Evidence-Based Guidelines for Nutritional Support of the Critically Ill: Results of a Bi-National Guideline Development Conference

An Australian and New Zealand Intensive Care Society

Clinical Trials Group Endorsed project

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Coogee, NSW

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Evidence-Based Guidelines for Nutritional Support of the Critically Ill: Results of a Bi-National Guideline Development Conference

First Edition

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Updated Version Notes

Version 7 contains critical appraisal summary sheets for trials that were reviewed in detail and determined not to be conducted in a critically ill patient population and identifies papers that were retrieved and found not to qualify for detailed review.

Executive Summary

The purpose of this guidelines initiative was to develop or update and validate an evidence-based feeding guideline for critically ill patients. A widely accepted methodology was adopted, which requires the identification of previously developed and validated evidence-based guidelines. The process then specifies a methodology for identifying and assimilating evidence that may be used to change or update the previously validated guidelines.

An extensive literature search was conducted (closeout date April 2003). Four hundred and sixty five full text papers were retrieved and reviewed. The only evidence-based guideline for feeding critically ill patients that had been validated in an RCT was identified (Martin et al. 2004). When evaluated in a cluster randomised trial including 499 patients from 14 hospitals, the adoption of this guideline resulted in a 10% reduction in mortality (p= 0.058) and an average decrease in hospital stay of 10 days (p=0.003). The process and evidence used to support and update this guideline is presented in this document.

The final ratified guideline was evaluated in a 27 hospital cluster randomised trial conducted in Australia and New Zealand.

Important: How to find a paper using RefID

Throughout this document, papers are referred to using a Reference Identifier (**RefID**) that was assigned to the paper for the conduct of this project.

At the end of this document, all references are sorted in alphabetical order by author. Each paper's **RefID** is reported immediately after the full citation found in the Reference List.

Papers can be searched in this document using the author name or using the **RefID**. For example, the paper by (Chuntrasakul et al. 1996) has **RefID 511**. To find the occurrences of this paper, search for Chuntrasakul or search for **RefID 511**. To conduct a search within Adobe Acrobat, click on the 'binoculars' icon or select Edit | Search from the toolbar menu.

Conference Participants

Hospital	Attendee
Auckland Hospital, NZ	1. Lyn Gillianders 2. James Judson
Epworth Hospital, VIC	3. Caroline Adams 4. Benno Ihle
Fremantle Hospital WA.	5. David Blythe 6. Liliana Sputore
John Hunter Hospital, NSW	7. Peter Harrigan 8. Samantha Saunders
Mater Misericordiae, QLD.	9. Sally McCray 10. TJ (John) Morgan
Princess Alexandria Hospital, QLD.	11. Azmat Ali 12. Chris Joyce
Royal Brisbane and Royal Womens Hospital, QLD.	13. Sharon Forbes 14. Jane Musial 15. Neil Widdicombe
Royal Hobart Hospital, TAS	16. Tony Bell 17. Suzie Cotton
Royal North Shore Hospital, NSW	18. Simon Finfer 19. Gwen Hickey
Royal Prince Alfred, NSW	20. Suzie Ferrie 21. Clive Woolfe
Sir Charles Gairdner, WA	22. Emma Spillman 23. Paul Woods
St Vincents Hospital, VIC	24. Melinda Bartlett 25. John Santamaria
The Canberra Hospital, ACT	26. Imogen Mitchell 27. Julie Nikolaidis
Western Hospital, VIC.	28. Michael Andrews 29. Craig French
Invited Recognised Experts:	30. Charlie Corke, VIC 31. Philippa Leese, NSW 32. Alan Spencer, QLD
Critical Appraisal Sub-committee	33. Anthoney Delaney, NSW 34. Gordon S. Doig, NSW 35. Fiona Simpson, NSW

Overview of process

This evidence-based guidelines development meeting was conducted in accordance with the methodology outlined in Browman's Practice Guideline Development Cycle (PGDC) (Browman et al. 1995). The PGDC is an explicit process that has been validated for the generation, implementation and evaluation of evidence based clinical practice guidelines (**Table 1)**. The PGDC process is employed by Cancer Care Ontario (www.cancercare.on.ca) to develop patient and practitioner-level evidence-based guidelines.

Table 1. The Practice Guidelines Development Cycle

1. Select/Frame clinical problem
- -frame the problem
- -select and prioritise topics
- -select outcome

2. Generate evidence-based recommendations (EBRs)
- -search for existing guidelines
- -gather and synthesise evidence
- -grade strength of evidence
- -generate preliminary EBRs

3. Ratify EBRs
- -disseminate preliminary EBRs
- -build consensus on final EBRs and ratify
- -document minority opinions

4. Formulate practice guidelines
- -disseminate ratified EBRs
- -apply modulating factors
- -formulate clinical practice guideline

5. Independent review
- -submit ratified EBRs and guidelines for independent review
- -adjust guideline with consensus
- -document modifications
- -submit guideline for approval

6. Negotiate practice policies
- -disseminate guidelines
- -apply non-clinical modulators
- -negotiate practice policies
- -monitor guideline/policy discordance

7. Adopt guideline, policies
- -submit guideline/policies for formal approval
- -document reasons for modification

8. Scheduled review
- -set expiry date
- -monitor trends prompting early reassessment

In short, the PGDC requires the generation of a series of *systematic reviews* covering optimally effective approaches to the diagnosis and treatment of a specific condition. These reviews are synthesised from the best available evidence and then graded to result in *evidence-based recommendations* (EBRs) (Cook et al. 1997). The EBRs are formally augmented with expert opinion and customised to local settings before being implemented as guidelines.

In advance of the meeting: an extensive literature review was undertaken; all randomised controlled trials were critically appraised for methodological quality; overviews of focussed clinical questions were compiled leading to evidence-based recommendations for optimally effective techniques; reprints and summaries of each trial were circulated.

At the meeting; evidence-based recommendations were reviewed and ratified and guideline statements compiled.

Article inclusion criteria and definitions.

Patient population

Previous meta-analyses have found differences in treatment effects (statistical and clinical heterogeneity) between studies performed on elective surgical patient populations and studies performed on critically ill patient populations (Heyland et al. 1998a), (Heyland et al. 2001). For this reason, only studies conducted in critically ill patient populations were included in the guideline process.

A study was deemed to include critically ill patients if:

- The patients were recruited in an Intensive Care Unit (ICU) and the study was conducted in an ICU.
- The inclusion criteria were such that the patients would normally be cared for in an ICU Eg; all patients were receiving mechanical ventilatory support.

A study was deemed *likely* to include critically ill patients if:

- The patients were suffering from a condition that *usually* requires care in an ICU. Eg; severe thermal burns of > 40-50% TBSA, Multi trauma patients that required urgent laparotomy or other operative interventions.
- The patients had an average ICU length of stay (LOS) of > 2 days or a significant proportion of the patients required a therapy that is delivered in the ICU (Eg; mechanical ventilation).
- A severity of illness score was reported that was commensurate with the patients being critically ill.

A study was judged *not* to include critically ill patients if:

- The patients had simple operative procedures that would *not normally* require admission to an ICU Eg; simple gastrectomy or hemi-colectomies.
- The exclusion criteria were such that patients with complicating medical conditions that might require admission to an ICU, such as cardiac failure, renal failure, diabetes or liver impairment, were not enrolled.
- The course of the patients as reported was uncomplicated eg; routine surgery, oral intake day 1 and then discharge from hospital day 5 or 6.

In some cases the information reported in the paper was not detailed enough to make an objective judgement. A degree of subjectivity in the judgements was required to determine whether a study involved critically ill patients. In order to avoid problems associated with this unavoidable subjectivity, all papers that *may have* included critically ill patients were presented at the guidelines meeting for consideration.

This definition of a critically ill patient population has been employed in at least two peer reviewed publications (Doig et al. 2005), (Simpson and Doig 2005).

Outcome selection

Outcome definitions were obtained from the seminal work by Prentice (Prentice 1989).

- A *clinically meaningful outcome* was defined as a direct measure of how a patient feels, functions or survives.

- A *surrogate outcome* was defined as a laboratory measurement or a physical sign used as a substitute for a clinically meaningful outcome.

- In order to be considered a validated surrogate outcome, and thus serve as a substitute for a clinically meaningful outcome, a surrogate outcome must:
    - be a correlate of the true clinical outcome and
    - fully capture the net effect of treatment on the clinical outcome

No nutritional, or other surrogate outcomes, met the above criteria and thus the guidelines process was restricted to the consideration of clinically meaningful outcomes.

Validity criteria

The CONSORT statement (http://www.consort-statement.org/) explicitly recognises the importance of the maintenance of allocation concealment (Schulz and Grimes 2002) through appropriate randomisation practices and the performance of an intention to treat (ITT) analysis based on all randomised patients (Lachin 2000) in order to reduce bias in conclusions drawn from randomised controlled trials (Begg et al. 1996),(Moher et al. 2001a),(Moher et al. 2001b).

Trials that violated allocation concealment by using a pseudo-randomisation process (Eg; allocation to treatment group by day of week, patient medical record number, etc.) were *not* eligible for consideration in this guideline process. Pseudo-randomised trials are known to over-inflate estimates of treatment effects by up to 40% (Juni et al. 2001). Similarly, because an ITT analysis cannot be conducted in the face of *significant* loss to follow-up, trials that included an excessive number of patients who were randomised and subsequently lost to follow-up were also not eligible for consideration in this guideline process.

The primary conclusions of this guidelines process are based on trials with a minimal amount of loss to follow-up (less than 5% of outcomes missing on all randomised patients). A sensitivity analysis was performed considering the results of trials with *less than* 10% loss to follow-up, where losses were reported by study arm, and is presented where such trials exist.

Because greater than 10% loss to follow-up has been considered an important quality criteria in previous methodological reviews of the critical care literature, greater than 10% loss to follow-up was set as the cut-off for consideration in the guidelines process (Graf et al. 2002),(Lachin 2000).

Levels of Evidence and Grades of Recommendation

The Levels of Evidence and Grades of Recommendation used throughout this document are based on previous publications in this field . A complete reference list and description can be found at www.EvidenceBased.net in the EBR section.

Table 2. Levels of Evidence

Level I • adequately powered† (low false +ve or false –ve), well conducted trials
Level II • small, under-powered (high false +ve and false –ve), well conducted trials
Level III* • non-randomised concurrent (contemporary) controls
Level IV* • non-randomised historical controls
Level V* • case series without controls

***** These Levels of Evidence were not considered at this guidelines conference.
† We defined **power** as a measure of the probability that a clinical trial will detect a treatment effect of a given magnitude (X), under the assumption that the treatment effect actually exists. To qualify as a Level I trial (**adequately powered**), the trialists must have established that it was plausible to assume that the treatment effect of magnitude X actually existed. Data from earlier trials is the best way to establish the plausibility of the magnitude of the expected treatment effect (Halpern et al. 2002).

Table 3. Grades of Recommendation

Description	Level of Evidence Required	Grade of Recommendation
More than one well conducted, adequately powered RCT with consistent results between studies (no heterogeneity)	I	A+
At least one well conducted, adequately powered RCT	I	A
More than one well conducted, adequately powered RCT with inconsistent results (heterogeneity) between studies.	I	A-
More than one well conducted RCT with consistent results between studies	II	B+
At least one well conducted RCT	II	B
More than one well conducted RCT with inconsistent results (heterogeneity) between studies	II	B-

Literature search

An extensive literature search was conducted for controlled trials of feeding interventions conducted in critically ill patients. Terms were also specified to identify methodologically rigorous guidelines, overviews and meta-analyses. A complete listing of search terms are available on request. On-line searching of Medline and EMBASE, and hand searching the reference lists of retrieved review papers, was undertaken. Recognised experts and industry were contacted for additional references. The final close-out date for this search process was April 2003.

Medline was searched using the PubMed search engine from 1966 to April 2003.

EMBASE was searched using OVID from 1980 to April 2003.

The reference lists of the following review articles were hand searched:

RefID 1244 (Heyland 2003)
RefID 1245 (Heyland et al. 2003)
RefID 241 (Novak et al. 2002)
RefID 249 (Booth et al. 2002)
RefID 256 (Heyland et al. 1996)
RefID 294 (Marik and Zaloga 2001)
RefID 310 (Heyland et al. 2001)
RefID 364 (Heyland 2000a)
RefID 383 (Heyland 2000b)
RefID 454 (Heyland et al. 1998a)
RefID 462 (Heyland 1998)
RefID 571 (Heyland et al. 1993)
RefID 609 (Heyland et al. 1994)
RefID 713 (Naylor et al. 1989)
RefID 955 (Heys et al. 1999)
RefID 957 (Beale et al. 1999)
RefID 1147 (Griffiths et al. 1996)
RefID 1173 (Heyland et al. 1998b)
RefID 1202 (Moore et al. 1992)
RefID 1208 (Lewis et al. 2001)
RefID 1213 /(Heyland et al. 2002)
RefID 1220 (Heyland and Samis 2003)
RefID 1222 (Garcia-de-Lorenzo et al. 2003)

Although the literature search itself was not limited to the identification of non-English language publications, the review process focussed on English language publications only (Juni et al. 2002). Similarly, only studies published full-paper format, that could be adequately critically appraised, were considered for review (Egger et al. 2003).

Literature retrieval and review

The Medline / EMBASE search retrieved 2,287 abstracts. Independent review of all abstracts (GSD and FS) identified approximately 465 papers that may have been controlled trials or review papers on the topic of interest. All 465 papers were retrieved. Review of these 465 papers (GSD and FS) identified 337 primary studies that evaluated feeding interventions. Detailed review or critical appraisal (GSD, FS and AD) of the 337 identified primary studies revealed:

103 Phase II studies (did not report any clinically meaningful outcomes)
42 studies not conducted in intensive care patients
27 papers that were not primary feeding studies
15 cross-over studies
12 papers on pre-operative interventions
8 observational studies (not RCTs)
7 non-English language studies
6 pseudo randomised trials
5 were based on sub-groups of patients from a larger published trial
1 post-operative intervention (oral intake for 10 weeks post surgery)

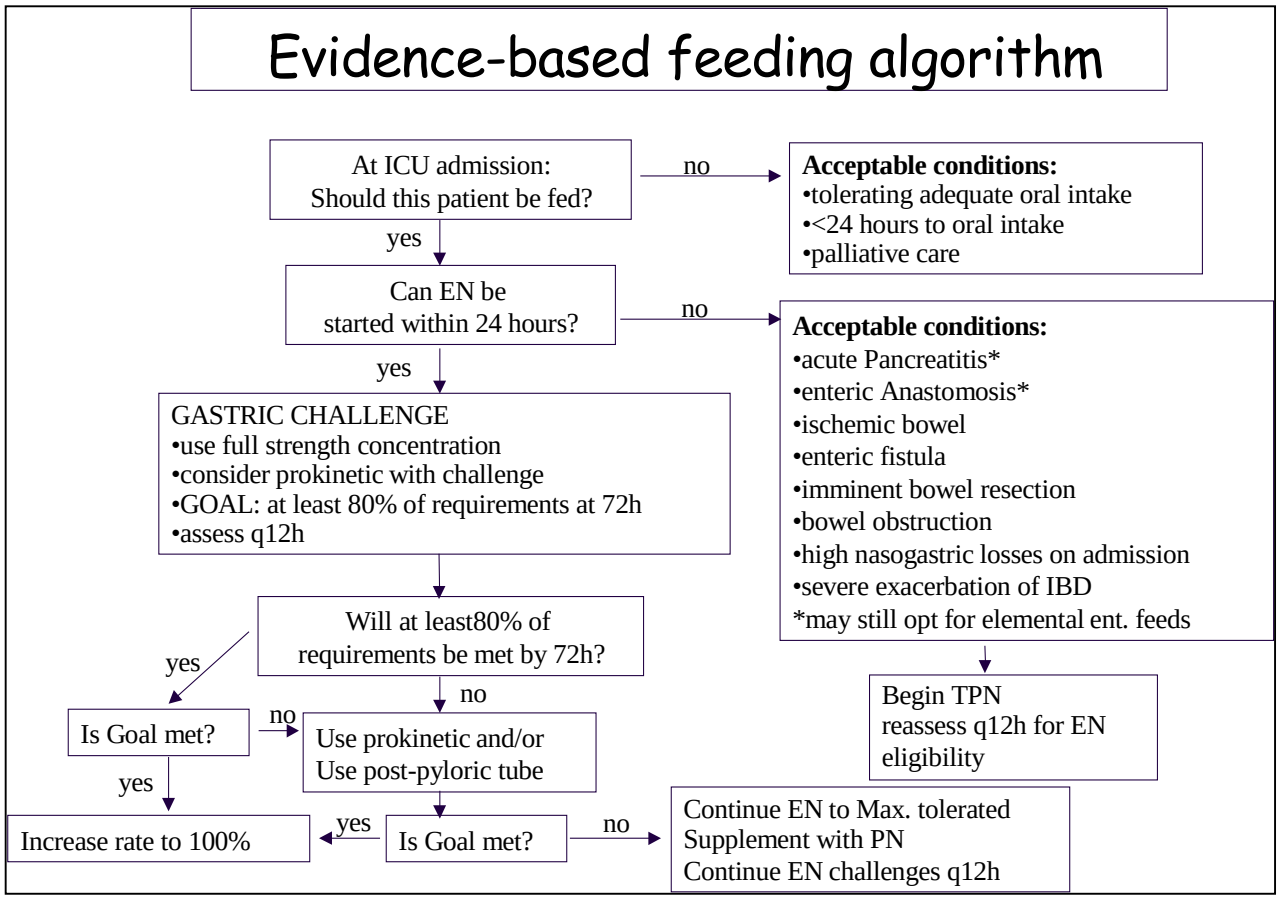
1 duplicate publication (part 1 of a 2 part publication. Part 2 was included in the guideline process)

The remaining 111 primary feeding studies were conducted in critically ill patients and reported clinically meaningful outcomes. All 111 were appraised in detail to determine validity (GSD, FS and AD). Additional details of this search and appraisal process have been published elsewhere (Doig et al. 2005).

The search identified one evidence-based guideline for nutritional support in the ICU that had previously been validated in a cluster randomised trial (Martin et al. 2004). The cluster randomised trial documented a 10% decrease in hospital discharge mortality and constitutes Level II evidence.

According to the methodology outlined in Browman's PGDC, the overall goal of the evidence-based consensus conference becomes the appraisal and update of the evidence supporting each individual EBR generated in this previously validated and published evidence-based guideline. The algorithmic representation of this validated evidence-based guideline is presented in Figure 1.

Figure 1. Algorithmic representation of ACCEPT evidence-based guideline.



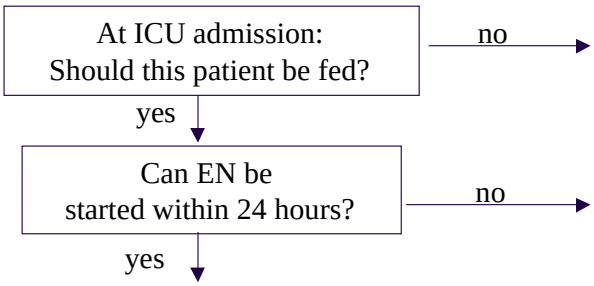
EN = enteral nutrition, PN = parenteral nutrition, IBD = inflammatory bowel disease

The ACCEPT trial algorithm constitutes Level II Evidence.

- 10% decrease in mortality (95% CI 0% to 26%)

The accept algorithm was decomposed into the following constituent evidence-based recommendations:

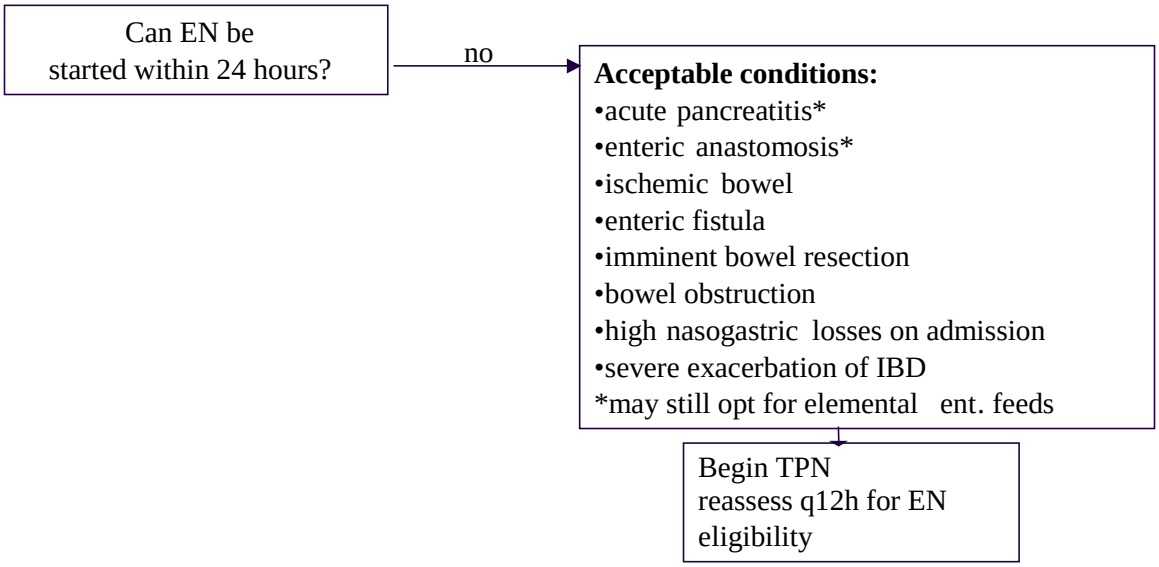
ACCEPT algorithm component:



Constituent EBRs:

- Enteral Nutrition vs. Standard Care
- Early Enteral Nutrition vs Late Enteral Nutrition

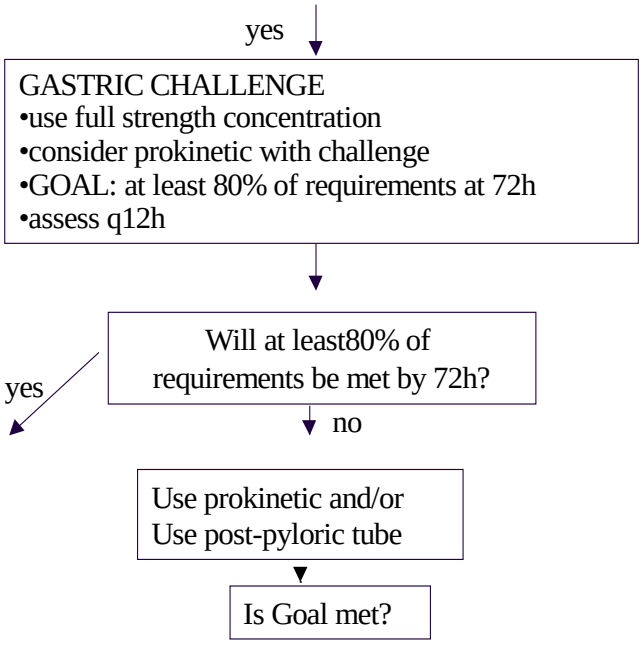
ACCEPT algorithm component:



Constituent EBRs:

- Parenteral Nutrition compared to Standard care
- Parenteral Nutrition compared to Enteral Nutrition
- Parenteral Nutrition compared to early Enteral Nutrition (<24h)
- Parenteral Nutrition compared to delayed Enteral Nutrition

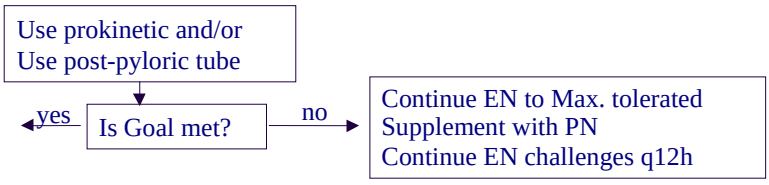
ACCEPT algorithm component:



Constituent EBRs:

- Gastric vs. post-pyloric
- Use of prokinetics
- Targets and advancement rates

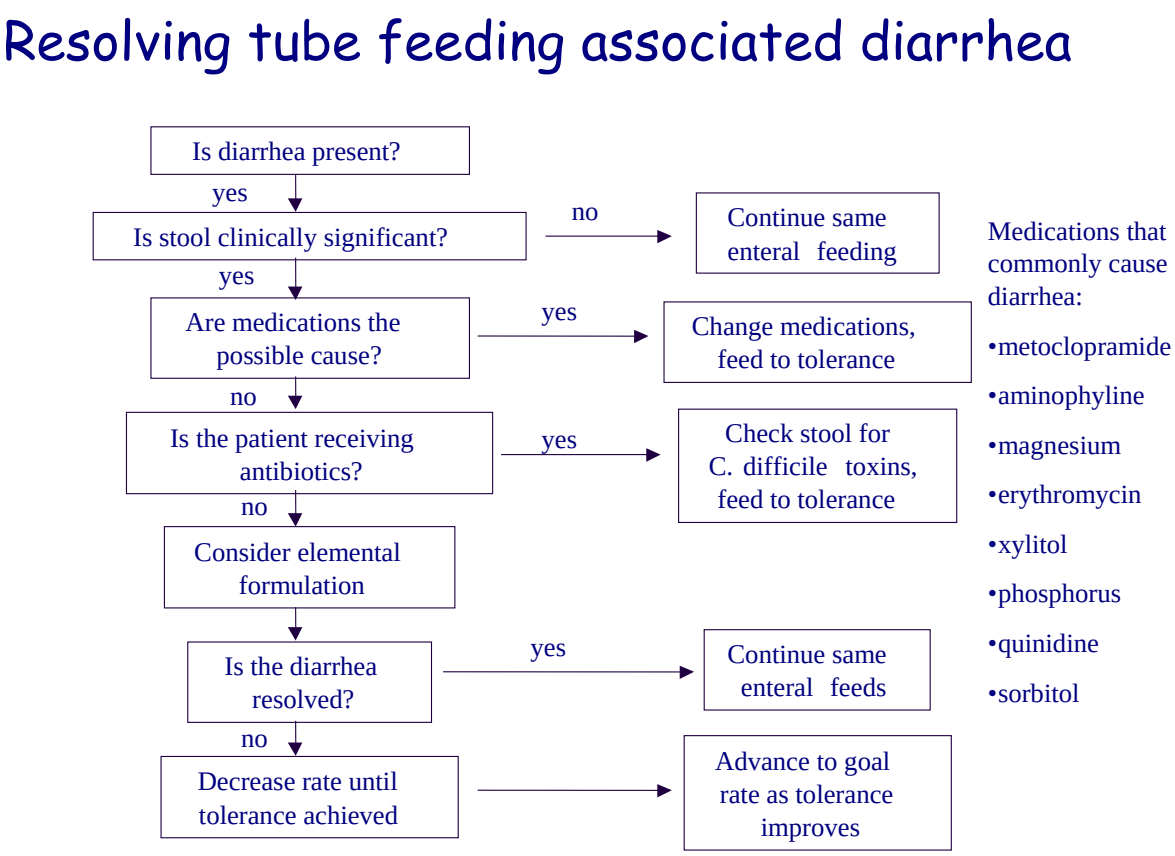
Accept algorithm component:



Core EBR Components of Algorithm:

- Enteral nutrition and parenteral nutrition compared to enteral nutrition alone

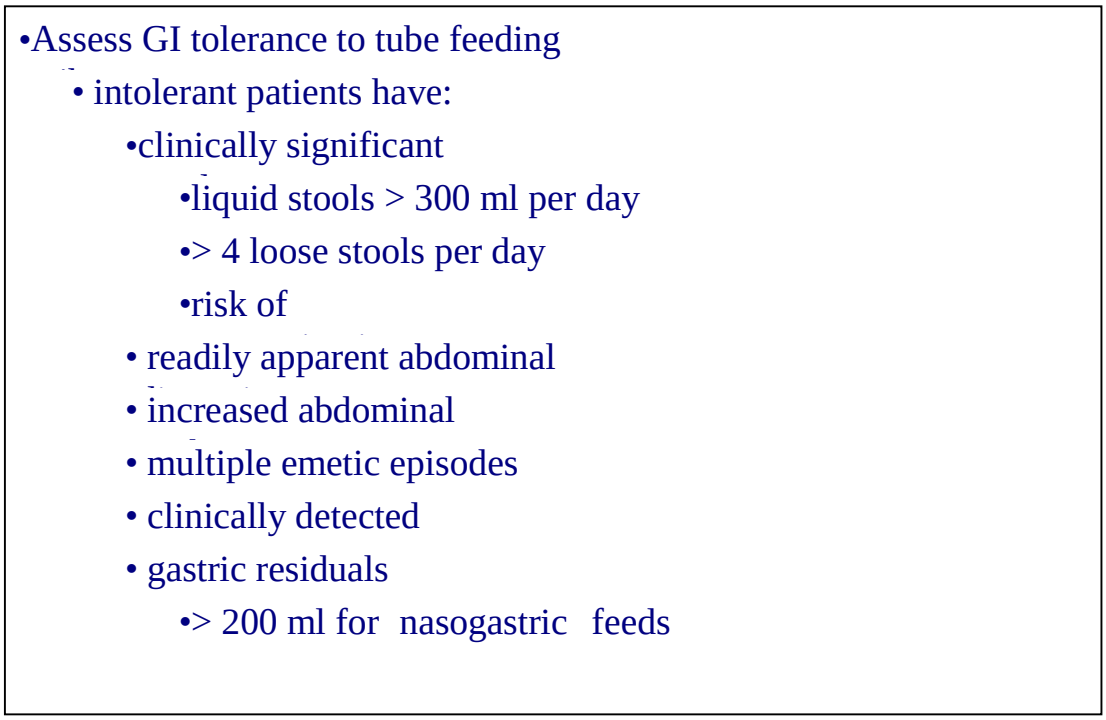
ACCEPT algorithm component



Constituent EBR

- Management of diarrhoea

ACCEPT algorithm component:



Constituent EBR

- Definition of tolerance and gastric residual volumes

The following section presents each EBR assessed at the conference, the evidence contributing to that EBR and the meta-analysis (where possible) of the evidence.

1) Enteral nutrition vs. standard care

5 Level II papers with no major flaws

RefID 511(Chuntrasakul et al. 1996)
Patient Population: Severe trauma
Study entry criteria: Injury severity score between 20 and 40.
Study intervention/s: Patients were randomised to receive: 1) early EN via NG-tube (± PN) or 2) IV fluids (5% dextrose and normal saline) and oral nutrition as soon as bowel function returned.

RefID 118(Pupelis et al. 2001)
Patient Population: Severe pancreatitis and peritonitis
Study entry criteria: Patients with severe acute pancreatitis according to the Atlanta classification system and APACHE II > 6 and patients with peritonitis secondary to GI perforation or bowel ischemia.
Study intervention/s: Patients were selected for 1) jejunal feeding or 2) control (IV electrolytes).

