Appendix 2. MEDLINE (OvidSP) search strategy

1. (feeding tube* or PEG line* or EN or ((enteral or enteric) adj5 (nutrition or feeding))).mp. or exp Enteral Nutrition/
2. ((nutrition adj5 venous line*) or PN or ((parenteral or intravenous) adj5 (nutrition or feeding))).mp. or exp Parenteral Nutrition/ or Plasma Substitutes/ or plasma substitute*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
3. (ICU or (critical* adj5 (ill* or care))).mp. or (septic* or sepsis).ti,ab. or Sepsis/ or Shock, Septic/ or exp Intensive Care Units/ or exp Critical Illness/ or exp Critical Care/ or Multiple Organ Failure/ or Systemic Inflammatory Response Syndrome/ or feeding therap*.ti,ab.
4. ((randomized controlled trial or controlled clinical trial).pt. or randomi?ed.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (animals not (humans and animals)).sh.
5. 1 and 2 and 3 and 4

Appendix 3. Embase (OvidSP) search strategy

1. (feeding tube* or PEG line* or EN or ((enteral or enteric) adj5 (nutrition or feeding))).mp. or exp enteric feeding/
2. ((nutrition adj5 venous line*) or PN or ((parenteral or intravenous) adj5 (nutrition or feeding))).mp. or exp Parenteral Nutrition/ or Plasma Substitute/ or plasma substitute*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
3. (patient* adj5 (ICU or (critically adj3 (ill* or care)))).mp. or ICU.ti,ab. or (critical* adj3 ill*).ti,ab. or (septic* or sepsis).ti,ab. or Sepsis/ or septic shock/ or exp Intensive Care Unit/ or Critical Illness/ or Multiple Organ Failure/ or Systemic Inflammatory Response Syndrome/ or exp Intensive Care/ or feeding therap*.ti,ab.

4. ((crossover procedure or double blind procedure or single blind procedure).sh. or (crossover* or cross over*).ti,ab. or placebo*.ti,ab,sh. or (doubl* adj blind*).ti,ab. or (controlled adj3 (study or design or trial)).ti,ab. or allocat*.ti,ab. or trial*.ti,ab. or randomized controlled trial.sh. or random*.ti,ab.) not ((exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.))
5. 1 and 2 and 3 and 4

WHAT'S NEW

Date	Event	Description
3 January 2019	Amended	Editorial team changed to Cochrane Emergency and Critical Care

CONTRIBUTIONS OF AUTHORS

Conceiving the review: ARB, SL.

Co-ordinating the review: SL.

Undertaking manual searches: SL, OSR.

Screening search results: SL, OSR.

Organizing retrieval of papers: OSR.

Screening retrieved papers against inclusion criteria: SL, OSR.

Appraising quality of papers: SL, OSR.

Abstracting data from papers: SL, OSR.

Managing data for the review: SL.

Entering data into Review Manager 5 (Review Manager 2014): SL, OSR.

Analysing Review Manager 5 statistical data: SL, OSR.

Interpreting data: all review authors.

Writing the review: SL, OSR.

Securing funding for the review: PA, AS.

Serving as guarantor for the review (one author): AS.

Taking responsibility for reading and checking the review before submission: SL.

DECLARATIONS OF INTEREST

SL's institution receives the National Institute for Health Research (NIHR) Cochrane Collaboration Programme Grant for programme of reviews in perioperative care, which supported her work on this review (see Sources of support).

OSR's institution receives the NIHR Cochrane Collaboration Programme Grant for programme of reviews in perioperative care, which supported his work on this review (see Sources of support).

PA's institution receives the NIHR Cochrane Collaboration Programme Grant for programme of reviews in perioperative care, which supported his work on this review (see Sources of support). Dr Alderson is employed by NICE, which has published a clinical guideline relevant to this topic (NICE 2006).

AS's institution receives the NIHR Cochrane Collaboration Programme Grant for programme of reviews in perioperative care, which supported his work on this review (see Sources of support).

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- NIHR Cochrane Collaboration Programme Grant, UK.

  'Back to normal': speed and quality of recovery after surgery, major injury and critical care. Project ref. 13/89/16

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes to the published protocol (Lewis 2016).

1. We changed the title to: Enteral versus parenteral nutrition and enteral versus a combination of enteral and parenteral nutrition for adults in the intensive care unit.
2. We added a new author, Oliver Schofield-Robinson, who independently carried out screening of search results and data collection. Andrew Butler did not contribute to completion of the review and was removed from the review author list.
3. We edited the criteria for considering studies in the review: we intended to include only participants who were in the ICU. We edited the criteria to only include studies of mixed population if more than 75% of participants were in the ICU; at protocol stage we had not anticipated that studies may have a mixed participant population.
4. Objectives: we noted a difference between the objectives and the outcomes in our published protocol. The list of review outcomes did not include a measure of length of hospital stay. We edited the objectives to state that we compared the effect of nutrition on the number of ICU-free stays up to day 28.
5. Unit of analysis: in the protocol, we stated "If multi-arm studies compare more than one relevant intervention (e.g. EN vs PN and EN vs EN and PN), we will include both comparison groups but will split the data for the intervention group - EN in this example - by using a 'halving' method to avoid double-counting, as recommended by Higgins 2011." In the review, we analysed outcome data as two separate comparisons (i.e. EN versus PN and EN versus EN and PN) and therefore we did not split data in multi-arm studies.
6. Summary of findings: we outlined in the published protocol (Lewis 2016), that we would include the following outcomes in the 'Summary of findings' table: mortality (in hospital, at 30 days, at 90 days, at 180 days); number of ICU-free days; number of ventilator-free days; and adverse events (as reported by study authors). We limited number the number of adverse events in the 'Summary of findings' table to four outcomes for each comparison group (aspiration, sepsis, pneumonia, and vomiting); we had not specified these in the protocol. Selection of appropriate adverse events was taken following discussion with a Consultant Anaesthetist in Intensive Care.

INDEX TERMS

Medical Subject Headings (MeSH)

*Critical Illness; *Intensive Care Units; Cause of Death; Combined Modality Therapy [methods]; Enteral Nutrition [*methods]; Hospital Mortality; Malnutrition [*prevention & control]; Parenteral Nutrition [*methods]; Pneumonia [epidemiology]; Randomized Controlled Trials as Topic; Time Factors; Vomiting [epidemiology]

MeSH check words

Adult; Humans