RefID 3(Page et al. 2002)
Patient Population: Esophagectomy patients (major upper GI surgery)
Study entry criteria: Esophageal resection for carcinoma.
Study intervention/s: On the morning following surgery, patients were randomised to receive: 1) enteral feeding or 2) control (IV crystalloids).

RefID 1069(Cabre et al. 2000)
Patient Population: Severe alcohol induced hepatitis
Study entry criteria: Patients admitted less than 72 hours had to meet all the following: 1) suffering from AH diagnosed on clinical and biological grounds in the setting of recent heavy drinking and histological confirmation whenever possible; 2) presence of severe disease as defined by at least one of: a) Maddrey's discrimination function > 32 or b) spontaneous overt hepatic encephalopathy.
Study intervention/s: Patients were randomised to receive: 1) EN or 2) steroids.

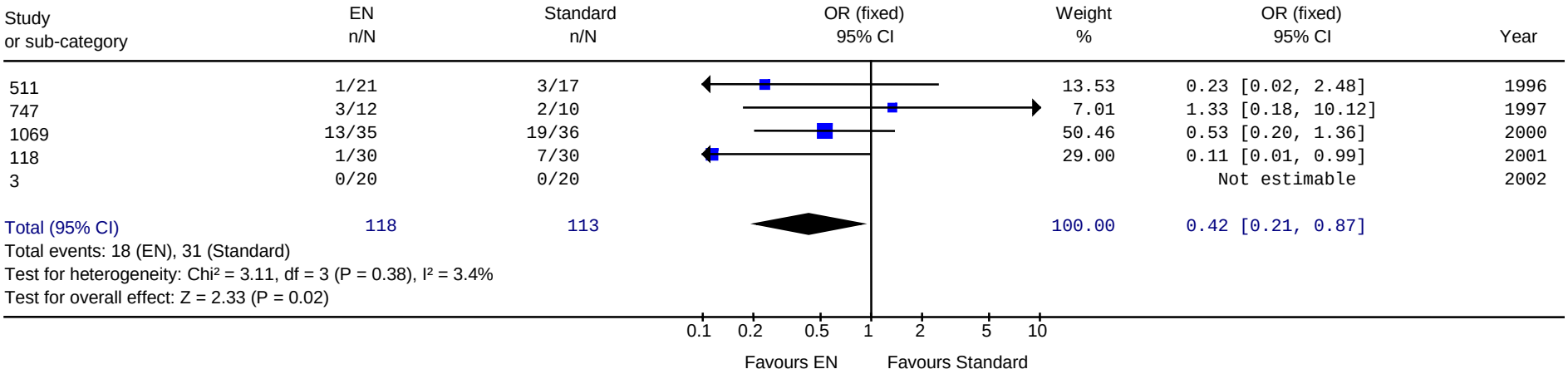
RefID 747(De Ledinghen et al. 1997)
Patient Population: Bleeding esophageal varices
Study entry criteria: Patients receiving sclerotherapy or banding for bleeding esophageal varices.
Study intervention/s: Patients were randomised to receive: 1) EN or 2) control.

EBR: Level II evidence, Grade B+ Recommendation supporting the use of EN compared to standard care

- **12% decrease in mortality (95% CI 2% to 21% decrease), p=0.02**
- **no heterogeneity, p=0.38**

Figure 2. Meta-analysis of enteral nutrition vs. standard care

Review: EN vs Standard care (less than 5% loss to follow-up)
Comparison: 01 EN and Standard Care
Outcome: 01 All mortality, ITT



2) Early enteral nutrition (<24 hours) vs. delayed enteral nutrition

2 Level II papers with no major flaws, 1 Level II paper with 6% loss to follow-up

RefID 181(Kompan et al. 1999)
Patient Population: Multiply injured surgical ICU patients
Study entry criteria: Multiply injured patients (ISS >25) with GCS ≥ 12 admitted in shock and stabilised (shock index of less than or equal to 1 and SBP of greater than or equal to 100mm Hg) within 6hrs of ICU admission.
Study intervention/s: Patients were randomised to 1) early EN (started not later than 6 hrs post ICU admission) vs 2) late EN (started greater than 24 hrs after ICU admission).

RefID 1174(Chiarelli et al. 1990)
Patient Population: Burn patients
Study entry criteria: Burn patients 25-70 years old, burn area of 25-60% of body surface area, no inhalation burns.
Study intervention/s: Patients were randomised by the "case-control" method to 1) very early enteral feeding (fed immediately after hospital admission) vs 2) late enteral feeding (fed 48 hrs after hospitalisation).

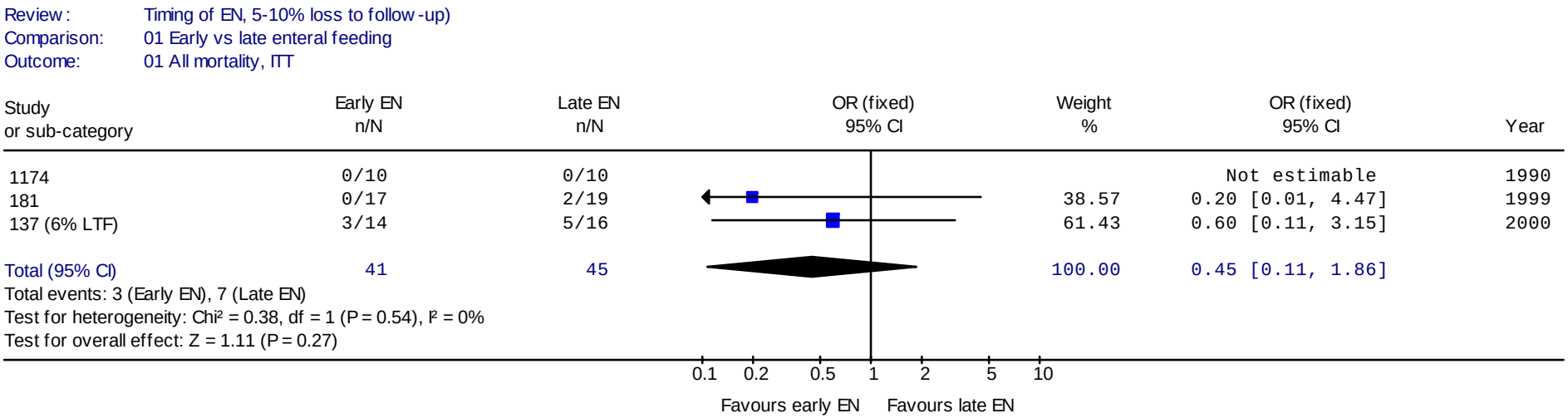
RefID 137(Minard et al. 2000) - 6% Loss to follow-up
Patient Population: Patients with severe closed head injury, managed in ICU
Study entry criteria: GCS <11 within the first 6 hours of injury
Study intervention/s: Patients were randomised to either 1) early enteral nutrition (EN) or 2) delayed EN (nasogastric feeding after the resolution of gastroparesis)

Early Enteral Nutrition vs Later Enteral Nutrition

EBR: Level II evidence, no significant findings

- **No changes to algorithm**

Figure 3**. Early enteral nutrition (<24 hours) vs delayed enteral nutrition**



3) Parenteral nutrition compared to standard care

5 Level II papers with no major flaws.

RefID 795(Wu et al. 1995) - no mortality events. Uninformative.
Patient Population: Aged surgical patients (> 70 yo) with gastric cancer.
Study entry criteria: Age > 70 with primary gastric cancer treated surgically. Patients must have had at least 2 of the following 3 criteria: 1) body weight loss < 20% of usual, 2) serum albumin > 3.0g/dl or 3) cell-mediated immunity multiskin tests > 2 positive.
Study intervention/s: Post-operatively, patients were randomised to: 1) TPN for 10 days post op or 2) standard 5% IV glucose.

RefID 602(Jeevanandam et al. 1994)}- no mortality events. Uninformative.
Patient Population: Multiple trauma patients.
Study entry criteria: Severely injured multiple trauma patients enrolled after admission to the trauma ICU of a Level I trauma centre.
Study intervention/s: Patients were randomised to receive: 1) glucose (25% dextrose infused at 4.1±0.5 mg glucose/kg/min) or 2) glucose with amino acids (250 to 300 mg N/kg/day [Aminosyn] and 4.8±0.6 mg glucose/kg/min as 25% dextrose)

RefID 1206(Sandstrom et al. 1993)
Patient Population: Major surgery or non-operative trauma patients.
Study entry criteria: Patients undergoing acute or elective major surgical procedures AND non-operative trauma patients requiring ICU admission.
Study intervention/s: Patients were randomised to receive 1) complete TPN (70% nonprotein calories, 30% fat and ~18020g nitrogen/day) or 2) plain D-glucose (250 to 300 g/day) with standard electrolytes.

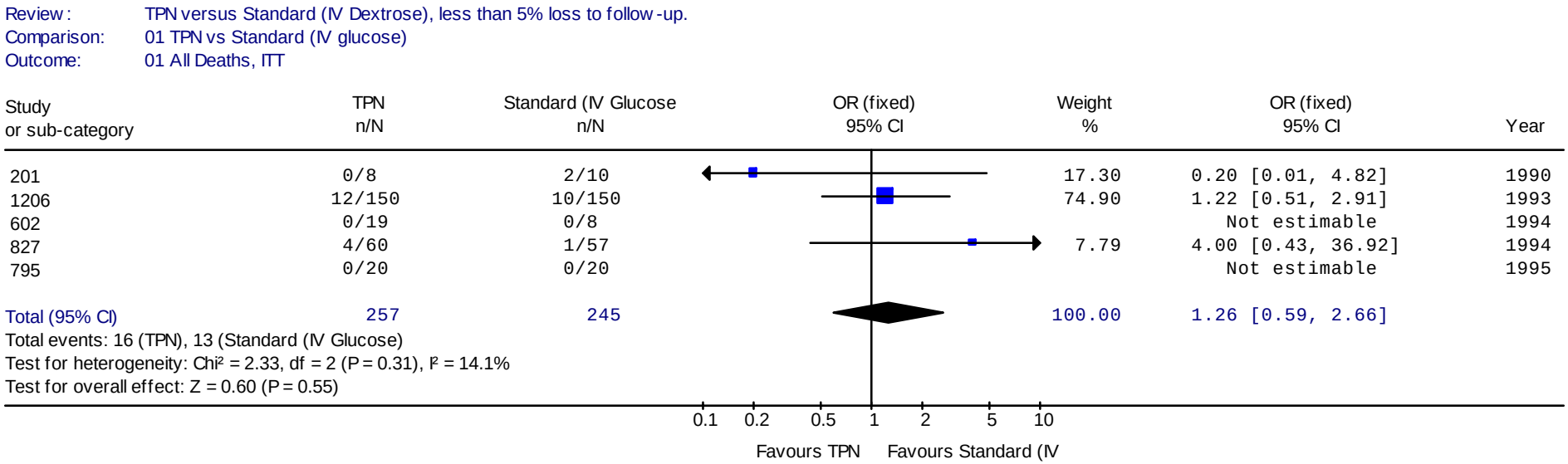
RefID 827(Brennan et al. 1994)
Patient Population: Major surgery patients
Study entry criteria: Patients receiving major pancreatic resection for malignancy.
Study intervention/s: Patients were randomised to 1) post-op routine adjuvant TPN or 2) dextrose (no routine TPN).

RefID 201(Reilly et al. 1990)
Patient Population: Liver transplant patients
Study entry criteria: Patients were enrolled either immediately before or after liver transplant. All patients met clinical criteria for transplant and were treated with the conventional immunosuppressive regimen of cyclosporine or steroids.
Study intervention/s: Patients were randomised to 1 of three groups: 1) TPN enriched with BCAA; 2) standard TPN or 3) IV glucose control.

Parenteral Nutrition compared to Standard care

EBR: Level II evidence, no significant findings

Figure 4. Parenteral nutrition compared to standard care



4) Parenteral nutrition compared to enteral nutrition

9 Level II papers with no major flaws, 2 Level II papers < 10% loss to follow-up

RefID 962(Woodcock et al. 2001)
Patient Population: All patients requiring nutritional support.
Study entry criteria: Actual or anticipated inadequate oral nutritional intake for 7 days or more with a reasonable doubt as to the adequacy of intestinal function.
Study intervention/s: Patients were randomised to receive; 1) TPN (KabiMix) or 2) EN (Osmolite).

RefID 835(Kudsk et al. 1994)
Patient Population: Trauma patients with sepsis.
Study entry criteria: Sub-group of a larger study: Trauma patients requiring a laparotomy with an Abdominal Trauma Index > 15.
Study intervention/s: Patients were randomised to receive: 1) EN (Vital HN, an elemental formula) or 2) TPN (Travasol).

RefID 223(Reynolds et al. 1997)
Patient Population: Major upper GI tract surgery
Study entry criteria: Patients undergoing surgery for esophageal, gastric or pancreatic cancer.
Study intervention/s: Patients were randomised to receive 1) post-op TPN or 2) post-op EN via a needle catheter jejunostomy, which was inserted in surgery.

RefID 1176(Rapp et al. 1983)
Patient Population: Head injured patients.
Study entry criteria: Penetrating missile wounds or blunt head trauma causing intracranial haematomas, a major focal neurological deficit and/or unconsciousness. Less than 48 hours from time of injury.
Study intervention/s: Patients were randomised to: 1) TPN or 2) standard EN (return of bowel sounds).

RefID 841(Dunham et al. 1994)
Patient Population: Mechanically ventilated blunt trauma patients.
Study entry criteria: Patients admitted to the ICU for blunt trauma within 12 hours of injury, who had been in the ICU less than 30 hours and required IMV. In addition, GCS ≥ 5, ISS ≥ 15, no spinal neuropath above T8, were unable to undergo GI endoscopy and expected to require IMV for at least an additional 48 hours.
Study intervention/s: Patients were randomised to receive: 1) EN and PN vs. 2) EN alone vs. 3) PN alone

RefID 1178(Adams et al. 1986)
Patient Population: Trauma patients
Study entry criteria: Trauma patients between 80% and 130% of desirable weight undergoing an emergent laparotomy.
Study intervention/s: During laparotomy, patients were randomised to: 1) TPN via a subclavian line or 2) EN via an 8Fr Witzel jejunostomy tube.

RefID 209(Kalfarentzos et al. 1997)
Patient Population: Severe acute pancreatitis.
Study entry criteria: Presence of three or more criteria according to the Imrie classification or APACHE II score > 8, C-reactive protein > 120mg/dl within 48 hours of admission and grade D or E Balthazar criteria by CT. All patients were located in the ICU.
Study intervention/s: Patients were randomised to: 1) TPN or 2) enteral nutrition.

RefID 79(Rayes et al. 2002a)
Patient Population: Major abdominal surgery.
Study entry criteria: Adult patients undergoing elective laparotomy and resection of the liver, stomach, colon or pancreas.
Study intervention/s: Patients were randomised to receive: 1) EN plus Lactobacillus planatarum 299 and 11.3 g/L oat fibre given twice a day (5.5 g/L soluble fibre and 5.7g/L insoluble fibre) or 2) EN with heat killed Lactobacillus plantarum 299 and 11.3 g/L oat fibre given twice a day or 3) TPN until oral intake was possible.

RefID 1003(Gianotti et al. 1997)
Patient Population: Gastric or pancreatic cancer patients.
Study entry criteria: Curative operation for gastric or pancreatic cancer.
Study intervention/s: Patients were randomised to receive: 1) enteral diet (Impact) which is supplemented with arginine (12.5 g/L) and omega-3 fats or 2) standard enteral formula with glycine replacing arginine and omega-6 fats replacing omega-3 fats (prepared by Novartis) or 3) TPN (isonitrogenous, isocaloric).

Level II studies with < 10% loss to follow-up
RefID 586(Borzotta et al. 1994) This paper contains 8.5% loss to follow-up (5 / 59).[GSD]
Patient Population: Severe closed head injury.
Study entry criteria: GCS ≤ 8, with coma persisting for at least 24 hours. Enrollment and randomisation had to occur within 72 hours of injury.
Study intervention/s: Patients were randomised to: 1) Parenteral (TPN) or 2) Enteral nutrition (EN) via surgically placed jejunal tube.

RefID 1179(Cerra et al. 1988) This study contains 5.7% loss to follow-up (4 / 70 patients).
Patient Population: Hypermetabolic SICU patients, 4 to 6 days after sepsis. Subgroup of a larger ongoing study.
Study entry criteria: Hypermetabolic SICU patients, enrolled within 4 to 6 days after the conduct of surgery and onset of sepsis.
Study intervention/s: Patients were randomised to 1) TPN or 2) EN (post-pyloric).

EBR: Level II evidence, Grade B+ Recommendation *in favour of PN*

- **5% decrease in mortality (95% CI 0% to 9% decrease), p=0.04**
- **no heterogeneity, p=0.50**

NB - this recommendation was further refined by comparing PN with early or later EN

Figure 5. Parenteral nutrition compared to enteral nutrition

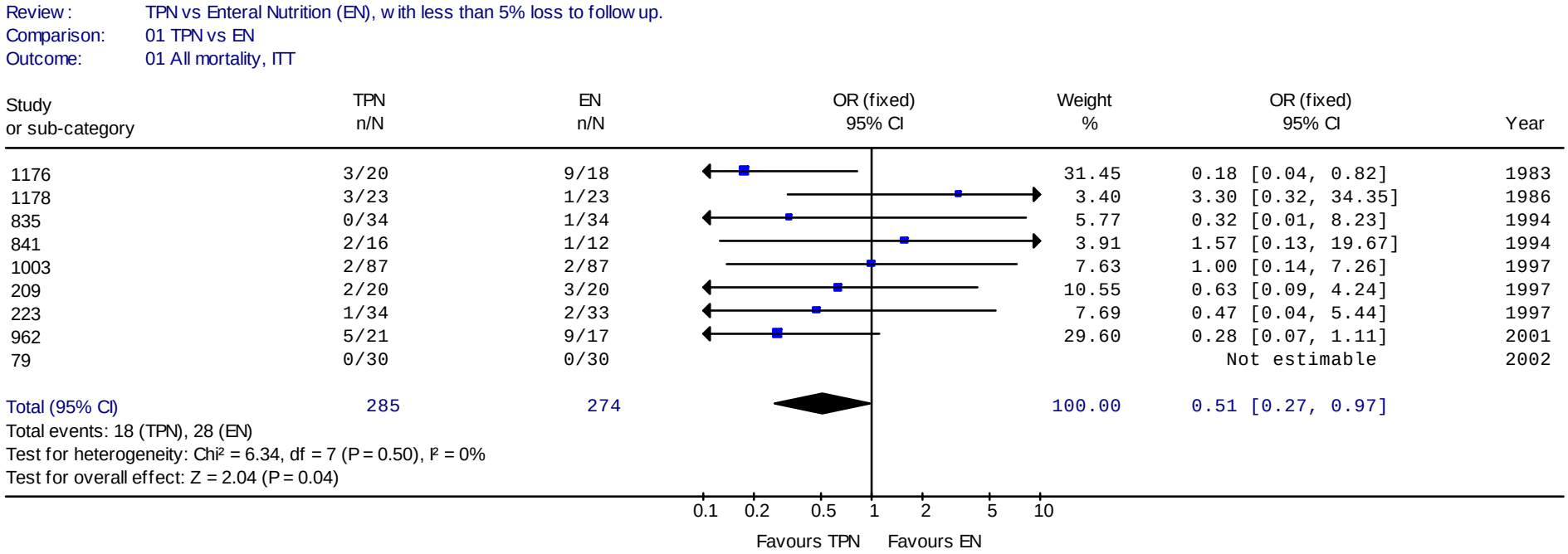
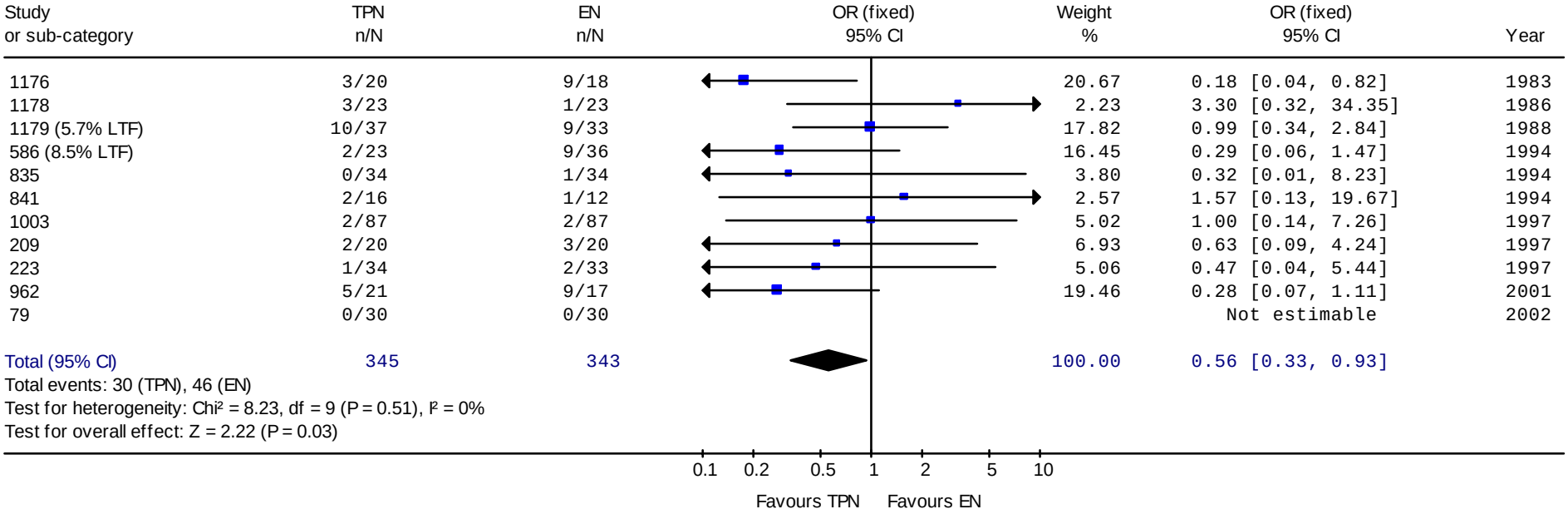


Figure 6. Parenteral nutrition compared to enteral nutrition, 5-10% loss to follow-up

Review: TPN vs Enteral Nutrition (EN)
Comparison: 01 TPN vs EN
Outcome: 01 All mortality, ITT, 5-10% loss to follow-up



5) Parenteral nutrition compared to early enteral nutrition (<24 hours)

6 Level II papers with no major flaws
RefID 835(Kudsk et al. 1994)
Patient Population: Trauma patients with sepsis.
Study entry criteria: Sub-group of a larger study: Trauma patients requiring a laparotomy with an Abdominal Trauma Index > 15.
Study intervention/s: Patients were randomised to receive: 1) EN (Vital HN, an elemental formula) or 2) TPN (Travasol).

RefID 223(Reynolds et al. 1997)
Patient Population: Major upper GI tract surgery
Study entry criteria: Patients undergoing surgery for esophageal, gastric or pancreatic cancer.
Study intervention/s: Patients were randomised to receive 1) post-op TPN or 2) post-op EN via a needle catheter jejunostomy, which was inserted in surgery.

RefID 841(Dunham et al. 1994)
Patient Population: Mechanically ventilated blunt trauma patients.
Study entry criteria: Patients admitted to the ICU for blunt trauma within 12 hours of injury, who had been in the ICU less than 30 hours and required IMV. In addition, GCS ≥ 5, ISS ≥ 15, no spinal neuropath above T8, were unable to undergo GI endoscopy and expected to require IMV for at least an additional 48 hours.
Study intervention/s: Patients were randomised to receive: 1) EN and PN vs. 2) EN alone vs. 3) PN alone

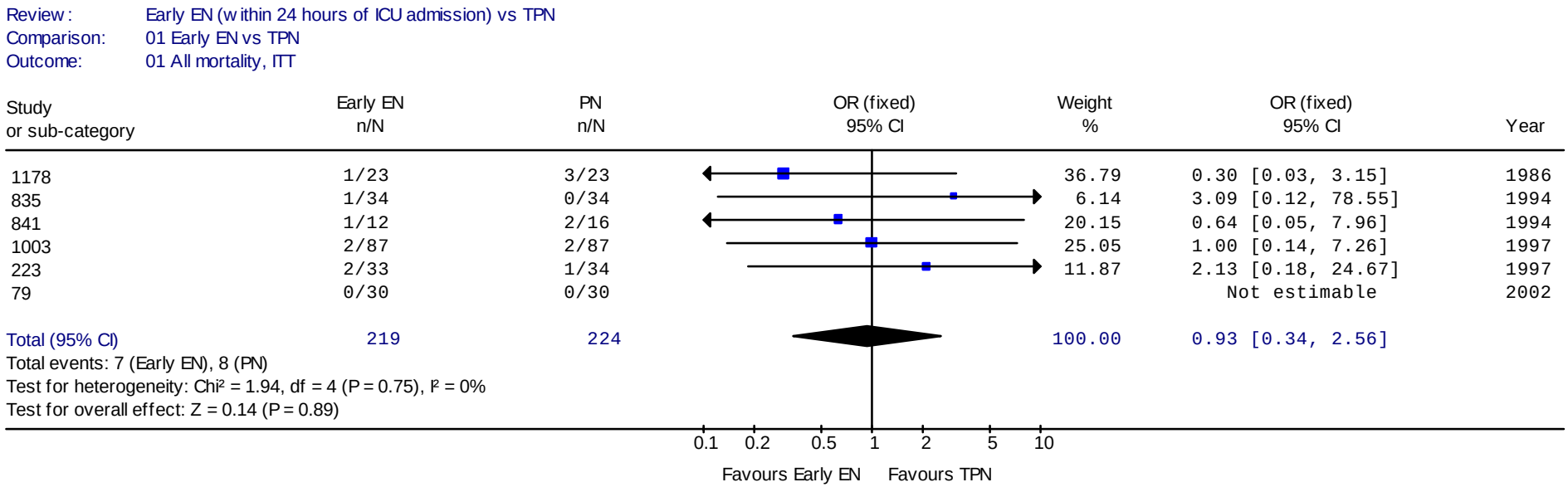
RefID 1178(Adams et al. 1986)
Patient Population: Trauma patients
Study entry criteria: Trauma patients between 80% and 130% of desirable weight undergoing an emergent laparotomy.
Study intervention/s: During laparotomy, patients were randomised to: 1) TPN via a subclavian line or 2) EN via an 8Fr Witzel jejunostomy tube.

RefID 79(Rayes et al. 2002a)
Patient Population: Major abdominal surgery.
Study entry criteria: Adult patients undergoing elective laparotomy and resection of the liver, stomach, colon or pancreas.
Study intervention/s: Patients were randomised to receive: 1) EN plus Lactobacillus planatarum 299 and 11.3 g/L oat fibre given twice a day (5.5 g/L soluble fibre and 5.7g/L insoluble fibre) or 2) EN with heat killed Lactobacillus plantarum 299 and 11.3 g/L oat fibre given twice a day or 3) TPN until oral intake was possible.

RefID 1003(Gianotti et al. 1997)
Patient Population: Gastric or pancreatic cancer patients.
Study entry criteria: Curative operation for gastric or pancreatic cancer.
Study intervention/s: Patients were randomised to receive: 1) enteral diet (Impact) which is supplemented with arginine (12.5 g/L) and omega-3 fats or 2) standard enteral formula with glycine replacing arginine and omega-6 fats replacing omega-3 fats (prepared by Novartis) or 3) TPN (isonitrogenous, isocaloric).

EBR: Level II evidence, no significant findings

Figure 7. Parenteral nutrition compared to early enteral nutrition (<24 hours)



6) Parenteral nutrition compared to delayed enteral

(EN > 24 h after ICU admit or injury)

3 Level II studies, no major flaws. 2 Level II studies < 10% loss to follow-up.

RefID 1176(Rapp et al. 1983)
Patient Population: Head injured patients.
Study entry criteria: Penetrating missile wounds or blunt head trauma causing intracranial haematomas, a major focal neurological deficit and/or unconsciousness. Less than 48 hours from time of injury.
Study intervention/s: Patients were randomised to: 1) TPN or 2) standard EN (return of bowel sounds).

RefID 209(Kalfarentzos et al. 1997)
Patient Population: Severe acute pancreatitis.
Study entry criteria: Presence of three or more criteria according to the Imrie classification or APACHE II score > 8, C-reactive protein > 120mg/dl within 48 hours of admission and grade D or E Balthazar criteria by CT. All patients were located in the ICU.
Study intervention/s: Patients were randomised to: 1) TPN or 2) enteral nutrition (within 48h of ICU admit).

RefID 962(Woodcock et al. 2001)
Patient Population: All patients requiring nutritional support.
Study entry criteria: Actual or anticipated inadequate oral nutritional intake for 7 days or more with a reasonable doubt as to the adequacy of intestinal function.
Study intervention/s: Patients were randomised to receive; 1) TPN (KabiMix) or 2) EN (Osmolite).

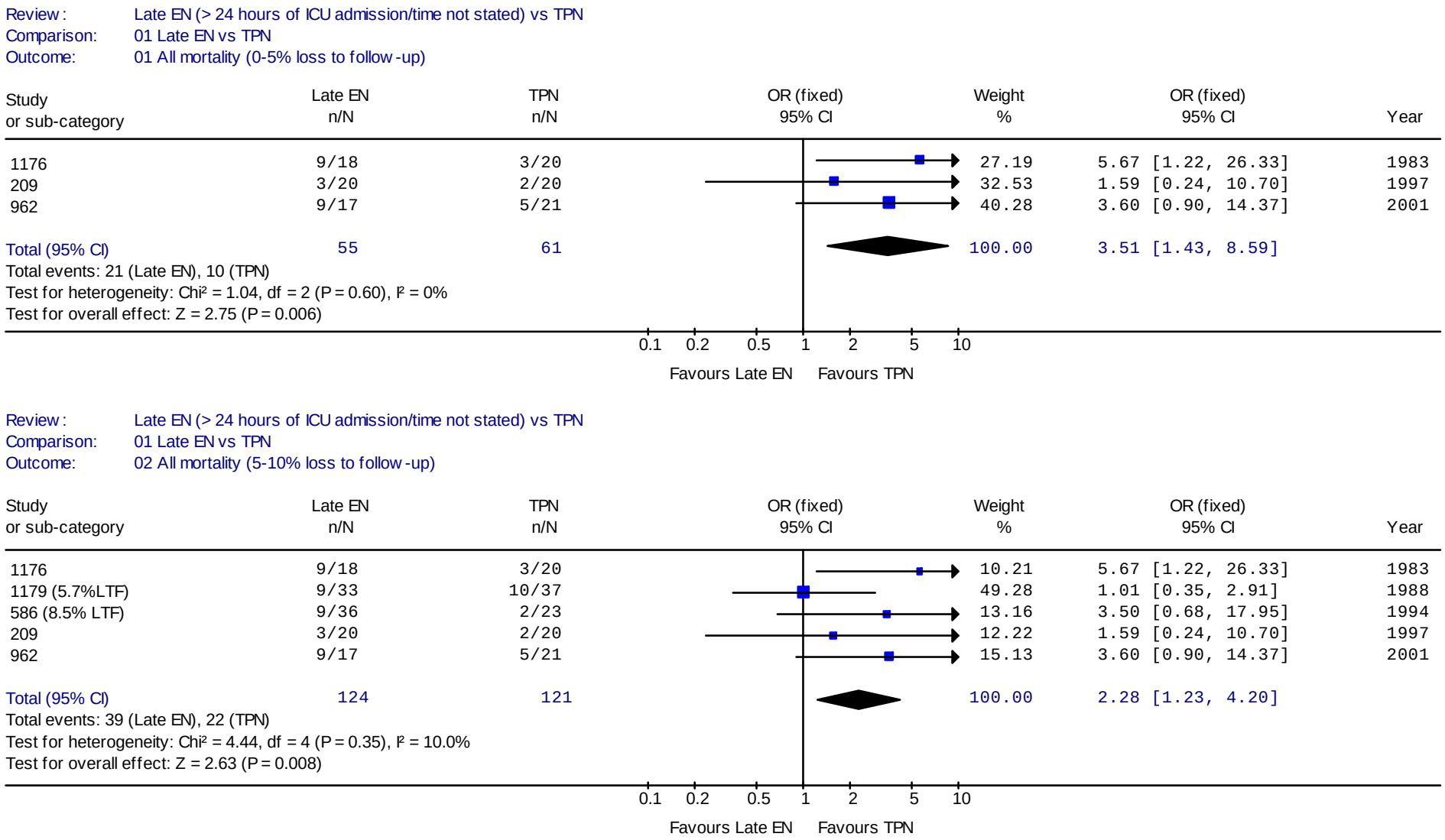
Level II studies with <10% loss to follow-up
RefID 586(Borzotta et al. 1994) This paper contains 8.5% loss to follow-up (5 / 59).[GSD]
Patient Population: Severe closed head injury.
Study entry criteria: GCS ≤ 8, with coma persisting for at least 24 hours. Enrollment and randomisation had to occur within 72 hours of injury.
Study intervention/s: Patients were randomised to: 1) Parenteral (TPN) or 2) Enteral nutrition (EN) via surgically placed jejunal tube.

RefID 1179(Cerra et al. 1988) This study contains 5.7% loss to follow-up (4 / 70 patients).
Patient Population: Hypermetabolic SICU patients, 4 to 6 days after sepsis. Subgroup of a larger ongoing study.
Study entry criteria: Hypermetabolic SICU patients, enrolled within 4 to 6 days after the conduct of surgery and onset of sepsis.
Study intervention/s: Patients were randomised to 1) TPN or 2) EN (post-pyloric).

EBR: Level II evidence, Grade B+ Recommendation *in favour of early PN*

- **23% decrease in mortality (95% CI 8% to 38%), p=0.006**
- **no heterogeneity, p=0.60**

Figure 8. Parenteral nutrition compared to delayed enteral (> 24 h or timing not determinate)



7) Gastric vs. post-pyloric enteral nutrition

7 Level II papers with no major flaws. 1 Level II paper with 6% loss to follow-up

RefID 166(Taylor et al. 1999)
Patient Population: Head injured patients.
Study entry criteria: Head injury requiring IMV, best GCS > 3, at least one reactive pupil within first 24 hours, > 10 years old, inability to take oral nutrition for more than 24 hrs, capacity to be fed enterally within 24 hrs of onset of injury.
Study intervention/s: Pts were randomised to receive 1) a pH sensor tube which was blindly placed into the intestine, if this could not be achieved, gastric placement was accepted. vs. 2) orogastric or nasogastric tubes.

RefID 379(Kearns et al. 2000)
Patient Population: Medical ICU patients.
Study entry criteria: All medical ICU patients who required mechanical ventilation and enteral nutrition.
Study intervention/s: Patients were randomised to: 1) small intestine feeding with a 12-Fr tube according to protocol vs. 2) gastric feeding tube tip placement.

RefID 427(Kortbeek et al. 1999)
Patient Population: Major trauma patients.
Study entry criteria: Within 72 hours of admission to ICU, ISS ≥ 16, projected to require mechanical ventilation for at least 48 hours.
Study intervention/s: Patients were randomised to receive: 1) fluroscopically guided duodenal feeding tubes vs. 2) gastric feeding tubes.

RefID 263(Davies et al. 2002)
Patient Population: Mixed (medical and surgical) ICU patients.
Study entry criteria: Any patient expected to require nutritional and critical care support for at least 3 days.
Study intervention/s: Patients were randomised to receive: 1) naso-jejunal feeding tube placed with endoscopic assistance vs. 2) nasally inserted gastric feeding tube.

RefID 302(Boivin and Levy 2001)
Patient Population: Medical, surgical and neuroscience intensive care patients. 99% were intubated and 53% were trauma patients.
Study entry criteria: All patients over the age of 18 in whom a decision was made to feed enterally by the treating team.
Study intervention/s: Patients were randomised to receive: 1) transpyloric feeding. vs. 2) gastric feeding (nasogastric or orogastric) with erythromycin (200mg iv q8h for 96 hrs).

RefID 324(Esparza et al. 2001)
Patient Population: Medical ICU patients.
Study entry criteria: Not explicitly stated.
Study intervention/s: Patients were randomised to receive 10-Fr feeding tube placed in: 1) the transpyloric position placed with the aid of erythromycin, metclopramide or fluoroscopy as necessary. vs. 2) gastric position.

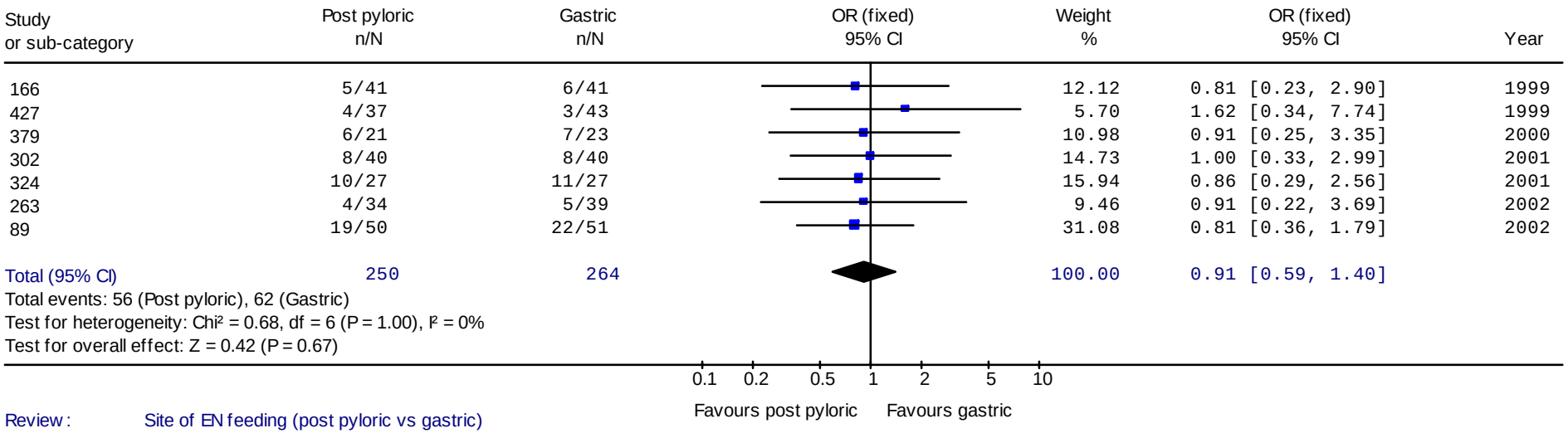
RefID 89(Montejo et al. 2002)
Patient Population: Adult ICU patients from 14 units.
Study entry criteria: Patients over the age of 18yrs who were deemed to need enteral nutrition > 5 days.
Study intervention/s: Patients were randomised to receive feeding via: 1) a dual lumen nasogastrojejunal tube placed within 36 hours of admission via endoscopy, fluoroscopic guidance, blind technique or by echography or 2) a nasogastric tube placed at admission.

Level II paper with 6% loss to follow-up
RefID 137(Minard et al. 2000)
Patient Population: Patients with severe closed head injury, managed in ICU
Study entry criteria: GCS <11 within the first 6 hours of injury
Study intervention/s: Patients were randomised to either 1) early enteral nutrition (EN) or 2) delayed EN (nasogastric feeding after the resolution of gastroparesis)

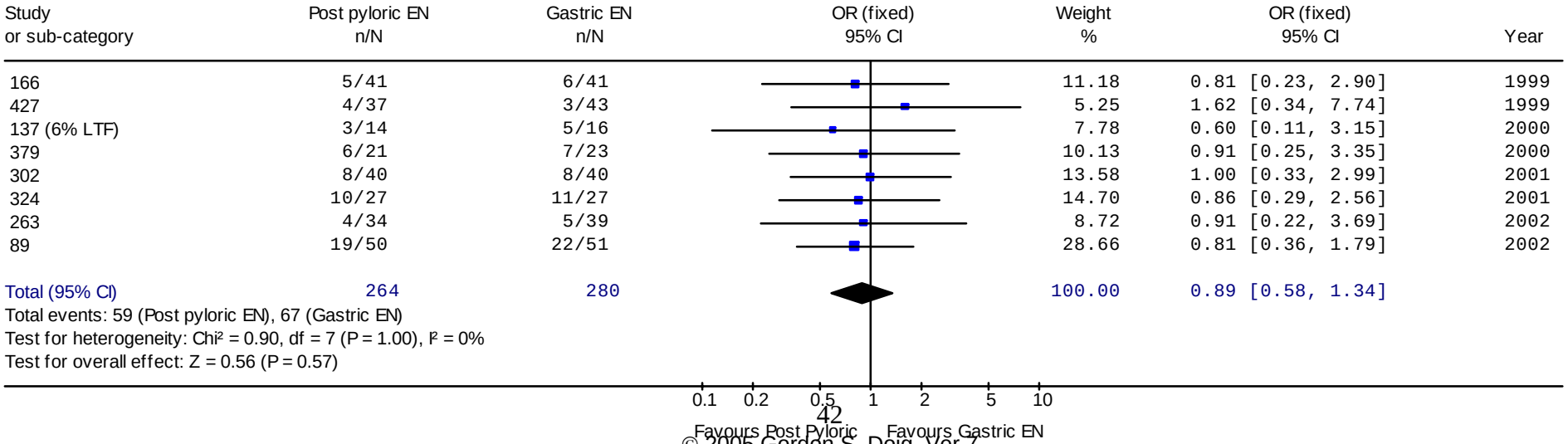
EBR: Level II evidence, no significant findings

Figure 9. Gastric vs. post-pyloric enteral nutrition

Review: Site of EN feeding (post pyloric vs gastric)
Comparison: 01 Post pyloric vs gastric EN
Outcome: 01 All mortality, ITT, 0-5% LTF



Review: Site of EN feeding (post pyloric vs gastric)
Comparison: 01 Post pyloric vs gastric EN
Outcome: 02 All mortality, ITT, 5-10% LTF



8) Use of prokinetics

5 Level II studies, no major methodological flaws

RefID 302(Boivin and Levy 2001)
Patient Population: Medical, surgical and neuroscience intensive care patients. 99% were intubated and 53% were trauma patients.
Study entry criteria: All patients over the age of 18 in whom a decision was made to feed enterally by the treating team.
Study intervention/s: Patients were randomised to receive: 1) transpyloric feeding. vs. 2) gastric feeding (nasogastric or orogastric) with erythromycin (200mg iv q8h for 96 hrs).
All transpylorically fed patients received a single dose of 200mg erythromycin iv 30 min prior to a 10-Fr weighted tube being placed . The tube was then advanced 100cm with the air insufflation technique. In the case of failure of placement, an unweighted feeding tube was used for placement with the above technique repeated. Time to intensive care feeding commencement was not stated for either group.

RefID 237(Berne et al. 2002)
Patient Population: All critically injured patients who received intragastric tube feedings within 72 hours of admission to the ICU.
Study entry criteria: At least one gastric residual greater than 150mls during the first 48hrs of stay.
Study intervention/s: Patients were randomised to either 1) erythromycin lactobionate (250mg of intravenous erythromycin administered every 6hrs) or 2) placebo (an equivalent volume of 5% dextrose in water q6h).

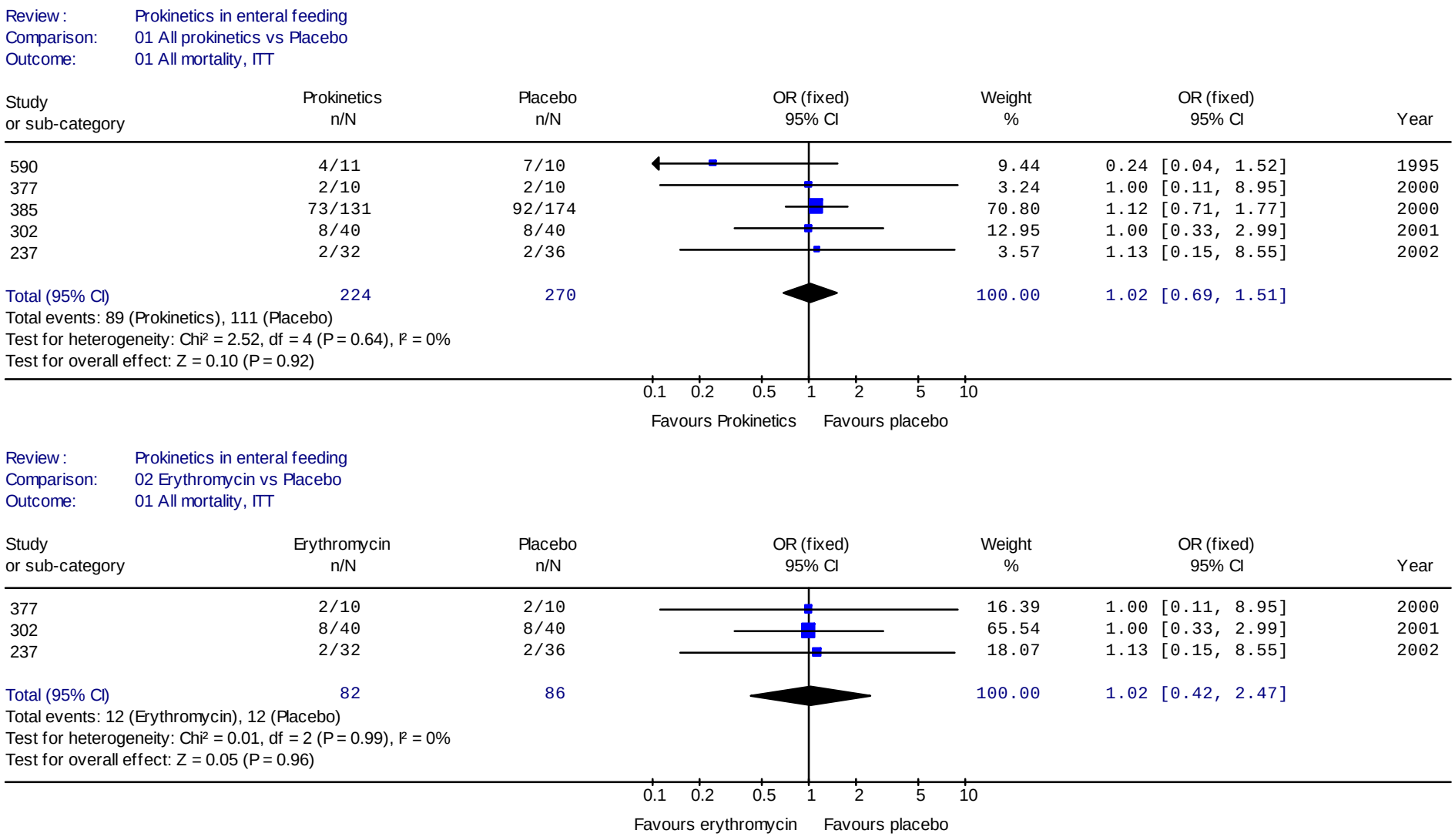
RefID 377(Chapman et al. 2000)
Patient Population: Mechanically ventilated intensive care patients with no history of gastrointestinal surgery.
Study entry criteria: A gastric aspirate greater than or equal to 250mls at least 6 hrs after commencing enteral feeding at greater than or equal to 40ml/hr.
Study intervention/s: After the initial aspirate (greater than or equal to 250mls) was discarded, the enteral feed (Ensure formula administered via a 14-Fr or larger nasogastric tube) was continued at the same rate for 3 hours. Patients were then randomised to receive either 1) a single dose of intravenous erythromycin (200mg in 20mls saline) or 2) placebo

RefID 590(Spapen et al. 1995)
Patient Population: Haemodynamically stable, sedated and mechanically ventilated patients.
Study entry criteria: Sedated patients on IMV requiring enteral feeding.
Study intervention/s: Critically ill patients were randomised to receive either 1) 10mg of cisapride four times a day or 2) no cisapride (enteral nutrition only).

RefID 385(Yavagal et al. 2000)
Patient Population: Adult intensive care patients.
Study entry criteria: Adult intensive care patients who required placement of a nasogastric tube for greater than 24 hours.
Study intervention/s: Patients were randomised to either 1) metoclopramide (10mg q8hrs) or 2) placebo via nasogastric tube.

EBR: Level II evidence, no significant findings

Figure 10. Use of prokinetics



9) Enteral nutrition and parenteral nutrition compared to enteral nutrition alone

4 Level II papers no major flaws

RefID 358(Bauer et al. 2000)
Patient Population: Medical and surgical ICU patients
Study entry criteria: Admitted to the ICU for longer than 2 days and expected to stay alive for at least 2 days. Expected to eat less than 20kcal/kg daily for more than 2 days and EN was expected to be progressively administered for more than 2 days.
Study intervention/s: Patients were randomised to receive: 1) enteral nutrition and parenteral nutrition (parenteral made up any deficiency in EN intake) or 2) enteral nutrition and placebo.

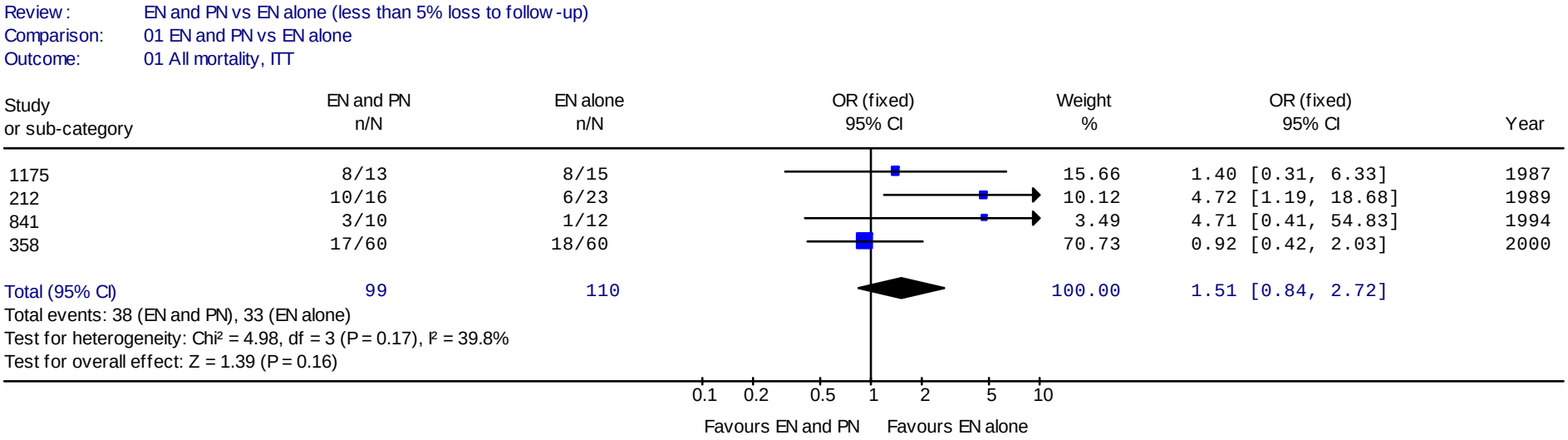
RefID 212(Herndon et al. 1989)
Patient Population: Patients with Burns > 50% TBSA
Study entry criteria: Consecutive patients presenting with > 50% TBSA
Study intervention/s: Patients were randomised to: 1) enteral nutrition with parenteral nutrition supplementation or 2) enteral nutrition only.

RefID 841(Dunham et al. 1994)
Patient Population: Mechanically ventilated blunt trauma patients.
Study entry criteria: Patients admitted to the ICU for blunt trauma within 12 hours of injury, who had been in the ICU less than 30 hours and required IMV. In addition, GCS ≥ 5, ISS ≥ 15, no spinal neuropath above T8, were unable to undergo GI endoscopy and expected to require IMV for at least an additional 48 hours.
Study intervention/s: Patients were randomised to receive: 1) EN and PN vs. 2) EN alone vs. 3) PN alone.

RefID 1175(Herndon et al. 1987)
Patient Population: Patients with Burns > 50% TBSA
Study entry criteria: Consecutive patients presenting with > 50% TBSA
Study intervention/s: Patients were randomised to: 1) enteral nutrition (upon return of GI function) with parenteral nutrition supplementation or 2) enteral nutrition upon return of GI function.

EBR: Level II evidence, no significant findings

Figure 11. Enteral nutrition and parenteral nutrition compared to enteral nutrition alone



10) Enteral nutrition supplemented with arginine compared to standard enteral nutrition

7 Level II papers with no major flaws, 3 Level II papers with < 10% loss to follow-up

RefID 1003(Gianotti et al. 1997)
Patient Population: Gastric or pancreatic cancer patients.
Study entry criteria: Curative operation for gastric or pancreatic cancer.
Study intervention/s: Patients were randomised to receive: 1) enteral diet (Impact) which is supplemented with arginine (12.5g/L) and omega-fats or 2) same enteral formula (Impact) with glycine replacing arginine, and omega-6 fats replacing omega-3 fats or 3) TPN (isonitrogenous, isocaloric).

RefID 438(Atkinson et al. 1998)
Patient Population: Critically ill ICU patients.
Study entry criteria: Admitted to ICU for less than 48 hours and expected to stay in the ICU for 3 days or longer, with no contra-indications to EN feeding.
Study intervention/s: Patients were randomised to receive: 1) arginine enhanced EN (Impact) or 2) isonitrogenous, isocaloric EN.

RefID 205(Gottschlich et al. 1990)
Patient Population: Burns patients.
Study entry criteria: Burns > 10% BSA, age ≥ 3, admitted within 5 days of burn.
Study intervention/s: Patients were randomised to: 1) EN supplemented with arginine (experimental formula); 2) standard EN (Osmolite plus ProMix RD, a protein powder) or 3) diluted standard EN (Traumacal).

RefID 248(Kudsk et al. 1996)
Patient Population: Trauma patients
Study entry criteria: Severely injured patients requiring emergency celiotomy with Abdominal Trauma Index ≥ 25 and ISS ≥ 21 who had early enteral access.
Study intervention/s: Patients were randomised to receive: 1) EN enhanced with glutamine, arginine, nucleic acids and omega-3 fatty acids (Immun-Aid) vs. 2) isocaloric, isonitrogenous control EN.

RefID 159(Galban et al. 2000)
Patient Population: Septic ICU patients.
Study entry criteria: Greater than 14 years old, with sepsis at time of randomisation (Bone criteria) and APACHE II score ≥ 10 at time of ICU admission.
Study intervention/s: Patients were randomised to: 1) EN supplemented with arginine (Impact) or 2) control EN (Precitene Hiperproteico, also known as Nutrodrip Protein).

RefID 13(Kemen et al. 1995)
Patient Population: Patients with upper GI cancer.
Study entry criteria: Patients with upper GI cancer who were to undergo major abdominal surgery.
Study intervention/s: Patients were randomised to receive: 1) arginine enhanced EN (Impact) or 2) isocaloric, isonitrogenous placebo diet (name not stated).

RefID 1214(Saffle et al. 1997)

Patient Population: Burns patients.
Study entry criteria: All burns patients ≥ 4 yo anticipated to require EN for at least 7 days in whom EN could be started within 48 hours of injury.
Study intervention/s: Patients were randomised to: 1) EN enhanced with arginine (Impact) or 2) standard high protein EN (Replete).

RefID 688(Cerra et al. 1991) - At least 5% loss to follow-up at 12 months. May be as high as 10% loss to follow-up at 6 months and 15% loss to follow-up at 12 months.[GSD]
Patient Population: ICU patients
Study entry criteria: Polytrauma, major elective general surgery or major surgical infection requiring ICU admission > 5 days and requiring mechanical ventilation. Judged able to tolerate EN for 7 to 10 days.
Study intervention/s: Patients were randomised to: 1) EN supplemented with arginine (Impact) or 2) standard EN (Osmolite HN)

RefID 304(Caparros et al. 2001) - 7.17% (17/237) differential loss to follow-up. Although it is reported that the 'investigators' remained blind to treatment for the diagnosis of nosocomial pneumonia and to the statistical analysis until after the 6mth follow-up, the healthcare team was not reported as being blinded. Because the subjective decision to feed was made by the healthcare team in an unblinded manner, it is possible that a significant amount of bias could have been introduced by the failure to report allocation of the 17 patients lost to follow-up.[GSD]
Patient Population: Critically ill patients.
Study entry criteria: ICU patients were enrolled if it was predicted that they would require enteral nutrition for at least 7 days.
Study intervention/s: Patients were randomised to: 1) EN enhanced with arginine (Stresson) or 2) standard EN (Nutrison Protein Plus).

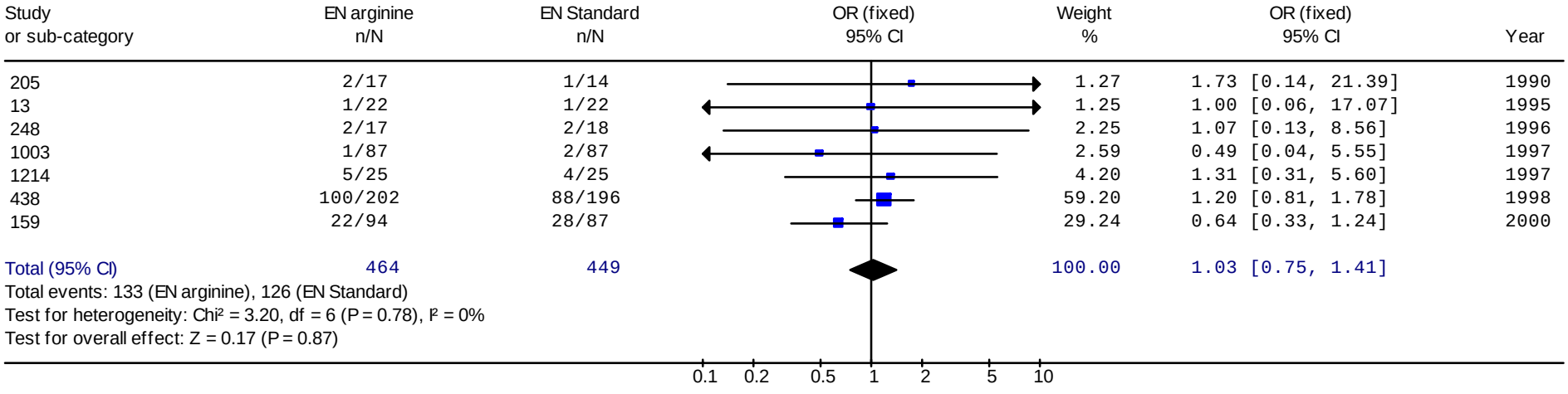
RefID 465(Senkal et al. 1997) - 6% (10/164) overall loss to follow-up is concerning. Since patients were excluded from follow-up due to poor intake, and it is possible that patients who do not tolerate an EN diet may have a higher risk of poor outcome, this lack of follow-up could represent an important source of bias.[GSD]
Patient Population: Surgical ICU patients.
Study entry criteria: Patients who underwent major GI surgery for upper GI cancer.
Study intervention/s: Patients were randomised to receive: 1) arginine enhanced EN (Impact) or 2) isocaloric, isonitrogenous placebo diet.

EBR: 7 Level II papers, no significant effects

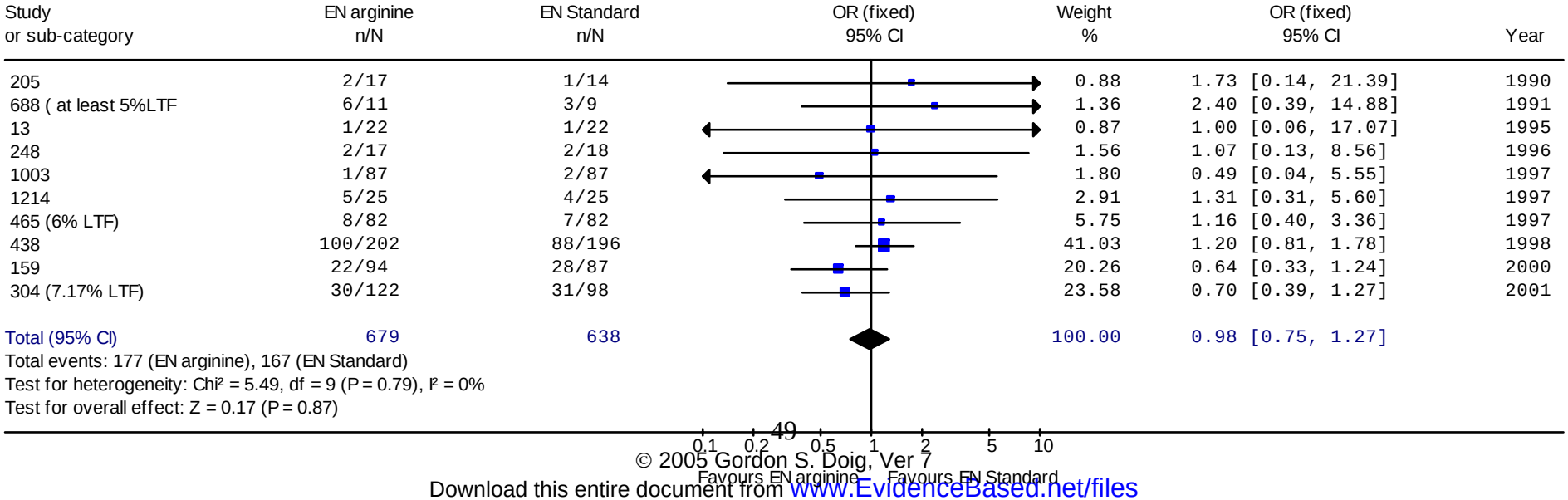
- **no recommendation can be made**

Figure 12. Enteral nutrition supplemented with arginine compared to standard enteral nutrition

Review: EN with arginine vs Standard EN
Comparison: 01 EN arginine vs Standard EN
Outcome: 01 All mortality, ITT, 0-5% loss to follow-up



Review: EN with arginine vs Standard EN
Comparison: 01 EN arginine vs Standard EN
Outcome: 02 All mortality, ITT, 5-10% loss to follow-up



11) Enteral nutrition supplemented with arginine vs parenteral nutrition

RefID 1219(Bertolini et al. 2003)
Patient Population: ICU patients with severe sepsis. (subgroup of ongoing study)
Study entry criteria: ICU patients judged to need mechanical ventilation and artificial nutrition for at least 4 days. This paper focuses on a sub-group who had sepsis at time of randomisation.
Study intervention/s: Patients were randomised to: 1) EN enhanced with arginine (Perative, arginine 6.8g/L) or 2) TPN.

Interim subgroup analysis of a larger ongoing study:
Trend towards a significant difference (p=0.072) in ICU mortality.
No significant difference in 28 day mortality (p=0.196).

Resulted in stop in enrolling septic patients in the larger ongoing trial. It was not explicitly stated what the formal, a priori established stopping threshold for this sub-group was set to. Both p-values reported above (0.072 and 0.196) would be considered very liberal and would not lead to a conservative decision to stop.

With regards to subgroup analysis, the following paper is a VERY informative read: Wedel H, DeMets D, Deedwainia P et al. Challenges of subgroup analyses in multinational clinical trials: Experiences from the MERIT-HF trial. Am Heart J 2001;142:502-11.

This paper reports and interprets a possible deleterious effect of a clinical trial detected on a subgroup of US hospitals. Their approach to interpreting this finding is based a widely accepted methodology for interpreting subgroup results (Hill AB. Principles on medical statistics. 9th Ed. Lancet Press, London, 1971). Using this approach, proposed by Sir Bradford Hill, a number of conditions/postulates are considered that may strengthen or weaken the causal inference associated with the subgroup finding:

Rule of chance / strength of association
- must consider multiplicity of testing
- investigate treatment x sub-group interaction term

Biologic gradient
- effect increases as dose increases or in relation to severity of disease

Consistency (internal/external)
- effect consistent on multiple end-points
- previously documented

Confounding
- investigate confounding in baseline, baseline treatment or follow-up treatment

Coherence / plausibility
- consistency of results across known, predefined risk groups

After considering each of these conditions in the context of their specific trial, the authors conclude that the "US subgroup mortality hazard ratio was due to chance."

If we apply the same rigorous process to drawing causal inferences from the Bertolini subgroup:
Rule of chance / strength of association
- must consider multiplicity of testing

At the very least, two groups were tested: the results of the overall trial AND the subgroup results. Combined with the fact that this is indeed an interim analysis, it is likely the minimum p-value that we should accept is 0.025. (0.05 divided by 2.... Bonferroni correction based on at least two looks at the data). In addition, although the authors do not state what the exact a priori stopping rule was for this subgroup, it is not likely the threshold was set at 0.05. Again, the authors would have taken at least two looks at this subgroup (the interim analysis and the final analysis), once again suggesting that a conservative guess at the appropriate p-value would be 0.025 (0.05 divided by 2 to account for the two looks and for alpha spending) before we can be reasonably certain a Type I error (declaring a difference when no difference exists) is not present.

Biologic gradient

• effect increases as dose increases or in relation to severity of disease

It would be interesting to note if mortality effect increased with increased feed intake or severity of sepsis. Others have documented an increase in treatment effect with sepsis drugs as APACHE II increases. It is likely the sample size of this subgroup is too small to perform this investigation.

Consistency (internal/external)

• effect consistent on multiple end-points (internal)

Technically, there is only a trend towards significance in ICU outcome (based on Fisher's Exact Test). This trend is not supported by 28 day mortality. The failure to demonstrate consistency across outcomes is important.

• previously documented (external)

The only other clinical trial of arginine enhanced EN that enrolled septic patients directly was by Galban (Galban et al. 2000). While not statistically significant, this trial does not provide evidence of harm in fact, the results suggest benefit.

Confounding

• investigate confounding in baseline, baseline treatment or follow-up treatment

The investigators did not investigate the issue of confounding. Confounding could be present if there is an imbalance in important baseline characteristics within this subgroup. There was no investigation of baseline balance in this subgroup.

Coherence / plausibility

• consistency of results across known, predefined risk groups

Since others have suggested that sepsis is indeed an extremely complex disease, we could debate this issue all day. In short, we are not aware of results from clinical trials of disease states that may be similar to sepsis, such as ARDS, that also demonstrate any evidence of harm.

In summary and consideration of these points, it is at least reasonable, if not likely, that the statistical trend towards harm found by this small subgroup analysis was due to chance alone.

Although within the context of a clinical trial, it may have been reasonable to stop recruitment of septic patients based on these findings, the findings cannot be used to drive clinical decision making to any degree of certainty.

Recommendations could not be made.

12) Parenteral nutrition with glutamine vs. standard parenteral nutrition

3 Level II papers with no major flaws, 1 Level II paper

RefID 507(Griffiths et al. 1997)
Patient Population: ICU patients who did not tolerate EN
Study entry criteria: Patients with an admission APACHE II score > 11 who did not tolerate EN within 48 hours post-admission or who had the following contraindications to EN at admission: major intra-abdominal sepsis; bowel resection; pancreatitis; or heavily bile-stained gastric aspirate > 1L in 24h in ventilated patients with major trauma or non-GI sepsis.
Study intervention/s: Patients were randomised to: 1) Glutamine enriched PN vs 2) standard PN.

RefID 87(Powell-Tuck et al. 1999)
Patient Population: Patients referred to nutrition team for PN.
Study entry criteria: Patients referred to nutrition team for PN.
Study intervention/s: Patients were randomised to: 1) PN supplemented with glutamine or 2) standard PN.

RefID 600(Tremel et al. 1994)
Patient Population: ICU patients.
Study entry criteria: Stable ICU patients within 2 days of admission.
Study intervention/s: Patients were randomised to receive: 1) PN supplemented with L-alanyl-L-glutamine or 2) isonitrogenous, isocaloric PN.

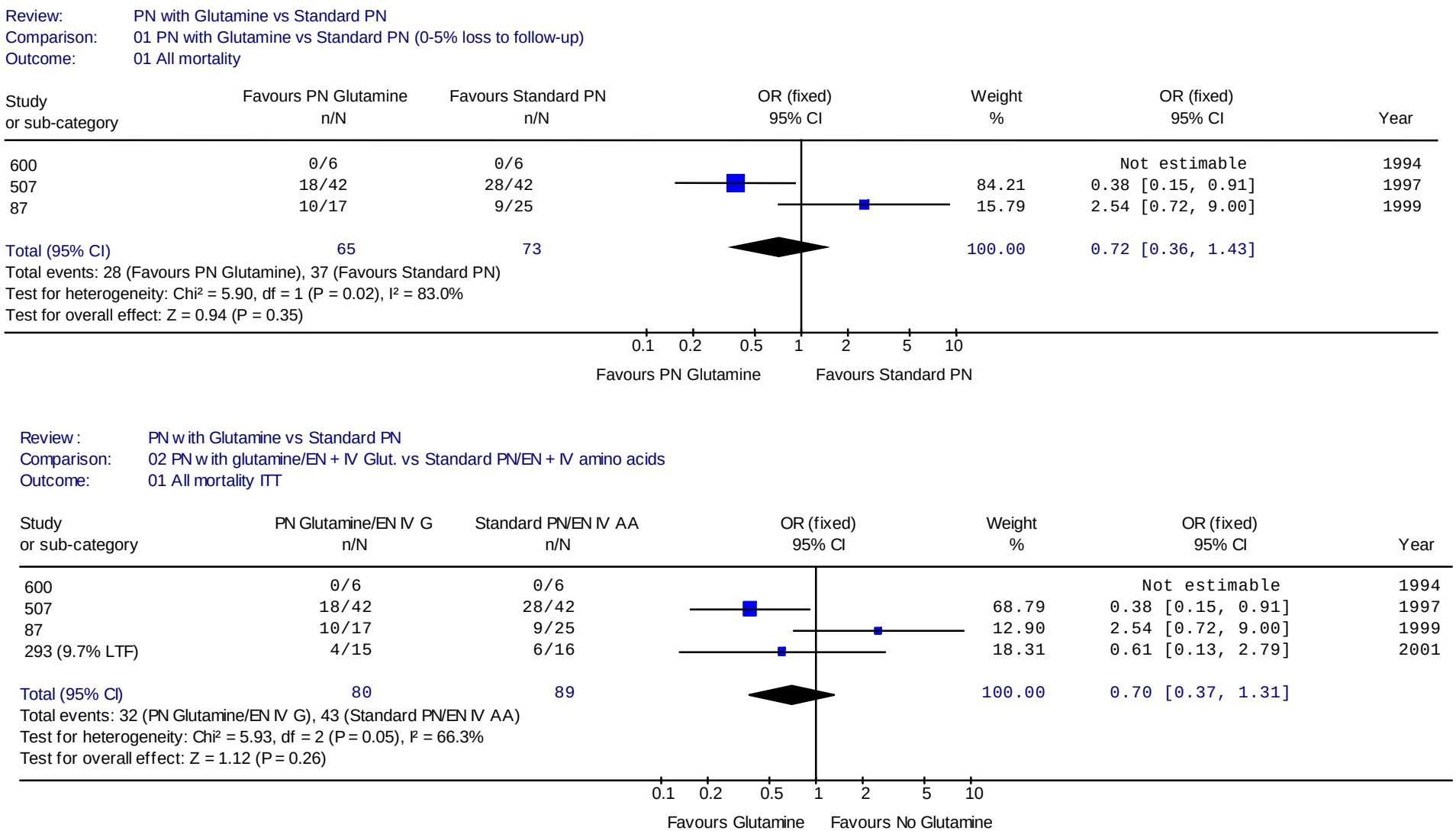
1 Level II paper with 9.7% loss to follow-up
RefID 293(Wischmeyer et al. 2001) There were 3 of 31 patients (9.7%) on whom outcomes were not reported. This could lead to significant bias in the interpretation of the conservative ITT.[GSD]
Patient Population: Severe burns
Study entry criteria: Patients with burns > 25% BSA, > 2 years old admitted within 72 hours of burn injury.
Study intervention/s: Patients were randomised to: 1) EN plus IV glutamine or 2) EN plus isonitrogenous control amino acid solution.

EBR: Level II studies with no flaws, Grade B- Recommendation for PN + Glutamine

- **no significant findings (p=0.26, heterogeneity present at p=0.05)**

Due to heterogeneity, these trials could not be pooled. Review of individual trials suggests that glutamine may be beneficial in select patients. To identify which patients, each constituent RCT should be reviewed and clinical judgement should be exercised.

Figure 13. Parenteral nutrition with glutamine vs. standard parenteral nutrition



13) Enteral nutrition with glutamine vs. standard enteral nutrition

1 Level II paper with no major flaws, 2 Level to papers with >5% loss to follow-up

RefID 6(Hallay et al. 2002)
Patient Population: Esophageal cancer patients
Study entry criteria: Patients requiring surgery for esophageal cancer.
Study intervention/s: Patients were randomised to: 1) glutamine rich EN (Stresson Multi-Fibre) vs. 2) glutamine poor EN (Nutrison Multi-Fibre).

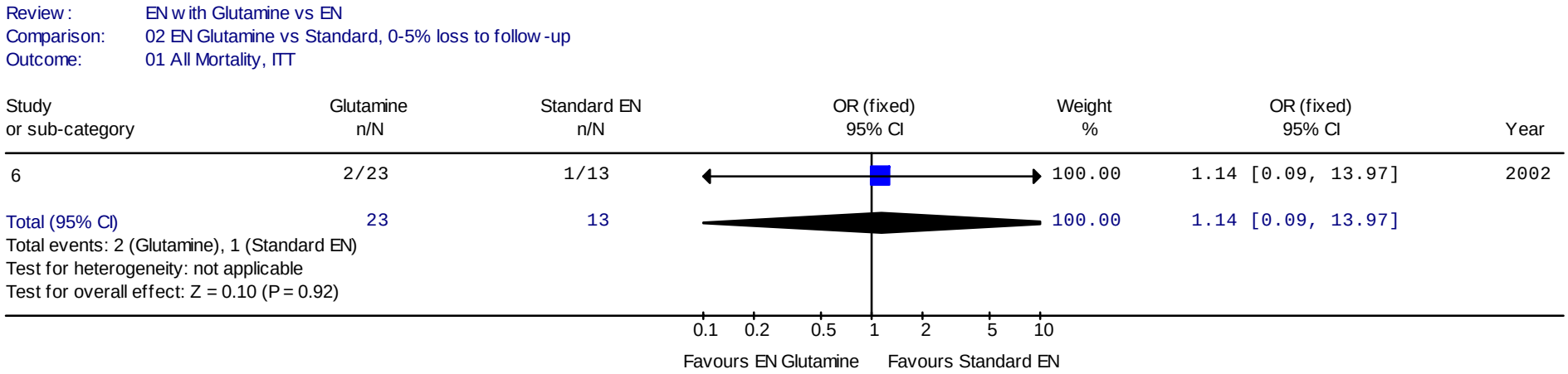
RefID 1187(Houdijk et al. 1998) Differential loss to follow-up of 6.25% (5 / 80) creates potential for bias in calculation of conservative ITT analysis.[GSD]
Patient Population: Multiple trauma.
Study entry criteria: Multiple trauma patients with age ≥ 18 and ≤ 65, ISS ≥ 20 and expected to survive longer than 48 hours (defined as GCS ≤ 8 AND ISS ≥ 50).
Study intervention/s: Patients were randomised to receive: 1) glutamine-supplemented enteral nutrition (Alitra Q) or 2) balanced isocaloric, isonitrogenous EN.

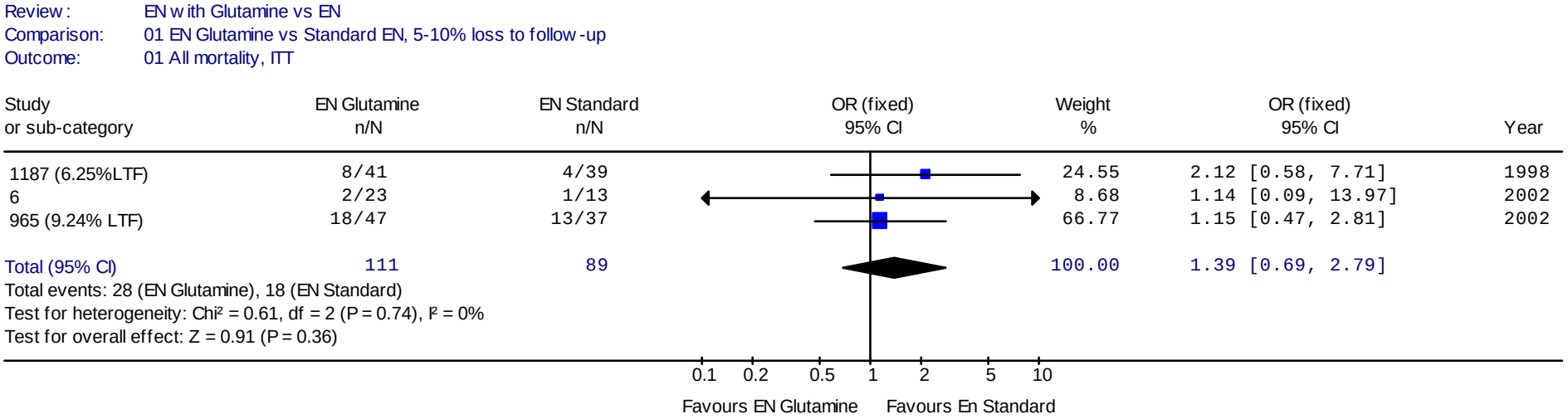
RefID 965(Conejero et al. 2002) Incomplete follow-up on 9.24% of all randomised patients (8 / 84) could result in significant bias in calculation of ITT analysis.[GSD]
Patient Population: ICU patients with SIRS (systemic inflammatory response syndrome).
Study entry criteria: ICU patients who develop SIRS after an acute event and who are expected to require EN for at least 7 days.
Study intervention/s: Patients were randomised to receive: 1) glutamine supplemented EN or 2) control EN diet (no glutamine).

EBR: Level II studies, two additional papers with < 10% loss to follow-up

- **no significant findings (p=0.36, no heterogeneity present at p=0.74)**

Figure 14. Enteral nutrition with glutamine vs. standard enteral nutrition





14) Hypocaloric (Dose) of parenteral nutrition

4 Level II trials with no major flaws

RefID 210(Frankenfield et al. 1997)
Patient Population: Multiply injured trauma patients requiring surgical ICU admission.
Study entry criteria: Expected to require IMV for at least 4 days and deemed unlikely to tolerate EN by the attending trauma surgeon.
Study intervention/s: Patients were randomised to 3 groups: 1) nonprotein calorie group: dextrose and lipid intake equal to measured energy expenditure 2) total calorie group: dextrose, lipid and protein intake equal to measured energy expenditure and 3) hypocaloric group: dextrose and lipid intake equal to 50% of measured energy expenditure.

RefID 496(Battistella et al. 1997)
Patient Population: Trauma patients
Study entry criteria: Trauma victims between the ages of 18 and 50 who required TPN on or after day 5 of injury.
Study intervention/s: Patients were randomised to receive: 1) TPN with intravenous fat emulsion (IVFE) or 2) TPN without IVFE.

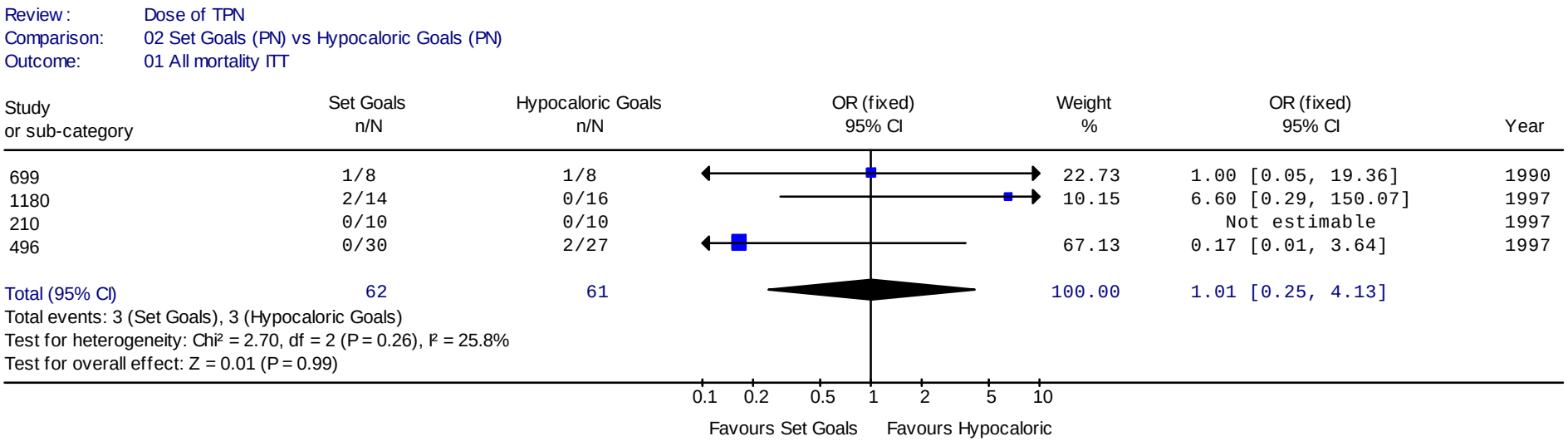
RefID 1180(Choban et al. 1997)
Patient Population: Obese patients
Study entry criteria: Obese patients > 130% IBW according to the formula of Hamwi and who required TPN.
Study intervention/s: Patients were randomised to receive: 1) hypoenergetic TPN or 2) standard TPN.

RefID 699(Iapichino et al. 1990)
Patient Population: Septic or traumatized patients.
Study entry criteria: Patients admitted to an ICU with sepsis (Bone criteria) and/or major trauma or major surgery.
Study intervention/s: Patients were randomised to: 1) High dose PN (30 Cal/kg body weight/day) enriched with BCAA; 2) High dose standard PN (30 Cal/kg body weight/day); 3) Low dose PN (15 Cal/kg body weight/day) enriched with BCAA; 4) Low dose standard PN (15 Cal/kg body weight/day)

Hypocaloric (Dose) of PN
4 Level II trials with no major flaws

- **No significant findings (p=0.99), no heterogeneity (p=0.26)**

Figure 15. Hypocaloric (Dose) of parenteral nutrition



15) Parenteral nutrition composition - Branched Chain Amino Acid (BCAA) content: High BCAA (>40%) vs. Low (<27%) content

6 Level II papers, no major flaws, 1 Level II paper with 9% loss to follow-up

RefID 11(Von Meyenfeldt et al. 1990)
Patient Population: Patients with sepsis and patients with trauma.
Study entry criteria: Patients with sepsis or who had suffered multiple trauma, undergone surgery for ruptured abdominal aortic aneurysm, severe non-septic pancreatitis, major GI surgery or non-septic enterocolitis.
Study intervention/s: Patients were randomised to receive: 1) PN enhanced with 50.2% BCAA or 2) standard PN with 15.6% BCAA.

RefID 10(Van, III et al. 1985)
Patient Population: Surgical ICU patients
Study entry criteria: Patients with a 'state of severe stress' (Geller criteria level > 4 which is defined as trauma and surgery or sepsis and surgery or trauma, sepsis and surgery) projected to need PN for at least 7 days with at least a 50% chance of survival.
Study intervention/s: Patients were randomised to: 1) PN with 45% BCAA or 2) PN with 25% BCAA.

RefID 514(Garcia-de-Lorenzo et al. 1997)
Patient Population: Septic patients
Study entry criteria: Septic patients admitted to an ICU who were in need of PN within the first three days of ICU admission and for at least 11 days.
Study intervention/s: Patients were randomised to receive: 1) PN with 23% BCAA (FreAmine [R]10%) and total protein intake of 1.5g/kg/day; 2) PN with 45% BCAA (FreAmine 6.9%) and total protein intake of 1.5 g/kg/day or 3) PN with 45% BCAA (FreAmine 6.9%) and total protein intake of 1.1g/kg/day.

RefID 699(Iapichino et al. 1990)
Patient Population: Septic or traumatized patients.
Study entry criteria: Patients admitted to an ICU with sepsis (Bone criteria) and/or major trauma or major surgery.
Study intervention/s: Patients were randomised to: 1) High dose PN (30 Cal/kg body weight/day) enriched with BCAA; 2) High dose standard PN (30 Cal/kg body weight/day); 3) Low dose PN (15 Cal/kg body weight/day) enriched with BCAA; 4) Low dose standard PN (15 Cal/kg body weight/day)

RefID 934(Cerra et al. 1983)
Patient Population: Multiple trauma or major general surgery.
Study entry criteria: Patients admitted to a surgical ICU within 24 hours of trauma or major surgery.
Study intervention/s: Patients were randomised to one of four groups: 1) PN enhanced with 0.7g/kg/day BCAA (~46% of total protein content); 2) PN enhanced with 0.5g/kg/day BCAA (50% of total protein content); 3) PN enhanced with 0.3g/kg/day BCAA (20% of total protein content) and; 4) PN enhanced with 0.15g/kg/day BCAA (15% of total protein content)

RefID 201(Reilly et al. 1990)
Patient Population: Liver transplant patients
Study entry criteria: Patients were enrolled either immediately before or after liver transplant. All patients met clinical criteria for transplant and were treated with the conventional immunosuppressive regimen of cyclosporine or steroids.
Study intervention/s: Patients were randomised to 1 of three groups: 1) TPN enriched with BCAA; 2) standard TPN or 3) IV glucose control.

RefID 206(Kuhl et al. 1990) - 2 of 22 patients (one from each group) were randomised but excluded from follow-up because they did not receive PN for at least 7 days.
Patient Population: Injured ICU patients.
Study entry criteria: Consecutive patients requiring PN for at least 7 days admitted to the ICU at a level 1 trauma centre due to injury.
Study intervention/s: Patients were randomised to receive: 1) PN with 46% BCAA or 2) PN with 21% BCAA.

EBR: Level II evidence, no major flaws
No significant effects on mortality (p=0.27), no heterogeneity (p=0.21)
- **No recommendations can be made.**

EBR: Level II evidence, loss to follow-up less than 10%

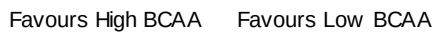
No significant effects on mortality (p=0.23), no heterogeneity (p=0.32)

Figure 16. Parenteral Nutrition Composition: Branched Chain Amino Acid (BCAA) content

Review: High (>40%) vs Low (<27%) dose BCAA in PN
Comparison: 01 High vs Low BCAA, 0-5% loss to follow-up
Outcome: 01 All mortality, ITT

Study or sub-category	High BCAA n/N	Low BCAA n/N	OR (fixed) 95% CI	Weight %	OR (fixed) 95% CI	Year
934	0/8	0/8			Not estimable	1983
10	1/6	4/6		13.38	0.10 [0.01, 1.54]	1985
11	17/49	16/52		40.70	1.20 [0.52, 2.75]	1990
201	1/10	0/8		1.91	2.68 [0.10, 75.12]	1990
699	2/11	3/11		9.85	0.59 [0.08, 4.50]	1990
514	5/25	10/22		34.16	0.30 [0.08, 1.09]	1997
Total (95% CI)	109	107		100.00	0.71 [0.39, 1.30]	

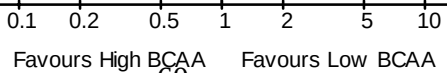
Total events: 26 (High BCAA), 33 (Low BCAA)
Test for heterogeneity: Chi² = 5.83, df = 4 (P = 0.21), I² = 31.4%
Test for overall effect: Z = 1.10 (P = 0.27)



Review: High (>40%) vs Low (<27%) dose BCAA in PN
Comparison: 02 High vs Low BCAA, 5-10% loss to follow-up
Outcome: 01 All mortality, ITT

Study or sub-category	High BCAA n/N	Low BCAA n/N	OR (fixed) 95% CI	Weight %	OR (fixed) 95% CI	Year
934	0/8	0/8			Not estimable	1983
10	1/6	4/6		12.18	0.10 [0.01, 1.54]	1985
11	17/49	16/52		37.05	1.20 [0.52, 2.75]	1990
201	1/10	0/8		1.74	2.68 [0.10, 75.12]	1990
206 (9% LTF)	2/11	3/11		8.97	0.59 [0.08, 4.50]	1990
699	2/11	3/11		8.97	0.59 [0.08, 4.50]	1990
514	5/25	10/22		31.10	0.30 [0.08, 1.09]	1997
Total (95% CI)	120	118		100.00	0.70 [0.39, 1.25]	

Total events: 28 (High BCAA), 36 (Low BCAA)
Test for heterogeneity: Chi² = 5.86, df = 5 (P = 0.32), I² = 14.7%
Test for overall effect: Z = 1.20 (P = 0.23)



Assorted topics and papers.

No three papers addressed topics similar enough to allow pooling of results in the following topics.

16) Targets and advancement rates

1 Level II study, no major flaws
RefID 175(Taylor 1999)
Patient Population: Mechanically ventilated head injury patients
Study entry criteria: Presence of head injury requiring mechanical ventilation (as determined by CT indicating significant risk of cerebral edema and increased ICP), best Glasgow Coma Scale score > 3 and at least one reactive pupil some time during the first 24 hours, age > 10, unable to take oral nutrition for at least 24 hours. Possible to start EN within 24 hours of injury.
Study intervention/s: Patients were randomised to: 1) feed started at a rate that would meet full estimated requirements or 2) feed rate started at 15ml/hr and increased to 30, 60 and 90 ml/hr as tolerated.

No significant findings.

17) Management of diarrhoea

No valid evidence reporting clinically meaningful outcomes.

18) Gastric residual values

No valid evidence reporting clinically meaningful outcomes.

19) Presence of lipids in parenteral nutrition

1 Level II study with no major flaws
RefID 496(Battistella et al. 1997)
Patient Population: Trauma patients
Study entry criteria: Trauma victims between the ages of 18 and 50 who required TPN on or after day 5 of injury.
Study intervention/s: Patients were randomised to receive: 1) TPN with intravenous fat emulsion (IVFE) or 2) TPN without IVFE.

No significant findings.

20) Composition of parenteral nutrition - Assorted

Level II papers with no major flaws

RefID 680(Jarnberg 1991)
Patient Population: ICU patients
Study entry criteria: Mechanically ventilated ICU patients in need of TPN for at least 7 days.
Study intervention/s: Patients were randomised to receive: 1) TPN with 20% Liposyn or 2) TPN with 20% Intralipid

RefID 41(Garnacho-Montero et al. 2002)
Patient Population: ICU patients with sepsis.

Study entry criteria: Patients undergoing surgery with peritonitis that met the Bone criteria for sepsis and were likely to require TPN for at least 10 days.
Study intervention/s: Patients were randomised to: 1) TPN with 10% medium/long chain triglycerides (Lipofundin) vs. 2) TPN with 10% long chain triglycerides (Intralipid).

RefID 437(Nijveldt et al. 1998)
Patient Population: Surgical ICU patients.
Study entry criteria: Surgical ICU patients expected to require at least 5 days of mechanical ventilation and needed TPN on clinical grounds. Patients met at least 3 of the 4 Bone criteria for sepsis.
Study intervention/s: Patients were randomised to receive: 1) TPN with 50% medium (MCT) and 50% long chain triglycerides (LCT) vs. 2) TPN with 100% long chain triglycerides (LCT).

RefID 717(Kari et al. 1989)
Patient Population: Critically ill patients.
Study entry criteria: Patients admitted to the ICU because of severe injury, infection or respiratory insufficiency.
Study intervention/s: Patients were randomised to receive PN with : 1) soy bean oil-egg phosphatide fat emulsion (Emulsan) as the lipid source vs 2) Intralipid as the lipid source.

RefID 496(Battistella et al. 1997)
Patient Population: Trauma patients
Study entry criteria: Trauma victims between the ages of 18 and 50 who required TPN on or after day 5 of injury.
Study intervention/s: Patients were randomised to receive: 1) TPN with intravenous fat emulsion (IVFE) or 2) TPN without IVFE.

No three papers are similar enough to combine.

No significant findings.

21) Composition of enteral nutrition - Assorted

5 Level II papers, no major flaws. 2 Level II papers, < 10% loss to follow-up

RefID 226(Brinson and Kolts 1988)
Patient Population: Medical and Surgical ICU patients with hypoalbuminemia and MOF
Study entry criteria: All patients admitted to the study ICUs with two or more major organ system failures and albumin < 2.5 g/dl.
Study intervention/s: Patients were randomised to receive: 1) a peptide based feed (Vital HN) or 2) standard EN (Osmolite HN).

RefID 476(De Bandt et al. 1998)
Patient Population: Burns patients.
Study entry criteria: Patients admitted to the ICU with thermal injury TBSA 20-50%.
Study intervention/s: Patients were randomised to 9 groups based on dose and route of ornithine α-ketoglutarate (OKG) administration: 1) 10g/day OKG as a single bolus, 2) 10 g OKG bolus bid, 3) 10 g OKG bolus tid , 4) 10 g/day OKG continuous (mixed with Osmolite feeds), 5) 20 g/day OKG continuous (mixed with Osmolite feeds), 6) 30 g/day OKG continuous (mixed with Osmolite feeds), 7) 10 g soy protein (Protil-1) per day (mixed with Osmolite feeds) , 8) 20 g soy protein

(Protil-1) per day (mixed with Osmolite feeds), 9) 30 g soy protein (Protil-1) per day (mixed with Osmolite feeds).

RefID 164(Jeevanandam and Petersen 1999)
Patient Population: Trauma patients.
Study entry criteria: Patients hospitalised in the trauma ICU.
Study intervention/s: Patients were randomised to: 1) EN (Two Cal HN) supplemented with OKG or 2) standard EN (Two Cal HN).

RefID 408(Heyland et al. 1999)
Patient Population: Critically ill patients.
Study entry criteria: Patients admitted to the ICU for less than 48 hours, expected to be ventilated for more than 48 hours and who were eligible to be fed enterally.
Study intervention/s: Patients were randomised to receive: 1) EN with a final pH of 3.5 vs. 2) EN with a final pH of 6.5.

RefID 415(Gadek et al. 1999)
Patient Population: ICU patients with ARDS
Study entry criteria: ICU patients between the ages of 18 and 80 with the diagnosis of a predisposing condition resulting in ARDS that included: acute bacterial, viral or fungal pneumonia, sepsis syndrome, aspiration, inhalation of gaseous agent (smoke or chemical), trauma and burns. Patients also had bronchoalveolar lavage , evidence of pulmonary inflammation as indicated by neutrophil count > 10%; PaO_2/FiO_2 ratio < 250 but > 100; and enteral access providing a mechanism of either gastric, duodenal or jejunal tube feeding.
Study intervention/s: Patients were randomised to: 1) EN with EPA (eicosapentaenoic acid) and DHA (docosahexaneoic acid) from fish oil, and GLA (gamma-linolenic acid) from borage oil vs. 2) isocaloric, isonitrogenous low carbohydrate, high fat EN.

RefID 18(Olah et al. 2002) - 5 (10%) patients were 'excluded'. Three due to intolerance of the feeding tube (self-removed) and 2 due to intolerance of EN due to 'severe ileus'. Group of randomisation or outcome are not reported for these 5 patients.
Patient Population: Acute pancreatitis
Study entry criteria: Typical clinical picture including abdominal pain, laboratory signs of pancreatitis (plasma amylase > 200 units/l) and a short duration of symptoms (admitted within 48 hours of onset).
Study intervention/s: Patients were randomised to receive: 1) EN (Nutrison Fibre) with added live lactobacillus and oat fibre vs. 2) EN (Nutrison Fibre) with added dead lactobacillus and oat fibre .

RefID 77(Rayes et al. 2002b) -10 (10%) patients did not complete the study (4 Group 1, 4 in Group 2 and 2 in Group 3) due to severe early complications. Outcomes are not explicitly reported in these 10 patients.
Patient Population: Liver transplant recipients.
Study entry criteria: Adult patients undergoing orthotopic liver transplantation with side to side anastomosis of the bile duct.
Study intervention/s: Patients were randomised to one of three groups: 1) Standard EN plus selective bowel contamination, 2) Fibre containing EN plus live Lactobacillus plantarum 299 or 3) Fibre containing EN plus heat killed Lactobacillus plantarum 299.

22) Enteral nutrition - Trace elements

RefID 1188(Berger et al. 1998)
Patient Population: Burns

Study entry criteria: Burns patients with > 30% TBSA
Study intervention/s: Patients were randomised to receive EN plus: 1) additional supplements of copper, selenium and zinc IV (in a 0.9% NaCl solution) or 2) placebo (0.9% saline solution).

23) Enteral nutrition - Carbohydrates / fats

RefID 1191(Garrel et al. 1995)
Patient Population: Burns patients
Study entry criteria: Thermal injury > 20% TBSA (not including 1st degree burn), admitted within 24 hours of burn injury.
Study intervention/s: Patients were randomised to: 1) 15% of total calories as fat (50% of fat calories came from fish oils) 2) 15% of total calories as fat or 3) 35% of total calories as fat.

RefID 213(Al Saady et al. 1989) - 35% loss to follow-up
Patient Population: Patients requiring artificial ventilation due to chronic obstructive airways disease, pneumonia, asthma, brain damage or surgery.
Study entry criteria: Patients with acute respiratory failure requiring artificial ventilation, who could be fed enterally. Patients were eligible to remain in the study if they tolerated 48 hours of EN which met their goal requirements whilst still ventilated.
Study intervention/s: Patients were randomised to receive either 1) High fat low carbohydrate EN (Pulmocare) or 2) Standard EN (Ensure Plus).

RefID 258(Kenler et al. 1996) - 30% loss to follow-up
Patient Population: Patients with upper GI cancer.
Study entry criteria: Patients scheduled for major abdominal surgery for upper GI cancer.
Study intervention/s: Patients were randomised to: 1) fish-oil based EN or 2) standard EN (Osmolite HN).

27) Enteral nutrition - Selenium

RefID 1190(Berger et al. 2001)
Patient Population: Severely injured patients.
Study entry criteria: Patients 18 to 75 years old admitted to the ICU within 24 hours of injury involving at least 2 body systems with ISS > 15.
Study intervention/s: Patients were randomised to receive: 1) 500ug IV Selenium (Se)/day for 5 days or 2) 500ug IV Se/day plus 150mg α-tocopherol/day and 13 mg zinc/day or 3) placebo.

24) Enteral nutrition - Probiotics

RefID 79(Rayes et al. 2002a)
Patient Population: Major abdominal surgery.
Study entry criteria: Adult patients undergoing elective laparotomy and resection of the liver, stomach, colon or pancreas.
Study intervention/s: Patients were randomised to receive: 1) EN plus Lactobacillus planatarum 299 and 11.3 g/L oat fibre given twice a day (5.5 g/L soluble fibre and 5.7g/L insoluble fibre) or 2) EN with heat killed Lactobacillus plantarum 299 and 11.3 g/L oat fibre given twice a day or 3) TPN until oral intake was possible.

25) Enteral nutrition - Intermittent vs. Continuous

RefID 541(Bonten et al. 1996)
Patient Population: Mechanically ventilated ICU patients.
Study entry criteria: All mechanically ventilated patients admitted to a mixed ICU or cardiothoracic ICU were eligible whenever enteral nutrition was started and at least 3 days of ventilation was expected.

Study intervention/s: Patients were randomised to: 1) intermittent enteral feeding (continuous over an 18 hour period, from 8am-2am) vs. 2) continuous (24 hour) enteral feeding.

26) Parenteral nutrition - Selenium

RefID 1177(Angstwurm et al. 1999)
Patient Population: Septic patients.
Study entry criteria: Patients admitted to the ICU for less than 24 hours with APACHE II ≥ 15, meeting the criteria for SIRS due to suspected infection.
Study intervention/s: Patients were randomised to: 1) sodium selenite in decreasing doses for a total of 9 days (535 μg for 3 days followed by 285 μg for 3 days and 155 μg for 3 days, and thereafter 35 μg per day or 2) 35 μg per day.

27) Parenteral nutrition - Intermittent vs. Continuous

RefID 1017(Forsberg et al. 1994)
Patient Population: Trauma or major surgery patients
Study entry criteria: Mechanically ventilated post-operative patients.
Study intervention/s: Patients were randomised to receive: 1) continuous TPN or 2) cyclic (12 h) TPN.

28) Tube placement methods

RefID 131(Huerta and Puri 2000)
Patient Population: Critically ill patients.
Study entry criteria: ICU patients with a tracheostomy or endotracheal tube, a functional GI tract and a high likelihood that their ICU stay would require a minimum duration of EN for 2 days and a maximum of 5 days.
Study intervention/s: Patients were randomised to receive: 1) 8 French feeding tubes placed under fluoroscopic guidance with the aid of metoclopramide (maximum of 20mg) or 2) feeding tube placed at the bedside and confirmed by x-ray.

29) Role of Indirect Calorimetry

RefID 911(Saffle et al. 1990)
Patient Population: Burns patients
Study entry criteria: All adult patients with TBSA > 25% who required enteral nutrition
Study intervention/s: This is a factorial trial. Patients were randomised to: 1) EN with target energy requirements calculated via Curreri formula OR 2) EN with target energy requirements calculated via indirect calorimetry. Patients were also randomised to: 3) Osmolite HN or 4) Isotein HN.

30) Enteral nutrition + parenteral nutrition vs parenteral nutrition

RefID 1003(Gianotti et al. 1997)
Patient Population: Gastric or pancreatic cancer patients.
Study entry criteria: Curative operation for gastric or pancreatic cancer.
Study intervention/s: Patients were randomised to receive: 1) enteral diet (Impact) which is supplemented with arginine (12.5 g/L) and omega-3 fats or 2) standard enteral formula with glycine replacing arginine and omega-6 fats replacing omega-3 fats (prepared by Novartis) or 3) TPN (isonitrogenous, isocaloric).

Evidence-based recommendations ratified at the guideline development conference

- **EN in preference to Standard Care (NPO), Grade B+ recommendation**
  5 Level II RCTs. Ratified by positive meta-analysis and validated evidence-based guideline (ACCEPT).

- **Early EN (<24 hours) in preference to delayed EN, Grade B recommendation**
  3 Level II RCTs. Ratified by validated evidence-based guideline (ACCEPT).

- **PN in preference to Standard Care (IV Glucose), Grade B recommendation**
  5 Level II RCTs. Ratified by validated evidence-based guideline (ACCEPT).

- **Early EN (<24 hours) in preference to PN, Grade B recommendation**
  6 Level II RCTs. Ratified by validated evidence-based guideline (ACCEPT).

- **PN in preference to delayed (>24 hours) EN, Grade B+ recommendation**
  5 Level II RCTs. Ratified by positive meta-analysis and validated evidence-based guideline (ACCEPT). The results of the meta-analysis supporting this EBR have been published elsewhere (Simpson and Doig 2005).

- **Post-pyloric feeding when gastric feeding not tolerated, Grade B recommendation**
  8 Level II RCTs. Ratified by validated evidence-based guideline (ACCEPT).

- **Use of prokinetics when gastric feeding not tolerated, Grade B recommendation**
  5 Level II RCTs. Ratified by validated evidence-based guideline (ACCEPT).

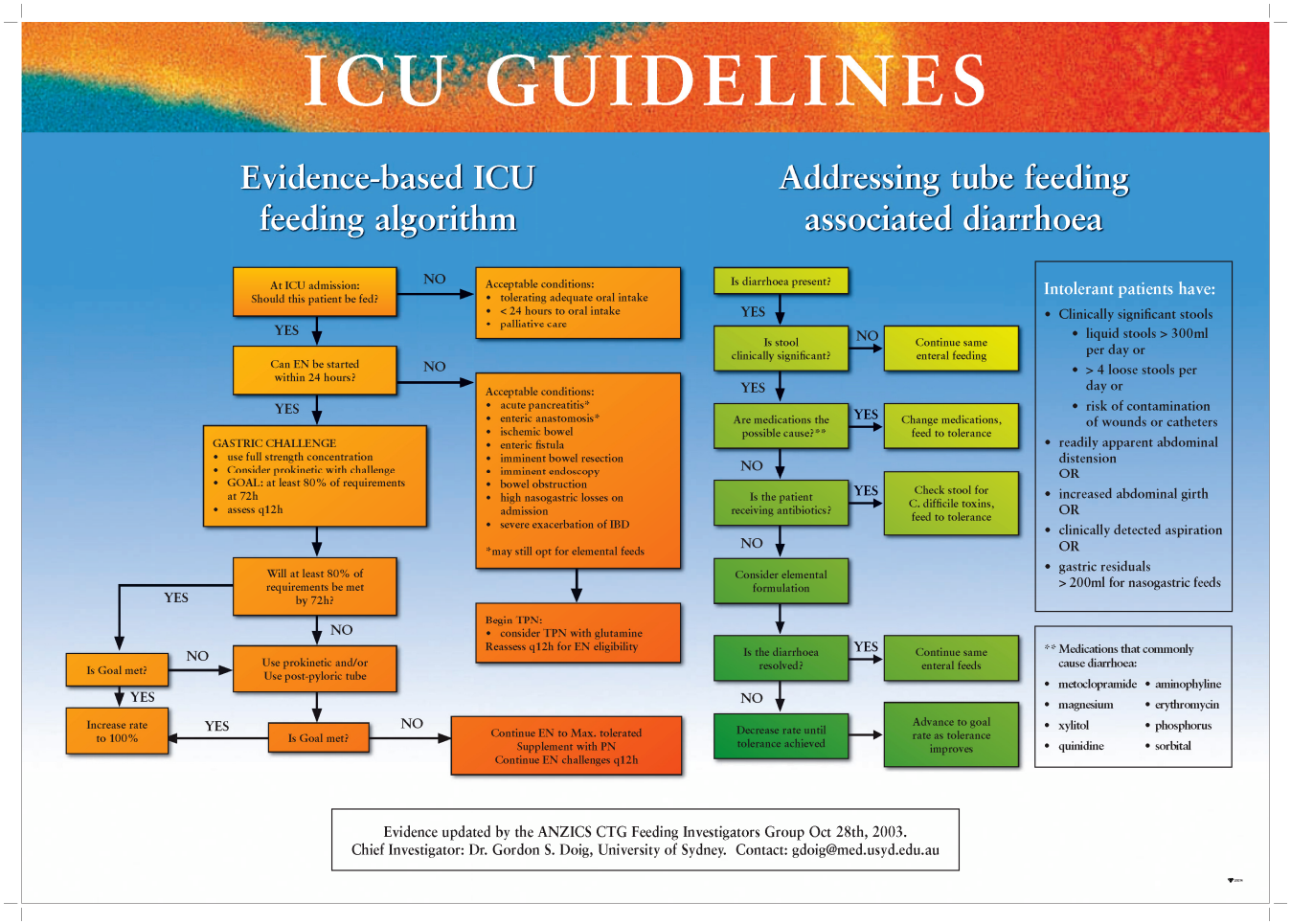
- **EN supplemented with PN if goals not met with EN alone (after attempts at post-pyloric feeding and use of prokinetics) by 72 hours, Grade B recommendation**
  4 Level II RCTs. Ratified by validated evidence-based guideline (ACCEPT).

- **PN with glutamine vs. standard PN, Grade B- recommendation**
  4 Level II RCTs. Ratified by meta-analysis, **heterogeneity present**.
  Glutamine *may* be beneficial in select patients. To identify which patients *may* benefit, each constituent RCT should be reviewed and clinical judgement should be exercised.

- **Management of diarrhoea, Grade B recommendation**
  Ratified by validated evidence-based guideline (ACCEPT).

- **Gastric residual values and tolerance, Level B evidence**
  Ratified by validated evidence-based guideline (ACCEPT).

Figure 17. Algorithmic representation of guideline generated from ratified EBRs.



For full resolution Poster (A3) sized version, download: http://www.EvidenceBased.net/files/Poster.pdf
For full resolution 2-sided Letter (A4) sized version, download: http://www.EvidenceBased.net/files/2sidedLetter.pdf
Both files are suitable for full colour printing.

Full page critical appraisal summaries

Please note: Some of the critical appraisal summaries included in the section titled ' RCTs excluded due to major methodological flaws' may appear incomplete. In these RCTs, the major flaw that was detected was considered so significant that it precluded the trial from consideration in the guidelines development process and thus the appraisal of other issues was considered unnecessary.

Important: Directions on how to find the summary for a specific paper

Unfortunately, the full page critical appraisals are NOT sorted by alphabetical order or RefID order. They are organised by topic of the EBR and the location of each paper's summary is indexed in the Table of Contents using its unique RefID.

Throughout this document, papers are referred to using a Reference Identifier (**RefID**) that was assigned to the paper for the conduct of this project.

At the end of this document, all references are sorted in alphabetical order by author. Each paper's **RefID** is reported immediately after the full citation found in the Reference List.

Papers can be searched in this document using the author name or using the **RefID**. For example, the paper by (Chuntrasakul et al. 1996) has **RefID 511**. To find the occurrences of this paper, search for Chuntrasakul or search for **RefID 511**. To conduct a search within Adobe Acrobat, click on the 'binoculars' icon or select Edit | Search from the toolbar menu.

RCTs conducted in critically ill patients, no major flaws

Topic: EN Composition: Borage oils

RefID **415**

Reference: (Gadek et al. 1999)

Patient Population: ICU patients with ARDS

Study entry criteria: ICU patients between the ages of 18 and 80 with the diagnosis of a predisposing condition resulting in ARDS that included: acute bacterial, viral or fungal pneumonia, sepsis syndrome, aspiration, inhalation of gaseous agent (smoke or chemical), trauma and burns. Patients also had bronchoalveolar lavage , evidence of pulmonary inflammation as indicated by neutrophil count > 10%; PaO_2/FiO_2 ratio < 250 but > 100; and enteral access providing a mechanism of either gastric, duodenal or jejunal tube feeding.

Study intervention/s: Patients were randomised to: 1) EN with EPA (eicosapentaenoic acid) and DHA (docosahexaneoic acid) from fish oil, and GLA (gamma-linolenic acid) from borage oil vs. 2) isocaloric, isonitrogenous low carbohydrate, high fat EN.

The two EN formulas differed only in their lipid composition and antioxidant levels. Both EN formulas contained 16.7% of total calories as protein, 28.1% as carbohydrate, and 55.2% as lipid. Both formulas were 1.5Cal/ml.
Group 1 received 20% of their fat as borage oil, 20% as fish oil, 25% as MCT oil, 31.8% as canola oil and 3.2% as soy lecithin. Group 2 received 96.8% of their fat as corn oil and 3.2% as soy lecithin.
EN was begun within 24 hours of meeting entry criteria via gastric, duodenal or jejunal feeding tubes at the discretion of the physician investigator. EN was commenced at 50% of calculated requirements (BEE using Harris Benedict equation x 1.3) for the first 24 hours, aiming to achieve at least 75% of requirements within 72 hours of feeding initiation.

Total number of patients randomised: 146 patients were randomised: 70 to Group 1 and 76 to Group 2.

Outcome by study arm:

Outcome Reporting
48 patients were deemed 'nonevaluable' (19 in Group 1 and 29 in Group 2) however, outcomes are reported on all 146 randomised patients.

Intention to Treat Mortality
Hospital discharge mortality:
11/70 Group 1 (borage oils) vs.
19/76 Group 2

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☒ Unclear ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☒ No ☐
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 90% of all randomised patients.

Reviewer comments (and initials):
Patients had ARDS and were recruited in the ICU. These patients are critically ill.[AD]

Topic: Evidence-based Feeding Guidelines

RefID **1227**

Reference: (Martin et al. 2004)

Patient Population: ICU patients

Study entry criteria: ICU patients with an expected stay of 2 days or longer

Study intervention/s: Hospitals were randomised to receive 1) evidence-based guidelines supported by an extensive educational intervention or 2) standard care (no intervention).

The key elements of the guideline included: 1) preference to early enteral nutrition 2) preference to EN vs. PN 3) preference to PN vs delayed feeding 4) continuous reassessment of patient on TPN q12hrs for EN suitability, 5) use of full strength initial EN challenge 6) consider prokinetic with initial EN challenge 7) increase EN rate over 72 hours to achieve at least 80% of goal 8) use of a prokinetic or a post-pyloric feeding if 80% of goal not reached by 72 hours, 9) after 72 hours, if 100% of estimated requirements cannot be met with EN, consider suplementing with PN 10) use of an objective definition of clinically significant diarrhoea 11) use of an objective definition of 'tolerance' of EN.

Both group 1 and 2 used the same EN formula (Ultrapak, Nestle Clinical Nutrition) in the run-in phase as well as throughout the study.
All sites used the Harris Benedict equation to estimate energy requirements, with two hospitals (one in each group) also using indirect calorimetry to adjust nutritional goals. Protein requirements were set at 1.5g protein/kg ideal body weight for both groups.

Total number of patients randomised: 14 hospitals were randomised: 7 hospitals were randomised to receive the guideline-based intervention (272 patients) and 7 received standard care (227 patients).

Outcome by study arm:

Outcome Reporting

Hospital discharge mortality was not available in 7 patients (3 intervention, 4 control) resulting in 1.4% loss to follow-up.

Intention to Treat Mortality

Hospital discharge mortality:
67 + 3 / 272 Group 1 (guideline) vs
82 + 4 / 227 Group 2 (standard care)
p < 0.05

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
Time from ICU admission to starting any form of nutrition was 1.52 days (group 1, guidelines arm) vs 1.85 days (group 2, standard care). Time from ICU admission to starting EN was 1.61 days (group 1 guidelines arm) vs 2.16 days (group 2, standard care) [FS].

Topic: EN & PN vs. EN alone

RefID **358**

Reference: (Bauer et al. 2000)

Patient Population: Medical and surgical ICU patients

Study entry criteria: Admitted to the ICU for longer than 2 days and expected to stay alive for at least 2 days. Expected to eat less than 20kcal/kg daily for more than 2 days and EN was expected to be progressively administered for more than 2 days.

Study intervention/s: Patients were randomised to receive: 1) enteral nutrition and parenteral nutrition (parenteral made up any deficiency in EN intake) or 2) enteral nutrition and placebo.
Patients were fed to a target of 25 kcal/kg body weight /day in both groups. Intervention was undertaken for 4 to 7 days.
Parenteral nutrition consisted of a 3 in 1 carbohydrate/fat and protein mix (Vitrimix) with soluble vitamins (soluvit). In the parenteral nutrition group (group 1), any deficiency in EN intake was made up with PN..
In the enteral group (group 2), patients were fed using a placebo solution (sodium chloride, intralipid and soluvit) and a bolus fed enterally using a non-commercial 1Cal/ml polymeric diet every four hours, five times a day.
Total number of patients randomised: 120 patients were randomised. 60 to each group.

Outcome by study arm:

Outcome Reporting
Outcomes are reported on all patients.

Intention to Treat Mortality
Mortality at day 90 post randomisation.
17/60 EN and PN group (group 1)
18/60 EN alone (group 2)

Methodological issues:

Method of randomisation reported:	Yes ☒ No ☐	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☒ No ☐
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
Sealed envelopes were used for randomisation. A non-commercial enteral formula was used in the enteral feeding group [FS].
Patients were admitted to a medical/surgical ICU. These patients were critically ill.[AD]

Topic: TPN vs. standard (All pts in this study receive TPN. The primary comparison concerns differing energy goals)

RefID **210**

Reference: (Frankenfield et al. 1997)

Patient Population: Multiply injured trauma patients requiring surgical ICU admission.

Study entry criteria: Expected to require IMV for at least 4 days and deemed unlikely to tolerate EN by the attending trauma surgeon.

Study intervention/s: Patients were randomised to 3 groups: 1) nonprotein calorie group: dextrose and lipid intake equal to measured energy expenditure 2) total calorie group: dextrose, lipid and protein intake equal to measured energy expenditure and 3) hypocaloric group: dextrose and lipid intake equal to 50% of measured energy expenditure.
Target intakes for all groups were 1.7g/kg body wt/d for protein, 4.5g/kg/d for carbohydrates, and 20% Intralipid made up the difference in calories (as required)
Parenteral nutrition was initiated within 48 hours of injury

Total number of patients randomised: Authors report that 30 patients completed the study (study period was 4 days), but do not report how many were randomised into the study. 10 patients in each group 'completed' the study.

Outcome by study arm:

Outcome Reporting

There is no reporting of mortality beyond day 4 of the study.

Intention to Treat Mortality

Day 4 outcomes:
0/10 Group 1 (dextrose and lipid) vs
0/10 Group 2 (TPN) vs.
0/10 Group 3 (hypocaloric dextrose and lipid)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
Lack of outcome reporting beyond day 4 precludes use of this study. Day 4 outcomes do not provide sufficiently long follow-up. Combined with lack of reporting of how many patients were randomised but did not complete day 4, this study cannot be considered further.[GSD]
These patients are critically ill.[AD]

Topic: TPN vs. standard

RefID **827**

Reference: (Brennan et al. 1994)

Patient Population: Major surgery patients

Study entry criteria: Patients receiving major pancreatic resection for malignancy.

Study intervention/s: Patients were randomised to 1) post-op routine adjuvant TPN or 2) dextrose (no routine TPN).
Feedings in both groups began on the first post-op day and continued until oral intake exceeded 1000kcal/day. TPN was delivered at 30 to 35 nonprotein kcal/kg/day and provided 1g protein/kg/day. 30% of calories came from fat. Control patients received a standard dextrose-containing salt solution.Control patients were allowed to receive TPN if a 'complication' occurred, however if they received TPN they were still analyzed in the Control group.

Total number of patients randomised: 117 patients were randomised. 60 to group 1 (TPN) and 57 to group 2 (control).

Outcome by study arm:

Outcome Reporting
Mortality is reported for all patients.

Intention to Treat Mortality
Median duration of follow-up was 16 months:
4/60 routine adjuvant TPN
1/57 dextrose (no routine TPN)

Methodological issues:

Method of randomisation reported:	Yes ☐	No ☒	Allocation concealed:	Yes ☐	Unclear ☒
Consecutive pts enrolled:	Yes ☐	No ☒	Blinding employed:	Yes ☐	No ☒
100% follow-up:	Yes ☒	No ☐	Reporting of losses by study arm	Yes ☒	No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
In many ICU's, these patients would be admitted for post-op monitoring. These patients are likely to be critically ill.[AD]

Topic: TPN vs. standard

RefID **1206**

Reference: (Sandstrom et al. 1993)

Patient Population: Major surgery or non-operative trauma patients.

Study entry criteria: Patients undergoing acute or elective major surgical procedures AND non-operative trauma patients requiring ICU admission.

Study intervention/s: Patients were randomised to receive 1) complete TPN (70% nonprotein calories, 30% fat and ~18020g nitrogen/day) or 2) plain D-glucose (250 to 300 g/day) with standard electrolytes.
Feedings were started at 7am on the day after surgery for both groups.
Patients received TPN or glucose until they were able to drink or eat freely. If a patient receiving glucose only was not able to drink or eat freely by day 15, they received TPN.

Total number of patients randomised: 300 patients were randomised: 150 to Group 1 (complete TPN) and 150 to Group 2 (D-glucose)

Outcome by study arm:

Outcome Reporting
Mortality is reported on all patients.

Intention to Treat Mortality
Hospital mortality:
12/150 Group 1 (TPN) vs.
10/150 Group 2 (glucose)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
Both groups received an average of 4 days of ICU care.[GSD]
The original paper is EXTREMLY confusing with regards to outcome comparisons. The only appropriate intention-to-treat analysis is the one reported above.[GSD]
Patients acute or elective major surgery or trauma managed non-operatively in the ICU. Average of 4 days in the ICU and 2 days on ventilator. These patients are critically ill.[AD]

Topic: TPN vs. standard

RefID **602**

Reference: (Jeevanandam et al. 1994)

Patient Population: Multiple trauma patients.

Study entry criteria: Severely injured multiple trauma patients enrolled after admission to the trauma ICU of a Level I trauma center.

Study intervention/s: Patients were randomised to receive: 1) glucose (25% dextrose infused at 4.1±0.5 mg glucose/kg/min) or 2) glucose with amino acids (250 to 300 mg N/kg/day [Aminosyn] and 4.8±0.6 mg glucose/kg/min as 25% dextrose)
Nutritional support was initiated after 48 to 60 hours of resuscitation and was continued for 4 days.

Total number of patients randomised: 18 patients were enrolled: 8 into Group 1 (glucose) and 10 into Group 2 (glucose plus amino acids).

Outcome by study arm:

Outcome Reporting

Intention to Treat Mortality
Day 4 outcomes:
0/8 Group 1 (glucose) vs
0/19 Group 2 (TPN).

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
Lack of outcome reporting beyond day 4 precludes use of this study. Day 4 outcomes do not provide sufficiently long follow-up. Due to the small sample size of each group and no reported deaths, this study is 'uninformative' with regards to the primary outcome of mortality.[GSD]
These patients are critically ill.[AD]

Topic: TPN vs. standard

RefID **795**

Reference: (Wu et al. 1995)

Patient Population: Aged surgical patients (> 70 yo) with gastric cancer.

Study entry criteria: Age > 70 with primary gastric cancer treated surgically. Patients must have had at least 2 of the following 3 criteria: 1) body weight loss < 20% of usual, 2) serum albumin > 3.0g/dl or 3) cell-mediated immunity multiskin tests > 2 positive.

Study intervention/s: Post-operatively, patients were randomised to: 1) TPN for 10 days post op or 2) standard 5% IV glucose.
TPN was provided at 35 nonprotein kcal//kg/day and 1.5 g/kg/day protein. 550 Cal/d were provided as lipid. All patients were permitted to eat post-operatively as clinically indicated.

Total number of patients randomised: 51 patients were selected, 40 were randomised: 20 were randomised to Group 1 and 20 to Group 2.

Outcome by study arm:

Outcome Reporting	Intention to Treat Mortality
It appears that 51 patients were screened for randomisation and 40 were randomised.	Hospital discharge: **0/20** Group 1 (TPN) vs. **0/20** Group 2 (glucose)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
No mortality events were reported by hospital discharge amongst randomised patients. Due to the small sample size of each group and no reported deaths, this study is 'uninformative' with regards to the primary outcome of mortality.[GSD]
Patients 7- years old with gastric cancer treated surgically. Elderly patients with average surgical duration of 6 to 8 hours. Likely to be admitted to ICU at least short term. These patients are likely to be critically ill.[AD]

Topic: PN vs. EN

RefID **1178**

Reference: (Adams et al. 1986)

Patient Population: Trauma patients

Study entry criteria: Trauma patients between 80% and 130% of desirable weight undergoing an emergent laparotomy.

Study intervention/s: During laparotomy, patients were randomised to: 1) TPN via a subclavian line or 2) EN via an 8Fr Witzel jejunostomy tube.
Both TPN and EN were begun on first post-op day. During the initial 12 months, basal energy requirements were estimated in both groups using the Harris-Benedict equation, multiplied by a stress factor of 1.68. During the final 18 months, the stress factor was increased to 2.0, with the EN group receiving an additional prescription of 20% more than the TPN group.
TPN consisted of equal parts of 25% dextrose and 4.25% amino acids (Travasol). 500mls of 10% Intralipid was optionally given twice weekly.
Enteral nutrition consisted of either Isocal HCN or Traumacal. Both groups feeding rates started at 50mls/hr for the first 24hours. TPN was then advanced as tolerated to goal rate. The enteral group (group 2) received ½ strength feeding, increasing by 25mls/hr every 8 hours until goal volume was achieved. Enteral feeding was then increased to full strength.

Total number of patients randomised: 46 patients were randomised: 23 to each group

Outcome by study arm:

Outcome Reporting
Outcomes were reported on all randomised patients.

Intention to Treat Mortality
Hospital discharge mortality:
3/23 Group 1 (TPN) patients died vs
1/23 Group 2 (EN) patients

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
Trauma patients who required urgent laparotomy. Patients were critically ill.[AD]

Topic: PN vs. EN

RefID **835**

Reference: (Kudsk et al. 1994)

Patient Population: Trauma patients with sepsis.

Study entry criteria: Sub-group of a larger study: Trauma patients requiring a laparotomy with an Abdominal Trauma Index > 15.

Study intervention/s: Patients were randomised to receive: 1) EN (Vital HN, an elemental formula) or 2) TPN (Travasol).
TPN was matched to group 1 to be similar in terms of protein, fat and carbohydrate content . EN and TPN was begun within 8 hours of surgery. Feeding goals in both groups were 1.5-2.0 g/kg/day protein/amino acids and 30-35 Cal/kg/day of non-protein calories.

Total number of patients randomised: 68 patients were randomised: 34 to Group 1 (EN) and 34 to Group 2 (TPN)

Outcome by study arm:

Outcome Reporting

- 1 Group 1 patient is reported to have died on day 4

No other mortality events were reported over the 10 day study period.

Intention to Treat Mortality

Day 10 mortality:
1/34 Group 1 (EN) vs.
0/34 Group 2 (TPN)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
Mortality is not reported beyond Day 10. This may not be sufficient for trauma patients.[GSD]
Average 3.3 ventilator days and 4.5-5.9 ICU days. These patients are likely to be critically ill.[AD]

Topic: PN vs. EN

RefID **962**

Reference: (Woodcock et al. 2001)

Patient Population: All patients requiring nutritional support.

Study entry criteria: Actual or anticipated inadequate oral nutritional intake for 7 days or more with a reasonable doubt as to the adequacy of intestinal function.

Study intervention/s: Patients were randomised to receive; 1) TPN (KabiMix) or 2) EN (Osmolite). Feeding goals in both groups were 30Cal/kg/day nonprotein calories and 9 g nitrogen/day.
Group 1 patients (TPN group) in intensive care also received 5-10mls enteral nutrition, which was increased according to tolerance.

Total number of patients randomised: 64 patients were randomised. Overall, 32 patients were randomised to Group 1 (TPN) and 32 were randomised to Group 2 (EN).
At time of randomisation, 38 of these patients were located in the ICU. Of these 38 ICU patients, 21 were randomised to Group 1(TPN) and 17 were randomised to Group 2 (EN).

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
	Overall Hospital mortality
	7/32 Group 1 (TPN) patients died vs.
	12/32 Group 2 (EN) patients died
	ICU Patient Hospital mortality
	5/21 Group 1 (TPN) ICU patients died vs.
	9/17 Group 2 (EN) ICU patients died

Methodological issues:

Method of randomisation reported:	Yes ☒ No ☐	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):

Time to feeding commencement for both groups was not stated [FS].
59% of patients were in the ICU at time of randomisation. Patients are likely to be critically ill.[AD]

Topic: PN vs. EN

RefID **209**

Reference: (Kalfarentzos et al. 1997)

Patient Population: Severe acute pancreatitis.

Study entry criteria: Presence of three or more criteria according to the Imrie classification or APACHE II score > 8, C-reactive protein > 120mg/dl within 48 hours of admission and grade D or E Balthazar criteria by CT. All patients were located in the ICU.

Study intervention/s: Patients were randomised to: 1) TPN or 2) enteral nutrition.
EN was begun within 48 hours of admission to the ICU once a 10Fr feeding tube was placed in the jejunum. Enterally fed patients received Reabilan HN (1.33Cal/ml, 58g protein/L, 52g fat/L), which was started at 25mls/hr (full strength) and increased by 25ml q4hrs until goal rate was achieved. TPN composition was unclear but included 20% fat emulsion, vamin, dextrose and vitamins and minerals. TPN began at 40mls/hr and increased by 20ml/hr q4hrs until target rate was achieved. Target feeding rate in both groups was to provide 1.5-2.0 g protein/kg/day and 30-35 Cal/kg/day.

Total number of patients randomised: 40 patients were randomised into the study. 20 in Group 1 and 20 in Group 2.

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
2 EN (Group 2) patients failed feeding tube placement and were 'excluded' from the study (lost to follow-up).	**2/20** Group 1 (TPN) patients died vs. **1+2/20** Group 2 (EN) patients dead or lost to follow-up

Methodological issues:

Method of randomisation reported:	Yes ☒ No ☐	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☒ No ☐	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
It is unclear as to when TPN was commenced (group 1) [FS]
Patients with severe, acute pancreatitis by clinical or CT criteria. All admitted to ICU, all ventilated. Patients are critically ill.[AD]

Topic: PN vs. EN

RefID **1179**

Reference: (Cerra et al. 1988)

Patient Population: Hypermetabolic SICU patients, 4 to 6 days after sepsis. Subgroup of a larger ongoing study.

Study entry criteria: Hypermetabolic SICU patients, enrolled within 4 to 6 days after the conduct of surgery and onset of sepsis.

Study intervention/s: Patients were randomised to 1) TPN or 2) EN (post-pyloric).
Both groups received 1.5 gm protein/kg/day, 30 nonprotein calories/kg/day.
EN was provided by nasoduodenal feeding tubes placed via endoscopy, fluoroscopy or surgical jejunostomy tubes.

Total number of patients randomised: 70 patients were entered (randomised) into the study: 37 to Group 1 (TPN) and 33 to Group 2 (EN).

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
2 Group 1 (TPN) patients were lost to follow-up due to recurrent line sepsis and excessive CVO_2	Hospital mortality **8+2/37** Group 1 (TPN) vs.
2 Group 2 (EN) patients were lost to follow-up due to severe, recurrent diarrhoea	**7+2/33** Group 2 (EN)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
This study contains 5.7% loss to follow-up (4 / 70 patients).
Average time to feeding commencement post randomisation for both groups was not provided.
10 patients in each group received TPN in the 4-6 days between surgery/septic event and randomisation into the study [FS]
Conducted in an ICU. Continued assigned form of feeding until mechanical ventilation discontinued. Patients are critically ill.[AD]

Topic: PN vs. EN

RefID **1176**

Reference: (Rapp et al. 1983)

Patient Population: Head injured patients.

Study entry criteria: Penetrating missile wounds or blunt head trauma causing intracranial haematomas, a major focal neurological deficit and/or unconsciousness. Less than 48 hours from time of injury.

Study intervention/s: Patients were randomised to: 1) TPN or 2) standard EN (return of bowel sounds).
TPN was begun within 48 hours of hospital admission. TPN solution contained 42.5g/L amino acids, and 25% dextrose. 250-500mls/d of 10% soybean oil was also provided. Electrolytes, vitamins and minerals were added as appropriate.
Nasogastric EN was begun as soon as bowel sounds were present and gastric residuals were less than 100mls/hr using Vital (42g protein/L, 10.8g fat/L, and 185g carbohydrate/L). EN patients were nursed with the head of the bed elevated to 30°.

Total number of patients randomised: 38 patients were randomised: 20 to Group 1 and 18 to Group 2.

Outcome by study arm:

Outcome Reporting
Outcomes are reported on all patients.

Intention to Treat Mortality
Hospital discharge mortality:
3/20 Group 1 (TPN) vs.
9/18 Group 2 (EN)
p=0.02

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
Average time to commencement of enteral feeding was not stated [FS]
Patients with head injury who would normally required neurosurgical ICU admission. Patients are critically ill.[AD]

Topic: PN vs. EN + EN and PN vs EN

RefID **841**

Reference: (Dunham et al. 1994)

Patient Population: Mechanically ventilated blunt trauma patients.

Study entry criteria: Patients admitted to the ICU for blunt trauma within 12 hours of injury, who had been in the ICU less than 30 hours and required IMV. In addition, GCS ≥ 5, ISS ≥ 15, no spinal neuropath above T8, were unable to undergo GI endoscopy and expected to require IMV for at least an additional 48 hours.

Study intervention/s: Patients were randomised to receive: 1) EN and PN vs. 2) EN alone vs. 3) PN alone.
The projected total non-protein calories administered for each group was 1.3 x the basal metabolic rate using the Harris Benedict Equation. All patients aimed to receive half of their goal requirements within 24 hrs and to meet their full requirements within 48 hrs of study randomisation.
Enteral patients were fed by transpyloric tube using a Traumacal, carbohydrate and protein powder mixture to ensure macronutrient similarity between enteral and parenteral products.
TPN consisted of 67 g/L amino acids and 231g/L dextrose. 30% of calories came from soybean oil. Standard multivitamin and mineral additives were added daily.

Total number of patients randomised: 38 patients were randomised. 10 to EN/PN, 12 to EN alone and 16 to PN alone.

Outcome by study arm:

Outcome Reporting

One patient in the PN group died at day 4. This patient was excluded from the primary analysis, but since the outcome was reported, can be included in an ITT analysis.

Intention to Treat Mortality

Hospital mortality
3/10 EN and PN (group 1)
1/12 EN alone (group 2)
2/16 PN alone (group 3)

Methodological issues:

Method of randomisation reported:	Yes ☐	No ☒	Allocation concealed:	Yes ☐	Unclear ☒
Consecutive pts enrolled:	Yes ☐	No ☒	Blinding employed:	Yes ☐	No ☒
100% follow-up:	Yes ☒	No ☐	Reporting of losses by study arm	Yes ☒	No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
The enteral product is not commercially available. Time to feeding commencement for both groups was not stated [FS].
Blunt trauma patients who required mechanical ventilation. Patients are critically ill.[AD]

Topic: PN vs. EN

RefID **223**

Reference: (Reynolds et al. 1997)

Patient Population: Major upper GI tract surgery

Study entry criteria: Patients undergoing surgery for esophageal, gastric or pancreatic cancer.

Study intervention/s: Patients were randomised to receive 1) post-op TPN or 2) post-op EN via a needle catheter jejunostomy, which was inserted in surgery.
Feeding was initiated at 9am, post-op Day 1.
TPN consisted of 2.5 L/day (providing 9.4 g nitrogen/day, 1800 nonprotein Cal/day (55% lipid). TPN regime was not specified.
EN consisted of 2L/day (providing 12.8 g nitrogen/day, 1680 nonprotein Cal/day (31% lipid). EN was commenced at 30mls/hr (full strength) and increased to tolerance.

Total number of patients randomised: 67 patients were randomised: 34 to Group 1 and 33 to Group 2.

Outcome by study arm:

Outcome Reporting
Outcomes are reported on all randomised patients.

Intention to Treat Mortality
30 day post-op mortality:
1/34 Group 1 (TPN) patients died vs
2/33 Group 2 (EN) patients

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☒ No ☐	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):

ICU admission rate or ICU LoS was not reported.[GSD]
53/67 had procedures which would commonly require short term ICU admission. These patients are likely to be critically ill.[AD]

Topic: Timing of EN (early vs late feeding)

RefID **1174**

Reference: (Chiarelli et al. 1990)

Patient Population: Burn patients

Study entry criteria: Burn patients 25-70 years old, burn area of 25-60% of body surface area, no inhalation burns.

Study intervention/s: Patients were randomised by the "case-control" method (unclear what this is) to 1) very early enteral feeding (fed immediately after hospital admission) vs 2) late enteral feeding (fed 48 hrs after hospitalisation).

Requirements for both groups was determined using the Curreri formula.
Two feeding mixtures (composed of blended egg, carrot, apple, meat, oil, cheese, and vitamins) were given to both groups via nasogastric tube. The nutrient dense mixture was given for the first 3-4 days (1900Cal/L and 79g protein/L), initially at 50ml/hr and no greater than a goal rate of 150ml/hr. After 3-4 days the patients requirements determined which mixture was chosen (either the above mixture or the second mixture of 940Cal/L and 44 g protein/L).

Total number of patients randomised: 20 patients (10 patients each group)

Outcome by study arm:

Outcome Reporting
Outcomes are reported in all patients.

Intention to Treat Mortality
28 day follow-up. All patients survived.
0/10 Group 1 (very early EN) vs
0/10 Group 2 (later EN)

Methodological issues:

Method of randomisation reported:	Yes ☒ No ☐	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
Due to the small group size and the lack of mortality events, this study becomes 'uninformative'.[GSD]
On average the very early feeding group was fed 4.4 hrs after injury vs 57.7hrs after injury (group 2). The formula fed was non-commercial. [FS].
These patients had burns to 25-60% BSA. These patients were likely to be critically ill.[AD]

Topic: Timing of EN (early vs late feeding)

RefID **181**

Reference: (Kompan et al. 1999)

Patient Population: Multiply injured surgical ICU patients

Study entry criteria: Multiply injured patients (ISS >25) with GCS ≥ 12 admitted in shock and stabilised (shock index of less than or equal to 1 and SBP of greater than or equal to 100mm Hg) within 6hrs of ICU admission.

Study intervention/s: Patients were randomised to 1) early EN (started not later than 6 hrs post ICU admission) vs 2) late EN (started greater than 24 hrs after ICU admission).

All EN was given via nasogastric tube. Aim of enteral and/or parenteral feeding was to meet 50% of the calculated feeding goals within 24hrs, 75% within 36hrs and 100% within 72hrs of ICU admission. Feeding goals for both groups were 0.2-0.3 g nitrogen/kg body weight/d and 25-35 non-protein Cal/kg body weight within the first 72 hrs of admission. Within the first 24 hrs post ICU admission group 2 received TPN (started within 6hrs of ICU admission) and in both groups TPN was added to meet nutritional requirements.
TPN consisted of glucose, amino acids and lipids (solution not specified). EN (Jevity formula, 16.7% protein, 29% lipid, 54.3% carbohydrate) was started at 20ml/hr and increased according to gastrointestinal tolerance.

Total number of patients randomised: 36 patients were randomised (17 group 1, 19 group 2)

Outcome by study arm:

Outcome Reporting

8 patients (3 in group 1 and 5 in group 2) were withdrawn from the study due to: 6 not having complete measurements taken, 1 due to paralytic ileus (group 2) and 1 protocol violation. Of the 8 patients withdrawn, it is reported that 1 Group B patient died.

Intention to Treat Mortality

Hospital mortality:
0/17 Group 1 (early EN) vs.
2/19 Group 2 (later EN)

Methodological issues:

Method of randomisation reported:	Yes ☒	No ☐	Allocation concealed:	Yes ☐	Unclear ☒
Consecutive pts enrolled:	Yes ☒	No ☐	Blinding employed:	Yes ☐	No ☒
100% follow-up:	Yes ☐	No ☒	Reporting of losses by study arm	Yes ☒	No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
These patients are trauma patients with at least one life threatening injury treated in an ICU. These patients are critically ill.[AD]

Topic: Site of EN feeding (post-pyloric vs. gastric) + Rate of EN (full strength vs. step up dose)

RefID **166**

Reference: (Taylor et al. 1999)

Patient Population: Head injured patients.

Study entry criteria: Head injury requiring IMV, best GCS > 3, at least one reactive pupil within first 24 hours, > 10 years old, inability to take oral nutrition for more than 24 hrs, capacity to be fed enterally within 24 hrs of onset of injury.

Study intervention/s: Pts were randomised to receive 1) a pH sensor tube which was blindly placed into the intestine, if this could not be achieved, gastric placement was accepted. vs. 2) orogastric or nasogastric tubes.
A gastric residual (GR) of less than or equal to 200mls was defined as the accepted threshold of tolerance for group 1. All intervention patients (Group 1) received full feeding from day 1 of ICU admission. Tolerance for group 2 was set to less than or equal to 150 GR and was checked q4hrs. Control patients (group 2) received 15ml/hr initial gastric feeding increasing to the target rate in the increments 30, 60 and 90ml/hr, as tolerated, to full feeding. Feeding was from 6am to 12pm only.
The formula used for both groups was Fresubin 750 (1.5Cal/ml and 12gN/L) for >12yrs old or Entera (1500Cal/L and 9gN/L) for those 10-12 yrs old. Estimated requirements were calculated as per protocol documentation for both groups.

Total number of patients randomised: 82 pts were randomised (41 vs. 41)

Outcome by study arm:

Outcomes Reporting
5 deaths in intervention (group 1) vs. 6 deaths in control (group 2)

Intention to Treat Mortality
Six Month mortality:
5/41 intervention (group 1) vs.
6/41 controls (group 2)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
Only 34% (14/41) of group 1 patients had intestinal tubes placed successfully [FS].
Head injured patients requiring mechanical ventilation. Will be admitted to ICU and were therefore critically ill.[AD]

Topic: Site of EN feeding (post-pyloric vs. gastric)

RefID **302**

Reference: (Boivin and Levy 2001)

Patient Population: Medical, surgical and neuroscience intensive care patients. 99% were intubated and 53% were trauma patients.

Study entry criteria: All patients over the age of 18 in whom a decision was made to feed enterally by the treating team.

Study intervention/s: Patients were randomised to receive: 1) transpyloric feeding. vs. 2) gastric feeding (nasogastric or orogastric) with erythromycin (200mg iv q8h for 96 hrs).All transpylorically fed patients received a single dose of 200mg erythromycin iv 30 min prior to a 10-Fr weighted tube being placed . The tube was then advanced 100cm with the air insufflation technique. In the case of failure of placement, an unweighted feeding tube was used for placement with the above technique repeated. Time to intensive care feeding commencement was not stated for either group.

Total number of patients randomised: 80 (40 vs. 40)

Outcome by study arm:

Outcomes Reporting

- one patient was withdrawn due to age exclusion alter enrollment but prior to receiving feeding (group 2)
- one patient was withdrawn from the transpyloric group (group 1) due to withdrawal of physician consent

Intention to Treat Mortality

7+1/40 transpyloric (group 1) vs.
7+1/40 gastric with erythromycin (group 2)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):

Reporting of loss to follow-up by study arm allows conservative assumptions for ITT analysis (GSD).
Time to placement of gastric tubes was 13 minutes vs 5 hours in the transpyloric group. [FS]
Patients were recruited in the medical, neurosurgical and surgical ICU. Patients are critically ill adults.[AD]

Topic: Site of EN feeding (post-pyloric vs. gastric)

RefID **324**

Reference: (Esparza et al. 2001)

Patient Population: Medical ICU patients.

Study entry criteria: Not explicitly stated.

Study intervention/s: Patients were randomised to receive 10-Fr feeding tube placed in: 1) the transpyloric position placed with the aid of erythromycin, metclopramide or fluoroscopy as necessary. vs. 2) gastric position.
All patients were fed Perative (an immunoenhanced formula), commencing at 20ml/hr and advanced 20ml every 4 hrs until goal rate achieved. Gastric residuals of greater than or equal to 150mls saw feeds ceased for 4 hrs and then resumed as per protocol if residuals were less than or equal to 150mls. Prokinetics were given at the discretion of the treating physician if gastric residuals remained elevated greater than 24hrs. Time to intensive care feeding commencement was not stated for either group.

Total number of patients randomised: 54 patients (27 vs. 27)

Outcome by study arm:

Outcomes Reporting
- all outcomes are reported

Intention to Treat Mortality
ICU Mortality (censored at day 8 post randomisation):
10/27 transpyloric fed (group 1) vs.
11/27 gastric fed (group 2)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
NB – follow-up in this paper was conducted for duration of ICU feeding (not ICU stay) or 8 days, whichever was longer. This may be the absolute minimum acceptable duration of follow-up. [GSD]
On average group 1 was fed for 4.1 days and group 2 for 3.6 days [FS].
Medical intensive care unit, mostly on ventilators. Patients are critically ill adults.[AD]

Topic: Site of EN feeding (post-pyloric vs. gastric)

RefID 89

Reference: (Montejo et al. 2002)

Patient Population: Adult ICU patients from 14 units.

Study entry criteria: Patients over the age of 18yrs who were deemed to need enteral nutrition > 5 days.

Study intervention/s: Patients were randomised to receive feeding via: 1) a dual lumen nasogastrojejunal tube placed within 36 hours of admission via endoscopy, fluoroscopic guidance, blind technique or by echography or 2) a nasogastric tube placed at admission.
Feeding in both groups was begun within 36 hours of admission. Feeds were delivered continuously and aimed to provide half of estimated requirements within the first 24hrs of feeding commencement and to fully meet requirements within the first 48 hrs of feeding.

Total number of patients randomised: 101 patients (50 in group 1 and 51 in group 2)

Outcome by study arm:

Outcomes Reporting
- 19 pts died in Group 1
- 22 pts died in Group 2

Intention to Treat Mortality
ICU discharge mortality, right censored at day 28:
19/50 nasogastrojejunal (group 1) vs.
22/51 gastric (group 2)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
Duration of follow-up was ICU stay, which is relatively short. (GSD)
On average group 1 had their gastric tubes placed 5.3 hrs after admission vs the nasogastrojejunal group which had their tubes placed 21hrs after admission. Time to initiation of feeding was 24 hrs for both groups. [FS]
Study conducted in ICU, patients were critically ill.[AD]

Topic: Site of EN feeding (post-pyloric vs. gastric)

RefID **263**

Reference: (Davies et al. 2002)

Patient Population: Mixed (medical and surgical) ICU patients.

Study entry criteria: Any patient expected to require nutritional and critical care support for at least 3 days.

Study intervention/s: Patients were randomised to receive: 1) naso-jejunal feeding tube placed with endoscopic assistance vs. 2) nasally inserted gastric feeding tube.

Total number of patients randomised: 73 patients (34 jejunal pts vs. 39 gastric pts)

Outcome by study arm:

Outcomes Reporting
- ICU outcome is reported on all patients

Intention to Treat Mortality
ICU discharge mortality:
4/34 jejunally fed (group 1) vs.
5/39 gastrically fed (group 2)

Methodological issues:

Method of randomisation reported:	Yes ☒ No ☐	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
Randomisation was by 'sealed' envelope. Research has demonstrated the importance of using 'opaque' sealed envelopes in order to ensure the maintenance of allocation concealment. (GSD)
The time to start of enteral nutrition from ICU admission was longer in the jejunally fed group than the gastrically fed group (81 hrs vs 55 hrs respectively). [FS]
Randomised in the ICU. These patients are critically ill.[AD]

Topic: Site of EN feeding (post-pyloric vs. gastric)

RefID **427**

Reference: (Kortbeek et al. 1999)

Patient Population: Major trauma patients.

Study entry criteria: Within 72 hours of admission to ICU, ISS ≥ 16, projected to require mechanical ventilation for at least 48 hours.

Study intervention/s: Patients were randomised to receive: 1) fluroscopically guided duodenal feeding tubes vs. 2) gastric feeding tubes.
Jevity formula was provided to all patients. Enteral feeds were begun as soon as the feeding tube was inserted by commencing at 25ml and increasing the rate every 4 hours until individual goal rates were achieved.

Total number of patients randomised: 80 patients (37 duodenal feeds vs. 43 gastric feeds)

Outcome by study arm:

Outcome Reporting
- outcomes are reported in all patients randomised

Intention to Treat Mortality
Hospital mortality:
- **4/37** duodenal feeds (group 1) vs.
- **3/43** gastric feeds (group 2)

Methodological issues:

Method of randomisation reported:	Yes ☒ No ☐	Allocation concealed:	Yes ☒ Unclear ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
On average it took 30 minutes to arrange and insert the duodenal tubes [FS]
Time to intensive care feeding commencement was not stated for either group *although time to full strength feeding was 34 hrs (group 1) versus 43.8 hrs (group 2).*. [FS].
Trauma patients requiring mechanical ventilation. These patients are critically ill adults.[AD]

Topic: Site of EN feeding (post-pyloric vs. gastric)

RefID **379**

Reference: (Kearns et al. 2000)

Patient Population: Medical ICU patients.

Study entry criteria: All medical ICU patients who required mechanical ventilation and enteral nutrition.

Study intervention/s: Patients were randomised to: 1) small intestine feeding with a 12-Fr tube according to protocol vs. 2) gastric feeding tube tip placement.
Both groups received 10mg of IV metclopramide before enteral feed commencement. Time to intensive care feeding commencement was not stated for either group.

Total number of patients randomised: 44 patients were randomised (21 small intestine vs. 23 gastric)

Outcome by study arm:

Outcome Reporting

- one patient in each arm dropped out of the study because *the indication for nasoenteral intubation resolved after randomisation but before placement of the feeding tube*

Intention to Treat Mortality

ICU mortality:
5+1/21 small intestine (group 1) vs.
6+1/23 gastric (group 2)

Methodological issues:

Method of randomisation reported:	Yes ☒ No ☐	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
Mechanically ventilated patients in the ICU. These patients were critically ill.[AD]

Topic: Role of Prokinetics in enteral feeding.

RefID **237**

Reference: (Berne et al. 2002)

Patient Population: All critically injured patients who received intragastric tube feedings within 72 hours of admission to the ICU.

Study entry criteria: At least one gastric residual greater than 150mls during the first 48hrs of stay.

Study intervention/s: Patients were randomised to either
1) erythromycin lactobionate (250mg of intravenous erythromycin administered every 6hrs) or
2) placebo (an equivalent volume of 5% dextrose in water q6h).

Treatment was continued until gastric feeding was no longer required or until the patient was discharged from the hospital. Patients with continued intolerance 48hrs after randomisation were changed to metoclopramide.
Impact with fibre (an immuno-enhanced formula) was advanced by 30ml every 4 hours to a predetermined rate in both groups. Average time to intensive care feeding commencement was not stated for either group.

Total number of patient's randomised: 68 patients (32 erythromycin group and 36 placebo group).

Outcome by study arm:

Outcome Reporting
Outcomes were reported in all patients.

Intention to Treat Mortality
Hospital mortality
2/32 (erythromycin group, group 1)
2/36 (placebo group, group 2)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☒ No ☐
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
IF all patients who were still intolerant at 48 hours were changed to metoclopramide, as stated in the protocol, this is actually a comparison of early erythromycin vs. late metoclopramide. [GSD]
Critically ill trauma patients. Average duration of ventilation of approx 11 days and 13 day median IC stay. These patients are critically ill.[AD]

Topic: Role of Prokinetics in enteral feeding.

RefID **377**

Reference: (Chapman et al. 2000)

Patient Population: Mechanically ventilated intensive care patients with no history of gastrointestinal surgery.

Study entry criteria: A gastric aspirate greater than or equal to 250mls at least 6 hrs after commencing enteral feeding at greater than or equal to 40ml/hr.

Study intervention/s: After the initial aspirate (greater than or equal to 250mls) was discarded, the enteral feed (Ensure formula administered via a 14-Fr or larger nasogastric tube) was continued at the same rate for 3 hours. Patients were then randomised to receive either
1) a single dose of intravenous erythromycin (200mg in 20mls saline) or
2) placebo
The dose was given over 20 minutes. The residual gastric contents were then aspirated and recorded 1 hour after the dose was given. On average the groups were fed for 1.6 (group 1) and 1.4 days (group 2) before the study was commenced. Time to intensive care feeding commencement was not stated for either group.

Total number of patient's randomised: 20 patients (10 erythromycin vs 10 placebo)

Outcome by study arm:

Outcome Reporting
Outcomes are reported on all patients.

Intention to Treat Mortality
Hospital Mortality
2/10 (erythromycin, group 1)
2/10 (placebo, group 2)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☒ No ☐
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
Patients are mechanically ventilated in an ICU. These patients are critically ill.[AD]

Topic: Role of Prokinetics in enteral feeding.

RefID **590**

Reference: (Spapen et al. 1995)

Patient Population: Haemodynamically stable, sedated and mechanically ventilated patients.

Study entry criteria: Sedated patients on IMV requiring enteral feeding.

Study intervention/s: Critically ill patients were randomised to receive either
1) 10mg of cisapride four times a day or
2) no cisapride (enteral nutrition only).

Both groups received a standard enteral feeding protocol of either Sondalis Iso (1 Cal/ml) or its high protein analog (Sondalis HP) which increased by 25ml/day until individual goals were achieved.
All patients received a 24-hr intravenous infusion of either 1200mg of cimetidine or 200mg of ranitidine, aiming at an intragastric pH of >4. Time to intensive care feeding commencement was not stated for either group.

Total number of patient's randomised: 21 patients (11 patients received cisapride and 10 patients received no cisapride)

Outcome by study arm:

Outcome Reporting
Outcomes reported on all patients.

Intention to Treat Mortality
Hospital Mortality
4/11 patients died (cisapride group, group 1)
7/10 patients died (no cisapride, group 2)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☒ No ☐	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
Baseline balance, with regards to severity of illness and other patient characteristics, was not reported [GSD]
Patients are mechanically ventilated in an ICU. These patients are critically ill.[AD]

Topic: Role of Prokinetics in enteral feeding.

RefID **385**

Reference: (Yavagal et al. 2000)

Patient Population: Adult intensive care patients.

Study entry criteria: Adult intensive care patients who required placement of a nasogastric tube for greater than 24 hours.

Study intervention/s: Patients were randomised to either
1) metoclopramide (10mg q8hrs) or
2) placebo via nasogastric tube.
Standard nasogastric enteral feeding was provided to both groups as per the unit protocol (no further details given). Time to intensive care feeding commencement was not stated for either group.

Total number of patient's randomised: 305 patients (131 received metoclopramide and 174 received placebo)

Outcome by study arm:

Outcome Reporting

Intention to Treat Mortality
Intensive care mortality
73/131 (metoclopramide group, group 1)
92/174 (placebo group, group 2)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☒ No ☐	Blinding employed:	Yes ☒ No ☐
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
Patients are admitted to an ICU. Overall mortality is approx 50%. These patients are critically ill.[AD]

Topic: EN & PN vs. EN alone

RefID **212**

Reference: (Herndon et al. 1989)

Patient Population: Patients with Burns > 50% TBSA

Study entry criteria: Consecutive patients presenting with > 50% TBSA

Study intervention/s: Patients were randomised to: 1) enteral nutrition with parenteral nutrition supplementation or 2) enteral nutrition only.
Enteral nutrition was begun upon the return of GI function with either milk or commercial formula. Parenteral nutrition (amino acids/dextrose/vitamins and minerals) was provided as per protocol. Caloric requirements for both groups were estimated using the Curreri formula (25 kcal/kg body weight/day + 40 kcal/%TBSA burned / day).

Total number of patients randomised: 39 consecutive admissions were randomised. 16 received enteral feeds supplemented by PN (group 1) and 23 received enteral feeds only (group 2).

Outcome by study arm:

Outcome Reporting
Outcomes were reported on all patients.

Intention to Treat Mortality
14 days after burn injury
10/16 enteral with PN supplementation (group 1)
6/23 enteral feeds only (group 2)
p<0.05

Methodological issues:

Method of randomisation reported:	Yes ☐	No ☒	Allocation concealed:	Yes ☐	Unclear ☒
Consecutive pts enrolled:	Yes ☒	No ☐	Blinding employed:	Yes ☐	No ☒
100% follow-up:	Yes ☒	No ☐	Reporting of losses by study arm	Yes ☒	No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
Milk was used as an enteral feed in some patients in the enteral feeding group [FS].
It is unclear as to when TPN was started [FS]
Burns patients with ≥ 50% BSA. These patients are critically ill.[AD]

Topic: EN & PN vs. EN alone

RefID **1175**

Reference: (Herndon et al. 1987)

Patient Population: Patients with Burns > 50% TBSA

Study entry criteria: Consecutive patients presenting with > 50% TBSA

Study intervention/s: Patients were randomised to: 1) enteral nutrition (upon return of GI function) with parenteral nutrition supplementation or 2) enteral nutrition upon return of GI function.
Enteral nutrition was begun upon the return of GI function with either milk or commercial formula (product not specified). Parenteral nutrition (amino acids/dextrose/vitamins and minerals) was provided as per protocol. Caloric requirements for both groups were estimated using the Curreri formula (25 kcal/kg body weight/day + 40 kcal/%TBSA burned / day).

Total number of patients randomised: 28 consecutive admissions were randomised. 13 received EN supplemented with PN (group 1) and 15 received EN alone (group 2).

Outcome by study arm:

Outcome Reporting
Outcomes were reported on all patients.

Intention to Treat Mortality
Hospital mortality
8/13 EN supplemented with PN (group 1)
8/15 EN only (group 2)

Methodological issues:

Method of randomisation reported:	Yes ☐	No ☒	Allocation concealed:	Yes ☐	Unclear ☒
Consecutive pts enrolled:	Yes ☒	No ☐	Blinding employed:	Yes ☐	No ☒
100% follow-up:	Yes ☒	No ☐	Reporting of losses by study arm	Yes ☒	No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
Milk was used as an enteral feed in some patients in the enteral feeding group [FS].
Patients with burns > 50% BSA. These patients are critically ill.[AD]

Topic: EN vs. Standard

RefID **511**

Reference: (Chuntrasakul et al. 1996)

Patient Population: Severe trauma

Study entry criteria: Injury severity score between 20 and 40.

Study intervention/s: Patients were randomised to receive: 1) early EN via NG-tube (± PN) or 2) IV fluids (5% dextrose and normal saline) and oral nutrition as soon as bowel function returned.

EN was begun immediately after resuscitation or surgery. If EN was insufficient, it was supplemented with TPN. Caloric requirements were calculated using the modified Harris Benedict equation. Traumacal was the EN formula used (1.5Cal/ml) which was begun at 30ml/hr (diluted 0.75Cal/ml) and increased in concentration until daily goals were met. TPN consisted of 10% dextrose, 12% amino acids and 10% lipids.

Total number of patients randomised: 38 patients were randomised: 21 to Group 1 and 17 to Group 2

Outcome by study arm:

Outcome Reporting
Outcomes are reported on all patients.

Intention to Treat Mortality
Hospital mortality:
1/21 Group 1 (EN supplemented with PN) vs.
3/17 Group 2 (oral diet at return of bowel function)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
It is unclear as to the number of patients in group 1 who received supplemental TPN [FS]
These patients were trauma patients with ISS 20-40, managed in a Trauma ICU. These patients were critically ill.[AD]

Topic: EN vs. Standard

RefID 3

Reference: (Page et al. 2002)

Patient Population: Esophagectomy patients (major upper GI surgery)

Study entry criteria: Esophageal resection for carcinoma.

Study intervention/s: On the morning following surgery, patients were randomised to receive: 1) enteral feeding or 2) control (IV crystalloids).

All patients received double lumen N-J tubes during surgery, prior to randomisation.
Group 1 received an isocaloric formula (1.048Cal/ml, 40g protein/L, formula name not provided) commencing at 25ml/hr and increasing q4hrs by 25ml/hr until goal rate achieved. Goal fluid rate was 35ml/kg body weight/day.
Group 2 received IV fluids consisting of 5% dextrose and 0.9% saline with potassium supplements as indicated. Oral intake was attempted in both groups on post-op day 4.

Total number of patients randomised: 40 patients were randomised: 20 to Group 1 and 20 to Group 2.

Outcome by study arm:

Outcome Reporting
Outcomes were reported on all patients.

Intention to Treat Mortality
Hospital mortality:
0/20 Group 1 (EN) vs
0/20 Group 2 (control IV dextrose)

Methodological issues:

Method of randomisation reported:	Yes ☒ No ☐	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☒ No ☐	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):

ICU admit rate and ICU LoS was not reported. Due to the low outcome rate in both groups and the relatively small group size, this study becomes ‘uninformative’.[GSD]
These patients were undergoing oesophageal resection via a thoraco abdominal approach. They may be admitted to an ICU. These patients are likely to be critically ill.[AD]

Topic: EN vs. Standard

RefID **1069**

Reference: (Cabre et al. 2000)

Patient Population: Severe alcohol induced hepatitis

Study entry criteria: Patients admitted less than 72 hours had to meet all the following: 1) suffering from AH diagnosed on clinical and biological grounds in the setting of recent heavy drinking and histological confirmation whenever possible; 2) presence of severe disease as defined by at least one of: a) Maddrey's discrimination function > 32 or b) spontaneous overt hepatic encephalopathy.

Study intervention/s: Patients were randomised to receive: 1) EN or 2) steroids.

Study treatment was begun no later than 72 hours post admission.Group 1 patients received sole nutrition support from an 2000Cal/d of Hepatical (1.3Cal/ml, 47 g protein/L, 23g fat/L, and 224g carbohydrate/L) for 28 days. Patients in the steroid therapy group received 40mg/day oral or IV prednisolone, once a day for 28 days. Patients in group 2 were also encouraged to eat 2,000Cal/day of a low sodium diet (goal of 1g/kg body weight/d).

Total number of patients randomised: 71 patients were randomised: 35 to Group 1 and 36 to Group 2.

Outcome by study arm:

Outcome Reporting
Outcomes are reported on all patients.

Intention to Treat Mortality
28 day mortality:
11/35 Group 1 (EN) vs
9/36 Group 2 (steroids)
One-year follow-up:
13/35 Group 1 (EN) vs.
19/36 Group 2 (steroids)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):

Although mortality rates are high, ICU admission rate and ICU LoS are not reported.[GSD]
Severe alcoholic hepatitis. The rates of complications and mortality make it likely that these patients ARE critically ill.[AD]

Topic: EN vs. Standard

RefID **747**

Reference: (De Ledinghen et al. 1997)

Patient Population: Bleeding esophageal varices

Study entry criteria: Patients receiving sclerotherapy or banding for bleeding esophageal varices.

Study intervention/s: Patients were randomised to receive: 1) EN or 2) control.

Group 1 received EN (Dripac Sondalis, a polymeric formula) from day 1 via a NGT through the second sclerotherapy session. Group 1 patients received 1665 Cal/d and 71 g protein/d from EN. On day 4 group 1 patients also commenced an oral diet as per group 2 regimen.
Group 2 received NPO until day 3, when a standard oral low sodium milk-based diet was introduced. Oral diet in group 1 and 2 consisted of 800Cal/d (day 4), 1400Cal/d (day 5) and 1800 Cal/d (day 6 and above).

Total number of patients randomised: 22 patients were randomised: 12 to Group 1 and 10 to Group 2.

Outcome by study arm:

Outcome Reporting
Outcomes were reported in all patients.

Intention to Treat Mortality
Hospital mortality:
3/12 Group 1 (EN) vs
2/10 Group 2 (control NPO for 3 days)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):

Although the mortality rate is rather high, ICU admit rate or ICU LoS are not reported.[GSD]
Group 1 received EN for an average of 8.6 days [FS]
Patients with cirrhosis and bleeding oesophageal varicies. These patients are likely to be critically ill.[AD]

Topic: EN Composition

RefID **226**

Reference: (Brinson and Kolts 1988)

Patient Population: Medical and Surgical ICU patients with hypoalbuminemia and MOF

Study entry criteria: All patients admitted to the study ICUs with two or more major organ system failures and albumin < 2.5 g/dl.

Study intervention/s: Patients were randomised to receive: 1) a peptide based feed (Vital HN) or 2) standard EN (Osmolite HN).

Both groups were fed via an 8-Fr NGT using 1 Cal/ml solutions containing 16.7% of calories as protein. EN was commenced at 50ml/hr ½ strength and increased by 25ml/day to a goal rate of 100ml/hr and then switched over to full strength feeding. Feeding goals were determined by nitrogen balance studies or 35Cal/kg ideal body weight to a maximum of 3L of formula/day. Patients were 'on-study' and received feeding for between 2 to 3 weeks, or until albumin reached 3 g/dl.

Total number of patients randomised: 14 patients were randomised: 7 to Group 1 and 7 to Group 2

Outcome by study arm:

Outcome Reporting

2 Group 2 patients died 6 and 12h post randomisation, but prior to receiving feeding.
2 Group 2 patients died during the study (2-3 wk follow-up)

Intention to Treat Mortality

Study follow-up mortality (5 to 21 days):
0/7 Group 1 (semi-elemental) vs
4/7 Group 2 (polymeric)

Methodological issues:

Method of randomisation reported:	Yes ☐	No ☒	Allocation concealed:	Yes ☐	Unclear ☒
Consecutive pts enrolled:	Yes ☐	No ☒	Blinding employed:	Yes ☐	No ☒
100% follow-up:	Yes ☒	No ☐	Reporting of losses by study arm	Yes ☒	No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):

Patients were present in the ICU anywhere between 9 and 143 (avg 38 days) days prior to randomisation. Mortality is not reported past the end of the study follow-up period, which ranged from 14 to 21 days (avg 16 days). Five day follow-up is not sufficiently long in this patient group.[GSD]
Patients in a medical or surgical ICU with evidence of multi-organ failure. These patients are critically ill.[AD]

Topic: EN vs. Standard

RefID **118**

Reference: (Pupelis et al. 2001)

Patient Population: Severe pancreatitis and peritonitis

Study entry criteria: Patients with severe acute pancreatitis according to the Atlanta classification system and APACHE II > 6 and patients with peritonitis secondary to GI perforation or bowel ischemia.

Study intervention/s: Patients were selected for 1) jejunal feeding or 2) control (IV electrolytes).

In Group 1, jejunal feeding was begun within 12 h post-op using full strength Nutrison Standard (polymeric formula) or Nutrison Pepti (oligopeptide formula). Formulas were commenced at 20-25ml/hr (full strength) to provide at least 300mls/day. Volume and speed of introduction of formula was individualised for each patient. Goal rate was 1000mls formula on day 3 post op.
Control patients received IV electrolytes until reintroduction of normal diet.

Total number of patients randomised: 60 patients were included in the study: 30 in Group 1 and 30 in Group 2

Outcome by study arm:

Outcome Reporting
Outcomes are reported on all patients.

Intention to Treat Mortality
Hospital mortality:
1/30 Group 1 (jejunally fed) vs.
7/30 Group 2 (control)
p=0.05

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):

All subjects were referred post-operatively to the ICU. 'Additional inclusion criteria' are described for patients 'recommended' for jejunal feeding, which include: consent, presence of a properly positioned and well-functioning N-J tube and no intraoperative evidence of ileus. [GSD]
Mean ICU stay was 13.9 days (group 1) and 16 days (group 2) [FS]
Patients with severe pancreatitis or secondary peritonitis. All pts were referred post-op to the ICU. These patients are critically ill.[AD]

Topic: EN Glutamine vs. PN

RefID **949**

Reference: (Hadfield et al. 1995)

Patient Population: Adult ICU patients.

Study entry criteria: Admitted to ICU and requiring more than 3 days of nutritional support.

Study intervention/s: Patients were randomised to receive: 1) EN supplemented with glutamine (Alitraq) vs. 2) standard TPN (Kabi 1 or Kabi 5, both of which contained no glutamine).

Requirements were calculated using the Harris Benedict Equation.
Total number of patients randomised: 24 patients were randomised: 13 to Group 1 (EN) and 11 to Group 2.

Outcome by study arm:

Outcome Reporting
Outcomes are reported for all randomised patients.

Intention to Treat Mortality
Hospital mortality:
2/13 Group 1 (EN) patients died vs
6/11 Group 1 (TPN) patients
p=0.08

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
It is unclear as to when feeding started in both groups in relation to ICU admission [FS]
Adult ICU patients for ≥ 72 hrs. Patients are critically ill.[AD]

Topic: EN Glutamine vs. EN

RefID 6

Reference: (Hallay et al. 2002)

Patient Population: Esophageal cancer patients

Study entry criteria: Patients requiring surgery for esophageal cancer.

Study intervention/s: Patients were randomised to: 1) glutamine rich EN (Stresson Multi-Fibre) vs. 2) glutamine poor EN (Nutrison Multi-Fibre).
Nutrison Multifibre consisted of 1Cal/ml, 41 g protein/L, 389g fat/L, 123g carbohydrate/L.
Stresson Multifibre consisted of 1.25Cal/ml, 75g protein/L, 13g glutamine/L, 417 g carbohydrate/L.
All EN was begun on post-op day 3 at 20ml/hr and increased to 1500-2000mls/day by post operative day 5.

Total number of patients randomised: 36 patients were randomised: 23 to Group 1 and 13 to Group 2.

Outcome by study arm:

Outcome Reporting
Outcomes are reported in all patients.

Intention to Treat Mortality
Hospital mortality:
2/23 Group 1 (glutamine EN) died vs
1/13 Group 2 patients

Methodological issues:

Method of randomisation reported:	Yes ☐	No ☒	Allocation concealed:	Yes ☐	Unclear ☒
Consecutive pts enrolled:	Yes ☐	No ☒	Blinding employed:	Yes ☐	No ☐
100% follow-up:	Yes ☒	No ☐	Reporting of losses by study arm	Yes ☒	No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
Average ICU LoS was reported between 7 and 11 days.[GSD]
Patients with oesophageal cancer. ICU LoS is reported as 7.7 to 11.9 days. These patients are likely to be critically ill.[AD]

Topic: EN Arginine vs. Standard EN

RefID **438**

Reference: (Atkinson et al. 1998)

Patient Population: Critically ill ICU patients.

Study entry criteria: Admitted to ICU for less than 48 hours and expected to stay in the ICU for 3 days or longer, with no contra-indications to EN feeding.

Study intervention/s: Patients were randomised to receive: 1) arginine enhanced EN (Impact) or 2) isonitrogenous, isocaloric EN.
Group 1 formula (Impact) consisted of 1.0Cal/ml, 134 g carbohydrate/L, 55.8 g protein/L (of which 12.5 g/L was L-arginine), 27.8 g fat/L. Group 2 formula was specially manufactured for the study was as listed above for group 1 excepting the absence of L-arginine. The target rate was 32Cal/kg/d and 1.8 g protein/d. Route of delivery was individually assessed.

Total number of patients randomised: 398 patients were randomised: 202 to Group 1 and 196 to Group 2.

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
8 patients were excluded from follow-up (5 in Group 1 and 3 in Group 2) due to 'errors in feed allocation after randomisation.'	Hospital mortality: **95+5 / 202** Group 1 (Impact) vs **85+3 / 196** Group 2 (Control)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☒ No ☐
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
It is unclear as to the average time to feeding commencement for both groups. Randomisation was within 48hrs of admission [FS]
The patients were all in the adult ICU. Most patients were mechanically ventilated. These patients are critically ill.[AD]

Topic: EN Arginine vs. Standard EN

RefID **159**

Reference: (Galban et al. 2000)

Patient Population: Septic ICU patients.

Study entry criteria: Greater than 14 years old, with sepsis at time of randomisation (Bone criteria) and APACHE II score ≥ 10 at time of ICU admission.

Study intervention/s: Patients were randomised to: 1) EN supplemented with arginine (Impact) or 2) control EN (Precitene Hiperproteico, also known as Nutrodrip Protein).

Group 1 formula (Impact) consisted of 1.0Cal/ml, 134 g carbohydrate/L, 55.8 g protein/L (of which 12.5 g/L was L-arginine), 27.8 g fat/L. Group 2 formula consisted of 1.22 Cal/ml, 148.2 g carbohydrate/L, 66.2 g protein/L, and 40.2 g fat/L. EN was started within 36 hours of the diagnosis of sepsis for both groups and increased to goal rate by study day 4. Goal rate was determined based on the Harris Benedict equation, and using a fixed stress factor of 1.3.Route of feeding was as per the physicians discretion.

Total number of patients randomised: 181 patients were randomised: 94 to Group 1 and 87 to Group 2.

Outcome by study arm:

Outcome Reporting

5 patients in Group 1 were excluded from follow-up due to not meeting inclusion/exclusion criteria (1 pt with myeloma, 1 pt with low APACHE II score, 1 with AIDS, 1 with tetanus and 1 who was pregnant). It is not clear whether these patients actually received feeds.

Intention to Treat Mortality

Hospital discharge mortality:
(17 + 5) / 94 in Group 1 (Impact) vs.
28 / 87 in Group 2 (Standard)

Methodological issues:

Method of randomisation reported:	Yes ☐	No ☒	Allocation concealed:	Yes ☐	Unclear ☒
Consecutive pts enrolled:	Yes ☐	No ☒	Blinding employed:	Yes ☐	No ☒
100% follow-up:	Yes ☐	No ☒	Reporting of losses by study arm	Yes ☒	No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):

It is somewhat concerning that all loss to follow-up was from one arm of the study. Reporting of outcomes from these patients would allow a true ITT analysis.[GSD]
Average time to feeding commencement was not stated for either group. It is noted that feeding was commence within 36 hrs of the diagnosis of sepsis [FS].
Patients were admitted to an ICU due to sepsis. Average APACHE II was round 18. These patients are critically ill.[AD]

Topic: EN Arginine vs. Standard EN + EN Composition (fats)

RefID **205**

Reference: (Gottschlich et al. 1990)

Patient Population: Burns patients.

Study entry criteria: Burns > 10% BSA, age ≥ 3, admitted within 5 days of burn.

Study intervention/s: Patients were randomised to: 1) EN supplemented with arginine (experimental formula); 2) standard EN (Osmolite plus ProMix RD, a protein powder) or 3) diluted standard EN (Traumacal).
Group 1 formula (experimental) consisted of 1.03 Cal/ml, 53.5 g protein/L (of which 6.1g was arginine), 13.9 g fat/L. Group 2 formula (Osmolite supplemented with ProMix RD protein powder) consisted of 1.09 Cal/ml, 55.8 g protein/L (with 1.9 g arginine), and 32.7 g fat/L. Group 3 formula (dilute Traumacal) consisted of 1.04 Cal/ml, 54.4g protein/L (of which 2.1g was arginine), 45.2 g fat/L.
Caloric goals were determined on admission by the Curreri formula and then by indirect calorimetry on a weekly basis. Goal requirements were determined to be 1.3 times the measured energy expenditure as per indirect calorimetry measurement.

Total number of patients randomised: 50 patients were randomised: 17 to Group 1, 14 to Group 2 and 19 to Group 3.

Outcome by study arm:

Outcome Reporting
Outcomes are reported on all patients.

Intention to Treat Mortality
Hospital discharge mortality:
2/17 Group 1 (arginine supplemented) vs.
1/14 Group 2 (added protein) vs.
7/19 Group 3 (dilute formula)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
Time to feeding commencement was not specifically stated for any of the groups. The formulas used are not commercially available (experimental formula) or are available but have been manipulated (Osmolite with added protein, dilute Traumacal) [FS]
Burns patients with TBSA ≥ 10%. Average burn size was 38 to 45%, average ventilator days was 9-14. These patients are critically ill.[AD]

Topic: EN Arginine vs. Standard EN

RefID **688**

Reference: (Cerra et al. 1991)

Patient Population: ICU patients

Study entry criteria: Polytrauma, major elective general surgery or major surgical infection requiring ICU admission > 5 days and requiring mechanical ventilation. Judged able to tolerate EN for 7 to 10 days.

Study intervention/s: Patients were randomised to: 1) EN supplemented with arginine (Impact) or 2) standard EN (Osmolite HN)
PN was begun for each patient within 24 hrs of injury and continued until they were admitted to the study (1.5-2.0 g/kg/day amino acids, 1.0g/kg/day IV fat, remaining calories as glucose to provide 30-35Cal/kg/day total).
Once randomised to the study a nasoduodenal tube was placed and feeds were started at full strength in order to reach goal rates by 36hrs of initiation. The Harris Benedict equation was used to determine estimated requirements with a fixed stress factor of 1.5.
Group 1 formula (Impact) consisted of 1.0Cal/ml, 130 g carbohydrate/L, 58.8 g protein/L (of which 12.5 g/L was L-arginine), and 27.8 g fat/L. Group 2 (Osmolite HN) consisted of 1.06 Cal/ml, 133.6 g carbohydrate/L, 42 g protein/L, and 34.8 g fat/L.

Total number of patients randomised: It is reported that 20 patients completed the study 11 in Group 1 and 9 to Group 2. It is unclear if 22 patients were randomised due to the reporting of '2 drop outs' who did not 'complete' the study.

Outcome by study arm:

Outcome Reporting

2 patients in Group 1 were drop-outs with regards to nutritional outcomes due to: 1 pt feeding tube dislodgment and 1 pt no tube feedings for 24 h.
1 additional Group 1 patient was lost to follow-up by 12 months.

Intention to Treat Mortality

Reported 6 month mortality was:
4 / 11 (or ***4+2 / 13***) Group 1 (Impact) vs.
1 / 9 Group 2 (control)
Reported 12 month mortality was:
(**5 + 1 loss to follow-up) /11** (or ***5+1+2/13***) Group 1 (Impact) vs.
3/9 Group 2 (control)

Methodological issues:

Method of randomisation reported:	Yes ☐	No ☒	Allocation concealed:	Yes ☒	Unclear ☐
Consecutive pts enrolled:	Yes ☐	No ☒	Blinding employed:	Yes ☐	No ☒
100% follow-up:	Yes ☐	No ☒	Reporting of losses by study arm	Yes ☒	No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
At least 5% loss to follow-up at 12 months. May be as high as 10% loss to follow-up at 6 months and 15% loss to follow-up at 12 months.[GSD]
EN was commenced on average 7-20 days after ICU admission in group 1 and 8-27 days in group 2 [FS].
Patients were in ICU ≥ 5 days and were receiving mechanical ventilation. These patients are likely to be critically ill.[AD]

Topic: EN Arginine vs. Standard EN (glutamine???)

RefID **1214**

Reference: (Saffle et al. 1997)

Patient Population: Burns patients.

Study entry criteria: All burns patients ≥ 4 yo anticipated to require EN for at least 7 days in whom EN could be started within 48 hours of injury.

Study intervention/s: Patients were randomised to: 1) EN enhanced with arginine (Impact) or 2) standard high protein EN (Replete).
Group 1 formula (Impact) consisted of 1.0Cal/ml, 134 g carbohydrate/L, 55.8 g protein/L (of which 12.5 g/L was L-arginine), 27.8 g fat/L. Group 2 formula consisted of 1.0Cal/ml, 113 g carbohydrate/L, 62.5 g protein/L (of which 2.36 g/L was arginine and 5.6 g/L was glutamine), 33g fat/L. Feeding in both groups was begun at 25ml/hr and increased by 25ml q4hrs until patients were receiving a goal intake of 30Cal/kg/day. Thereafter indirect calorimetry was used to estimate ongoing nutritional requirements (resting energy expenditure plus 10%).
Oral intake was permitted as tolerated.

Total number of patients randomised: 50 patients were randomised: 25 to Group 1 and 25 to Group 2.

Outcome by study arm:

Outcome Reporting

1 Group 2 patient was excluded from data analysis because his 'outcomes were influenced primarily by abdominal trauma and varied greatly from those of all other patients. Mortality is not reported for this patient.

Intention to Treat Mortality

Hospital mortality:
5 / 25 Group 1 (Impact) vs
3 +1 / 25 Group 2

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☒ Unclear ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☒ No ☐
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
Although mortality is not reported for the single post-hoc excluded patient, loss to follow up is 2% and the original Group of randomisation is reported. A conservative ITT can be calculated.[GSD]
Burns patients with average TBSA 35%. Over 50% had inhalational injury requiring an average ventilator days over 10. These patients are critically ill.[AD]

Topic: EN Arginine vs. PN and EN + PN vs. EN

RefID **518**

Reference: (Braga et al. 1995)

Patient Population: Gastric or pancreatic cancer surgery patients.

Study entry criteria: Curative operation for gastric or pancreatic cancer.

Study intervention/s: Patients were randomised to receive: 1) enteral diet (Impact) which is supplemented with arginine and omega-3 fats or 2) same enteral formula (Impact) with glycine replacing arginine and omega-6 fats replacing omega-3 fats or 3) TPN (isonitrogenous, isocaloric).

Daily feeding goal for all three groups was 25Cal/kg and 0.25g nitrogen/kg. Enteral diets were begun within 12 hours post-op by jejunostomy or nasojejunal tube. On first 4 days post-op, enteral intake was supplemented with PN in both groups.

Total number of patients randomised: 77 patients were randomised: 24 to Group 1 (Impact), 24 to Group 2 (modified Impact) and 27 to TPN.

Outcome by study arm:

Outcome Reporting

Intention to Treat Mortality
Hospital discharge mortality:
0/24 Group 1 (Impact) vs
0/24 Group 2 (EN) vs.
0/27 Group 3 (PN)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☒ No ☐	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):

No patient died during the post-operative course (hospital discharge). Due to the relatively small number of patients in each group, and the lack of mortality, this study becomes 'uninformative'.[GSD] It is unclear as to when was TPN started [FS]
Study started in the surgical ICU. These patients are likely to be critically ill.[AD]

Topic: EN Arginine vs. TPN

RefID **1219**

Reference: (Bertolini et al. 2003)

Patient Population: ICU patients with severe sepsis. (sub group of ongoing study)

Study entry criteria: ICU patients judged to need mechanical ventilation and artificial nutrition for at least 4 days. This paper focuses on a sub-group who had sepsis at time of randomisation.

Study intervention/s: Patients were randomised to: 1) EN enhanced with arginine (Perative, arginine 6.8g/L) or 2) TPN.
Perative consisted of 55% carbohydrate, 25% fat, 21% protein, and 1.3 Cal/ml. EN was started at 10Cal/kg and progressed to 25-28 Cal/kg by the forth day.
TPN consisted of 59% carbohydrate, 23% fat, 18% protein, 1.2 Cal/ml. Goal TPN was 25-28 Cal/kg/day.
Feeds were commenced within 48 hours of admission in all patients.

Total number of patients randomised: Of 237 patients randomised, 39 had severe sepsis at time of randomisation: 18 to Group 1 and 21 to Group 2

Outcome by study arm:

Outcome Reporting
Outcomes are reported on all patients.

Intention to Treat Mortality
ICU mortality:
8/18 Group 1 (Perative) vs.
3/21 Group 2 (PN)

28 day mortality:
8/18 Group 1 (Perative) vs.
5/21 Group 2 (PN)

Methodological issues:

Method of randomisation reported:	Yes ☒ No ☐	Allocation concealed:	Yes ☒ Unclear ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
These patients were in an ICU needing mechanical ventilation for at least 4 days. These patients ARE critically ill.[AD]

Topic: PN vs. EN + EN arginine vs. Standard EN (vs. PN)

RefID 518 (we should probably only include ref 1003)

Reference: (Braga et al. 1995)

Patient Population: Gastric or pancreatic cancer patients.

Study entry criteria: Curative operation for gastric or pancreatic cancer.

Study intervention/s: Patients were randomised to receive: 1) enteral diet (Impact) which is supplemented with arginine (12.5g/L) and omega-fats or 2) same enteral formula (Impact) with glycine replacing arginine, and omega-6 fats replacing omega-3 fats or 3) TPN (isonitrogenous, isocaloric).
Daily feeding goal for all three groups was 25Cal/kg and 0.25g nitrogen/kg. Enteral diets were begun within 12 hours post-op by jejunostomy or nasojejunal tube. On first 4 days post-op, enteral intake was supplemented with PN in both groups.

Total number of patients randomised: 77 patients were randomised: 24 to Group 1 (Impact), 24 to Group 2 (modified Impact) and 27 to TPN.

Outcome by study arm:

Outcome Reporting

Intention to Treat Mortality
Hospital discharge mortality:
0/24 Group 1 (Impact) vs
0/24 Group 2 (EN) vs.
0/27 Group 3 (PN)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☒ No ☐	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):

No patient died during the post-operative course (hospital discharge). Due to the relatively small number of patients in each group, and the lack of mortality, this study becomes 'uninformative'.[GSD] It is unclear as to when was TPN started [FS]
Study started in the surgical ICU. These patients are likely to be critically ill.[AD]

Topic: EN arginine vs. Standard EN (vs. PN) + PN vs. EN + EN&PN vs. PN

RefID **1003**

Reference: (Gianotti et al. 1997)

Patient Population: Gastric or pancreatic cancer patients.

Study entry criteria: Curative operation for gastric or pancreatic cancer.

Study intervention/s: Patients were randomised to receive: 1) enteral diet (Impact) which is supplemented with arginine (12.5 g/L) and omega-3 fats or 2) standard enteral formula with glycine replacing arginine and omega-6 fats replacing omega-3 fats (prepared by Novartis) or 3) TPN (isonitrogenous, isocaloric).

Daily feeding goal for all three groups was 25Cal/kg and 0.25g nitrogen/kg. Enteral diets were begun within 6 hours post-op by jejunostomy or nasojejunal tube. On first 4 days post-op, enteral intake was supplemented with PN in both groups.

Total number of patients randomised: 260 patients were randomised: 87 to Group 1, 87 to Group 2 and 86

Outcome by study arm:

Outcome Reporting
Outcomes were reported in all randomised patients.

Intention to Treat Mortality
Hospital discharge mortality:
1/87 Group 1 (Impact) vs.
2/87 Group 2 (Standard EN) vs.
2/87 Group 3 (TPN)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):

It is unclear as to when was TPN started [FS]
Study started in the surgical ICU. These patients are likely to be critically ill.[AD]

Topic: EN Arginine vs. Standard EN (involves pre-op intervention)

RefID **1218**

Reference: (Snyderman et al. 1999)

Patient Population: Patients requiring surgery for head and neck cancer.

Study entry criteria: Patients with stage II-IV squamous cell carcinoma of the oral cavity, pharynx or larynx undergoing curative surgery and requiring post-op nutritional supplementation.

Study intervention/s: Patients were randomised to: 1) EN supplemented with arginine (Impact) 2) standard EN 3) pre and post-op Impact or 4) pre and post op standard feed.
Since Group 3 and 4 require pre-op intervention, only Group 1 and 2 will be considered.
Group 1 formula (Impact) consisted of 1.0Cal/ml, 134 g carbohydrate/L, 55.8 g protein/L (of which 12.5 g/L was L-arginine), 27.8 g fat/L. The standard EN (group 2) used a variety of different enteral formulas depending on the patient (Replete, Resource, Isosource, Jevity, Vivonex, or Osmolite formulas) although Replete was used in 78% of cases. Replete consisted of 25% protein (no added arginine), 30% fat and 45% carbohydrate.
Postoperatively, both groups aimed to receive at least 1000mls/day of formula for 7 days.

Total number of patients randomised: 136 patients were randomised:

Outcome by study arm:

Outcome Reporting

7 patients were withdrawn from the study pre-operatively. Outcomes for these patients are not reported.

Intention to Treat Mortality

Mortality:
0 / 82 Group 1 and 3 (post-op and pre and post-op Impact)
0 / 47 Group 2 and 4 (post-op and pre and post-op standard feed)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☐ No ☒

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):

No mortality events are reported for any patients. Additionally, direct comparisons between Group 1 and Group 2 were not conducted. This paper represents a factorial design but is not reported appropriately. It is not possible to compare the effects of the post-op diets directly. This study in uninformative.[GSD]
It is unclear as to time of commencement of postoperative feeding in both groups [FS]
Patients having ENT/otolaryngeal surgery for cance rof orcal cavity, plarynx or larynx. ICU LoS 7-10 days. These patients are likely to be critically ill.[AD]

Topic: EN Arginine vs. standard EN

RefID 13

Reference: (Kemen et al. 1995)

Patient Population: Patients with upper GI cancer.

Study entry criteria: Patients with upper GI cancer who were to undergo major abdominal surgery.

Study intervention/s: Patients were randomised to receive: 1) arginine enhanced EN (Impact) or 2) isocaloric, isonitrogenous placebo diet (name not stated).
Group 1 formula (Impact) consisted of 1.0Cal/ml, 134 g carbohydrate/L, 56 g protein/L (of which 12.5 g/L was L-arginine), 28 g fat/L. Group 2 formula was exactly the same in terms of the above macronutrients excepting it did not contain any L-arginine. Feeding was via a needle catheter jejunostomy, which was placed intraoperatively, with feeding commencing postoperative day 1. Feeding began at 20ml/hr and aimed to provide 25Cal/kg/day by postoperative day 5.

Total number of patients randomised: 44 patients were randomised: 22 to Group 1 and 11 to Group 2.

Outcome by study arm:

Outcome Reporting

"On review of eligibility criteria" 2 patients were deemed 'ineligible'. 1 due to inadvertent j-tube removal within 3 days of placement and 1 due to death within 48 hours post-op. One patient in each group. The early death was not attributed to a particular group and outcome was not reported for the other patient. 4.5% loss to follow-up.

Intention to Treat Mortality

Hospital discharge mortality:
0+1 / 22 Group 1 (Impact) vs.
0+1 / 22 Group 2

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☒ No ☐	Blinding employed:	Yes ☒ No ☐
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☐ No ☒

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):

Although the methods section reports that 'deaths were recorded' clinical outcomes are not explicitly reported, except for the 1 excluded patient. Conservative ITT analysis based on mortality uses only 'excluded' patients.[GSD]
Patients undergoing major GI surgery for upper GIT malignancy. APACHE II on day 1 was 11.5. These patients are likely to be critically ill.[AD]

Topic: EN Composition: Carbohydrate/Fats %Fat calories and type of Fat

RefID **1191**

Reference: (Garrel et al. 1995)

Patient Population: Burns patients

Study entry criteria: Thermal injury > 20% TBSA (not including 1st degree burn), admitted within 24 hours of burn injury.

Study intervention/s: Patients were randomised to: 1) 15% of total calories as fat (50% of fat calories came from fish oils) 2) 15% of total calories as fat or 3) 35% of total calories as fat.

Groups 1 and 2 received the same amount of total calories from fat (15%), carbohydrate (60%) and proteins (25%). Group 1 received 50% of its fat calories as omega 3 fats, 40% from soybean oil and 10% from MCT oil. Group 2 received 80% of its fat calories from soybean oil and 20% from MCT oil.
Group 3 received 35% of total calories from fat, 40% from carbohydrate and 25% from protein. EN was begun within 24 hours of admission via a naso-enteral tube inserted via endoscopy. Starting rate was 30ml/hr and increased up to 60ml/hr depending on tolerance.
PN was started at the same time as EN in order to better meet requirements (Vamine, 20% glucose and 10% Intralipid). In those receiving EN and fish oils, fish oil (MaxEPA) was added via the feeding tube to ensure the patient received 50% of their fat calories from this source.
Oral intake was permitted and mirrored the energy composition of the enteral formula to which the patient had been randomised.
Individual goals were calculated using the Curreri formula and adjusted if required using indirect calorimetry (measured twice a week).

Total number of patients randomised: 43 patients were randomised: 13 to Group 1, 14 to Group 2 and 16 to Group 1.

Outcome by study arm:

Outcome Reporting
Outcomes are reported for all patients.

Intention to Treat Mortality
Hospital discharge mortality:
1/13 Group 1 (low fat, 50% fish oil) vs
2/14 Group 2 (low fat) vs
5/16 Group 2 (standard 35% fat)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☒ Unclear ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☒ No ☐
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
The three enteral formulas used in this study were made especially for the study [FS]
Patients with burns. Average 40% TBSA, approx 50% had inhalational injury. PaO2/FiO2 ratio < 200 suggests mechanical ventilation was required in a significant number. These patients are critically ill.[AD]

Topic: PN Glutamine vs. PN

RefID **507**

Reference: (Griffiths et al. 1997)

Patient Population: ICU patients who did not tolerate EN

Study entry criteria: Patients with an admission APACHE II score > 11 who did not tolerate EN within 48 hours post-admission or who had the following contraindications to EN at admission: major intra-abdominal sepsis; bowel resection; pancreatitis; or heavily bile-stained gastric aspirate > 1L in 24h in ventilated patients with major trauma or non-GI sepsis.

Study intervention/s: Patients were randomised to: 1) Glutamine enriched PN vs 2) standard PN.

Three litre all-in-one solutions were used for both groups and contained 15.5 g nitrogen, 2300 non-nitrogen calories (500mls of 20% lipid (Elolipid), 500mls 20% glucose, and 500mls 50% glucose). Group 1 received 2.5% of their amino acids in the form of L-glutamine, group 2 received no glutamine.

Total number of patients randomised: 84 patients were randomised: 42 to Group 1 and 42 to Group 2.

Outcome by study arm:

Outcome Reporting
Outcomes are reported in all patients.

Intention to Treat Mortality
Hospital mortality:
18/42 Group 1 (glutamine) vs
25/42 Group 2
6 month mortality
18/42 Group 1 (glutamine) vs
28/42 Group 2
p=0.049

Methodological issues:

Method of randomisation reported:	Yes ☒	No ☐	Allocation concealed:	Yes ☒	Unclear ☐
Consecutive pts enrolled:	Yes ☐	No ☒	Blinding employed:	Yes ☒	No ☐
100% follow-up:	Yes ☒	No ☐	Reporting of losses by study arm	Yes ☒	No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
Both groups were in hospital 5 days before feeding commenced (2 of these days were in ICU) [FS]
Patients in an ICU, APACHE ≥ 11 with an expected protracted illness. Most patients were receiving mechanical ventilation. APACHE score 17 to 18. These patients were critically ill.[AD]

Topic: PN Glutamine vs. PN

RefID 87

Reference: (Powell-Tuck et al. 1999)

Patient Population: Patients referred to nutrition team for PN.

Study entry criteria: Patients referred to nutrition team for PN.

Study intervention/s: Patients were randomised to: 1) PN supplemented with glutamine or 2) standard PN.
Both groups received the same TPN (composition not provided) excepting that group 1 received 20g glutamine as a proportion of the amino acid content.

Total number of patients randomised: 168 patients were randomised *but only 42 of these were ICU patients: 17 to Group 1 and 25 to Group 2.*

Outcome by study arm:

Outcome Reporting
Outcomes are reported on all patients.

Intention to Treat Mortality
Hospital discharge mortality (ICU patients):
10/17 Group 1 (glutamine) vs
9/25 Group 2

Methodological issues:

Method of randomisation reported:	Yes ☒ No ☐	Allocation concealed:	Yes ☒ Unclear ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☒ No ☐
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
It is unclear as to when feeding started in both groups [FS]
Patients who were referred for TPN. 25% required an ICU admission. TPN was used for median of 7 to 8 days. These patients are likely to be critically ill.[AD]

Topic: PN L-alanyl-L-Glutamine vs. PN

RefID **600**

Reference: (Tremel et al. 1994)

Patient Population: ICU patients.

Study entry criteria: Stable ICU patients within 2 days of admission.

Study intervention/s: Patients were randomised to receive: 1) PN supplemented with L-alanyl-L-glutamine or 2) isonitrogenous, isocaloric PN.

Both groups received 0.26 g nitrogen/kg/day (1.5 g amino acids/kg/day) and 155kj/kg/day (~37Cal/kg/day). 60% of nonprotein energy came from glucose-fructose-xylitol (CombiSteril FGX) and 34% from lipid (Lipovenos 20%). Group 1 received 300mg/kg/day alanyl glutamine as part of their protein intake (Aminosauren 10% DP solution); group 2 received no glutamine (Traumasteril 10% solution).

Total number of patients randomised: 12 patients were randomised: 6 to Group 1 and 6 to Group 2.

Outcome by study arm:

Outcome Reporting

Intention to Treat Mortality
No mortality events are reported over the **9 day follow-up** period of the trial.
0/6 Group 1 (glutamine) vs
0/6 Group 2

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):

Due to the failure to report any mortality events and the relatively short duration of follow-up, this study becomes 'uninformative'.[GSD]
Patients were randomised in the ICU. These patients are likely to be critically ill.[AD]

Topic: PN BCAA vs. standard PN and PN Dose (30kcal/kg day vs. 15kcal/kg/day).

RefID **699**

Reference: (Iapichino et al. 1990)

Patient Population: Septic or traumatized patients.

Study entry criteria: Patients admitted to an ICU with sepsis (Bone criteria) and/or major trauma or major surgery.

Study intervention/s: Patients were randomised to: 1) High dose PN (30 Cal/kg body weight/day) enriched with BCAA; 2) High dose standard PN (30 Cal/kg body weight/day); 3) Low dose PN (15 Cal/kg body weight/day) enriched with BCAA; 4) Low dose standard PN (15 Cal/kg body weight/day)

Amino acid content of all solutions totalled 0.3 g nitrogen/kg/day and differed only in BCAA content. PN feeding began 24-36 hours after admission for all groups.

Total number of patients randomised: 16 patients were randomised. 4 patients were randomised into the trial twice (authors report outcomes by 4 groups of 5 patients each).

Outcome by study arm:

Outcome Reporting

Intention to Treat Mortality
ICU discharge mortality:
Low vs. High dose:
1/8 Low dose vs.
1/8 High dose
BCAA enriched vs Standard
2/6 BCAA enriched PN vs.
0/10 Standard PN

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):

16 patients were randomised to result in 4 groups of 5 patients each. 4 patients received treatment in 2 different groups (crossed over). The nutritional intervention lasted only 2 days. Mortality was reported at ICU discharge. 4 patients received more than one intervention. Conservative ITT analysis taking into account the group to which the patient was initially randomised and the factorial nature of the trial is presented above.[GSD]
Patients were admitted to the ICU with sepsis and trauma or surgery and sepsis. APACHE II 10 to 22. ISS 13 to 43. These patients were critically ill.[AD]

Topic: PN Dose, hypocaloric vs. normal

RefID **1180**

Reference: (Choban et al. 1997)

Patient Population: Obese patients

Study entry criteria: Obese patients > 130% IBW according to the formula of Hamwi and who required TPN.

Study intervention/s: Patients were randomised to receive: 1) hypoenergetic TPN or 2) standard TPN.

Goal protein intake for both groups was 2 g protein/kg ideal body weight/day. Group 2 (standard TPN group) received twice the amount of carbohydrate (150g/L vs 75 g /L) and fat (40g/L vs 20g/L) as group 1.

Total number of patients randomised: 30 patients were randomised: 14 to Group 1 and 16 to Group 2

Outcome by study arm:

Outcome Reporting
Outcomes are reported on all patients.

Intention to Treat Mortality
Hospital discharge mortality:
0/16 Group 1 (hypoenergetic) vs.
2/14 Group 2

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☒ No ☐
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):

Approximately 50% of patients were located in the ICU at time of randomisation. Randomisation was stratified by ICU location, so both arms were balanced with regards to location of patient at randomisation.[GSD]
Time to TPN commencement is not stated for either group [FS]
Obese patients who needed TPN. 13/30 were admitted to the ICU. APACHE II of those admitted to the ICU was 4-5. Hospital LoS was 15 to 29 days. Diagnoses were mostly cancer or pancreatic disease. These patients are likely to be critically ill.[AD]

Topic: EN intermittent vs. continuous

RefID **541**

Reference: (Bonten et al. 1996)

Patient Population: Mechanically ventilated ICU patients.

Study entry criteria: All mechanically ventilated patients admitted to a mixed ICU or cardiothoracic ICU were eligible whenever enteral nutrition was started and at least 3 days of ventilation was expected.

Study intervention/s: Patients were randomised to: 1) intermittent enteral feeding (continuous over an 18 hour period, from 8am-2am) vs. 2) continuous (24 hour) enteral feeding.

EN formula (Nutrison) was given intragastrically for both groups. Feeding was commenced at 6pm on study day 1, with 500mls of formula provided. Feeding rates for both groups increased by 500mls/day to a goal volume of 2,000ml/day by day 4 and thereafter. Gastric residuals of >400mls/day saw EN reduced or ceased in both groups.

Total number of patients randomised: 60 patients were randomised: 30 to each group

Outcome by study arm:

Outcome Reporting
Outcomes are reported in all patients.

Intention to Treat Mortality
ICU mortality:
2/30 Group 1 (intermittent) vs
4/30 Group 2
During study (14 day follow-up)
7/30 Group 1 (intermittent) vs.
2/30 Group 2
Conservative mortality from all reports:
7/30 Group 1 (intermittent)
4/30 Group 2

Methodological issues:

Method of randomisation reported:	Yes ☒	No ☐	Allocation concealed:	Yes ☐	Unclear ☒
Consecutive pts enrolled:	Yes ☐	No ☒	Blinding employed:	Yes ☐	No ☒
100% follow-up:	Yes ☒	No ☐	Reporting of losses by study arm	Yes ☒	No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):

The average duration of ICU stay after randomisation was approximately 8 to 9 days. 14 day follow-up reports additional mortality in Group 1 but less mortality in Group 2. A conservative interpretation should consider all known mortality events.[GSD]
On average patients spent 4.5 days (group 1) and 4 days (group 2) in ITU before EN was commenced [FS]
Patients were receiving mechanical ventilation in an ICU. Avg APACHE II 17 to 19. These patients are critically ill.[AD]

Topic: EN administration rate and site of feeding (gastric versus post pyloric)

RefID **175**

Reference: (Taylor 1999)

Patient Population: Mechanically ventilated head injury patients

Study entry criteria: Presence of head injury requiring mechanical ventilation (as determined by CT indicating significant risk of cerebral edema and increased ICP), best Glasgow Coma Scale score > 3 and at least one reactive pupil some time during the first 24 hours, age > 10, unable to take oral nutrition for at least 24 hours. Possible to start EN within 24 hours of injury.

Study intervention/s: Patients were randomised to: 1) feed started at a rate that would meet full estimated requirements or 2) feed rate started at 15ml/hr and increased to 30, 60 and 90 ml/hr as tolerated.

Energy expenditure was estimated using the Schofield equation plus an increment of 30% for head injury and 10% for diet-induced thermogenesis. Energy provided by the 10% Intralipid carrier for propofol and IV dextrose was deducted from goal caloric requirements. Nitrogen was supplied at 0.24g/kg/day for both groups excepting for obese patients (eg. BMI 30-40, 75% of nitrogen requirements were delivered to the patient).
Both groups received Fresubin 750 (if over 12 years old) which provided 1500Cal/L and 12g nitrogen/L. If 10-12 years of age, Entera formula was provided (1500Cal/L and 9g protein/L).
Group 1 received EN via enteric feeding (blind placement, radiologically confirmed), although in some cases where this was not possible feeding was given via the stomach. Group 2 received EN via orogastric or nasogastric tube.
Both groups had EN commenced within 24 hours of injury and given over a total of 18 hours (nil feeds 12 midnight – 6am). In Group 2, gastric residuals were aspirated every 2 hours. If two consecutive aspirates were < 50 ml, feed rate was increased. If aspirates were 50 to 150 ml, the rate remained the same. If aspirates were > 150 ml, the rate was reduced by 50%. Group 1 received EN at the full rate regardless of the gastric residual.
Total number of patients randomised: 82 patients were randomised: 41 to each group.

Outcome by study arm:

Outcome Reporting
Outcomes were reported in all patients.

Intention to Treat Mortality
6 month mortality:
5/51 Group 1 (full strength rate) vs.
6/41 Group 2

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
Only 34% (14/41) of group 1 patients had intestinal tubes placed successfully [FS].

These patients had severe head injuries and required mechanical ventilation. These patients are critically ill.[AD]
Topic: PN Composition: Selenium

RefID **1177**

Reference: (Angstwurm et al. 1999)

Patient Population: Septic patients.

Study entry criteria: Patients admitted to the ICU for less than 24 hours with APACHE II ≥ 15, meeting the criteria for SIRS due to suspected infection.

Study intervention/s: Patients were randomised to: 1) sodium selenite in decreasing doses for a total of 9 days (535 μg for 3 days followed by 285 μg for 3 days and 155 μg for 3 days, and thereafter 35 μg per day or 2) 35 μg per day.

Parenteral nutrition (PN) was started within the first 24 hours of treatment for both groups. PN consisted of 134 g/L of amino acids (20g/L of which was glutamine), 3.4g/kg/day of glucose and 700mg/kg/day of lipids.

Total number of patients randomised: 42 consecutive patients were enrolled: 21 into Group 1 and 21 into Group 2.

Outcome by study arm:

Outcome Reporting
Outcomes are reported in all patients.

Intention to Treat Mortality
Hospital discharge mortality:
7/21 Group 1 (se+) vs.
11/21 Group 2 (se control)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☒ No ☐	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
Patients with severe sepsis admitted to an ICU. APACHE score 17 to 19, ICU LoS 11 to 14 days. These patients are critically ill.[AD]

Topic: Indirect Calorimetry vs Curreri + EN Composition

RefID **911**

Reference: (Saffle et al. 1990)

Patient Population: Burns patients

Study entry criteria: All adult patients with TBSA > 25% who required enteral nutrition

Study intervention/s: This is a factorial trial. Patients were randomised to: 1) EN with target energy requirements calculated via Curreri formula OR 2) EN with target energy requirements calculated via indirect calorimetry. Patients were also randomised to: 3) Osmolite HN or 4) Isotein HN.

Energy requirements in group 2 (indirect calorimetry group) were undertaken three times a week using the MGM-II machine. Whenever possible measurements were made first thing in the morning. Total goal calories were equal to 1.2 X MEE. Patients were begun on enteral feedings as soon as fluid resuscitation was complete.
All patients were fed using a nasojejunal tube. Once the position of the tube was radiologically confirmed, feedings were commenced at 50ml/hr (full strength) and gradually increased to goal rate. The two formulas used differed primarily in their non-protein calorie-nitrogen ratio. Osmolite HN (1.06 Cal/ml, 16.7% of calories from protein, 53.5% of calories from carbohydrate, 30% of calories from fat) had a ratio of 125:1 and Isotein HN (1.04 Cal/ml, 22.4% of calories from protein, 52.2% of calories from carbohydrate, 25.3% of calories from fat) had a ratio of 86:1.
All patients were permitted access to oral diet as medically indicated, and enteral feeding ceased when patients were able to support themselves via oral diet alone.

Total number of patients randomised: 49 patients 'completed the study': 23 in Group 1, 26 in Group 2, 24 in Group 3 and 25 in Group 4.

Outcome by study arm:

Outcome Reporting
Outcomes are reported in all patients.

Intention to Treat Mortality
Hospital mortality:
Energy requirement
2/23 Group 1 (Curreri) vs.
3/26 Group 2 (Indirect calorimetry)
Feed composition
2/24 Group 3 (Osmolite) vs.
3/25 Group 4 (Isotein)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
Patients with thermal burns, average TBSA 47%. These patients are likely to be critically ill.[AD]

Topic: EN Composition: Acidified feeds

RefID **408**

Reference: (Heyland et al. 1999)

Patient Population: Critically ill patients.

Study entry criteria: Patients admitted to the ICU for less than 48 hours, expected to be ventilated for more than 48 hours and who were eligible to be fed enterally.

Study intervention/s: Patients were randomised to receive: 1) EN with a final pH of 3.5 vs. 2) EN with a final pH of 6.5.

Vital High Nitrogen was used as the base feed in both arms. Group 1 feeds were produced by adding 1 sachet of Vital HN to 2.2ml of 37% hydrochloric acid and 237.8mls of water. Group 2 feeds were produced by adding 1 sachet of Vital HN to 240mls water (pH 6.5).
Feeding was initiated within 48 hours of admission via a gastrically placed large or small bore feeding tube. All patients had their head of bed elevated at 30 degrees. Feeds commenced at 25ml/hr and increased q4hrs to goal rate, assuming gastric residuals (GR) were less than 200mls.If GR were greater than 200mls feeding was temporarily ceased. TPN was used if clinically indicated to optimise caloric intake.
Dietitian assessment determined energy requirements for each patient.

Total number of patients randomised: 120 patients were randomised: 61 to Group 1 and 59 to Group 2.

Outcome by study arm:

Outcome Reporting
Outcomes are reported on all 120 randomised patients.

Intention to Treat Mortality
Hospital discharge mortality:
15/61 Group 1 (acidified feeds) vs.
7/59 Group 2

Methodological issues:

Method of randomisation reported:	Yes ☒ No ☐	Allocation concealed:	Yes ☒ Unclear ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☒ No ☐
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):

Patients in an ICU expected to be ventilated for ≥ 48 hours. These patients are critically ill.[AD]

Topic: EN Composition: Immune-enhancing diet (Immun-Aid)

RefID **248**

Reference: (Kudsk et al. 1996)

Patient Population: Trauma patients

Study entry criteria: Severely injured patients requiring emergency celiotomy with Abdominal Trauma Index ≥ 25 and ISS ≥ 21 who had early enteral access.

Study intervention/s: Patients were randomised to receive: 1) EN enhanced with glutamine, arginine, nucleic acids and omega-3 fatty acids (Immun-Aid) vs. 2) isocaloric, isonitrogenous control EN.

Per litre group 1 formula (Immun-Aid) consisted of 1 Cal/ml, 13 g nitrogen/L, 120g carbohydrate/L, 22g fat/L. Group 2 formula (control EN) consisted of 0.99Cal/ml, 13g nitrogen/L, 123.2g carbohydrate/L, 24.6g fat/L. One litre of formula for group 2 was constructed using 4 cans of Promote (commercially available formula), 22g protein powder (Casec) and 50ml water.
EN was begun within 8 hours of surgery via a 7 French needle catheter jejunostomy tube or standard catheter (surgeons discretion), inserted distal to the ligament of Treitz. Feeding goals were to provide 0.32-0.38g nitrogen/kg/day.

Total number of patients randomised: 54 patients comprised the study population, 35 patients were randomised: 17 to Group 1 and 18 to Group 2.

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
1 patient in each Group died before day 5 and was excluded from outcome analysis.	Hospital mortality: **2/17** Group 1 (Immun-Aid) vs. **2/18** Group 2

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☒ No ☐
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
Patients without early enteral access at celiotomy served as controls.
The formula used in group 2 (control EN) is not commercially available. Feedings started at 1.63 days (group 1) and 1.97 days (group 2) [FS]
Patients had trauma and required urgent laparotomy. 2.6 to 5.4 days of mechanical ventilation, 5.8 to 9.5 days in the ICU. These patients are likely to be critically ill.[AD]

Topic: EN Composition: ornithine α-ketoglutarate (OKG)

RefID **476**

Reference: (De Bandt et al. 1998)

Patient Population: Burns patients.

Study entry criteria: Patients admitted to the ICU with thermal injury TBSA 20-50%.

Study intervention/s: Patients were randomised to 9 groups based on dose and route of ornithine α-ketoglutarate (OKG) administration: 1) 10g/day OKG as a single bolus, 2) 10 g OKG bolus bid, 3) 10 g OKG bolus tid , 4) 10 g/day OKG continuous (mixed with Osmolite feeds), 5) 20 g/day OKG continuous (mixed with Osmolite feeds), 6) 30 g/day OKG continuous (mixed with Osmolite feeds), 7) 10 g soy protein (Protil-1) per day (mixed with Osmolite feeds) , 8) 20 g soy protein (Protil-1) per day (mixed with Osmolite feeds), 9) 30 g soy protein (Protil-1) per day (mixed with Osmolite feeds).
Once fluid resuscitated, patients were fed Osmolite for 24-48 hours after burn. All groups were then changed to Dripsol 81 formula (1 Cal/ml, 18% protein, 23% fat and 59% carbohydrate) and fed continuously via nasogastric tubes. OKG or Protil-1 supplementation commenced on study day 2.When OKG was given as a bolus it was dissolved in 200mls of water and given via the enteral tube.
Individual nutritional requirements were estimated for all groups using the Harris Benedict equation. Energy intakes were gradually upgraded from 530Cal/day to 3500Cal/day by day 8 post injury. Nitrogen intake was also increased to a goal rate of 26g/day by day 8.

Total number of patients randomised: 54 patients were randomised: 5 to Group 1, 4 to Group 2, 6 to Group 3, 6 to Group 4, 6 to Group 5, 5 to Group 6, 6 to Group 7, 5 to Group 8 and 5 to Group 9.

Outcome by study arm:

Outcome Reporting
Outcomes are reported on all patients.

Intention to Treat Mortality
Hospital mortality:
1/5 Group 1 (10g single dose OKG)
1/4 Group 2 (10 g bid OKG)
0/6 Group 3 (10 g tid OKG)
1/6 Group 4 (10 g OKG continuous)
1/6 Group 5 (20 g OKG continuous)
1/5 Group 6 (30 g OKG continuous)
1/6 Group 7 (10 g soy)
0/5 Group 8 (20 g soy)
1/5 Group 9 (30 g soy)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
?Composition of Dripsol 81 (under table 1) seems to be quite different to the total diet combination [fs]
Patients with thermal burns admitted to a burns ICU. Avg TBSA 25 to 40%. These patients are likely to be critically ill.[AD]

Topic: EN Composition: ornithine α-ketoglutarate (OKG)

RefID **164**

Reference: (Jeevanandam and Petersen 1999)

Patient Population: Trauma patients.

Study entry criteria: Patients hospitalised in the trauma ICU.

Study intervention/s: Patients were randomised to: 1) EN (Two Cal HN) supplemented with OKG or 2) standard EN (Two Cal HN).

Two Cal HN was given to both groups (2Cal/ml, 13.4 g nitrogen/L, 17% of total calories comes from protein, 43% of total calories comes from carbohydrate and 40% of total calories from fat). Group 1 had 2.62g of their total nitrogen intake replaced with OKG. All patients were fed using nasoenteric tubes excepting one patient who had a surgically placed jejunostomy insitu. EN commenced at least 48-60 hours after injury.
Total number of patients randomised: 14 patients were randomised: 7 to each group

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
	Day 4 of EN (study outcome): 0/7 Group 1 (OKG) vs. 0/7 Group 2

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):

The follow-up time for this group of severely injured patients was 4 days post-onset of EN. This is probably not sufficiently long enough for this group of patients. In addition, since no mortality events were observed in either arm (by day 4), this study becomes 'uninformative'.[GSD]

Patients suffering from blunt or penetrating trauma in a trauma ICU. Avg ISS of 27. These patients are likely to be critically ill.[AD]

Topic: PN Lipids, Dose of PN.

RefID **496**

Reference: (Battistella et al. 1997)

Patient Population: Trauma patients

Study entry criteria: Trauma victims between the ages of 18 and 50 who required TPN on or after day 5 of injury.

Study intervention/s: Patients were randomised to receive: 1) TPN with intravenous fat emulsion (IVFE) or 2) TPN without IVFE.

Both groups received standard TPN, which was administered based on each patients ideal body weight. Group 1 (IVFE) aimed to receive 30 nonprotein calories/kg/day (25% of total calories coming from Intralipid) and 1.5g/kg/day amino acids. 10 or 20% Intralipid was provided overnight for 10-12 hours. Group 2 received the same TPN solution as group 1 except that they received no lipid component. As a result group 2 received a solution which was isonitrogenous but non-isocaloric.
TPN was started at half the goal rate on study day 1 and increased to goal rate on study day 2.
If TPN was commenced before day 5 of injury the patient was enrolled in the study but not randomised until day 5.

Total number of patients randomised: 57 patients were randomised: 30 to Group 1 and 27 to Group 2.

Outcome by study arm:

Outcome Reporting
Outcomes are reported on all randomised patients.

Intention to Treat Mortality
Hospital outcome mortality:
0/30 Group 1 (IVFE) vs.
2/27 Group 2

Methodological issues:

Method of randomisation reported:	Yes ☐	No ☒	Allocation concealed:	Yes ☐	Unclear ☒
Consecutive pts enrolled:	Yes ☐	No ☒	Blinding employed:	Yes ☐	No ☒
100% follow-up:	Yes ☒	No ☐	Reporting of losses by study arm	Yes ☒	No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
TPN was started on average 4 days (group1, IVFE group) and 5 days (group 2) after injury [FS]
Trauma patients who required TPN. APACHE II scores average 22-23, ICU LoS averaged 18-29 days and mechanical ventilation averaged 15-27 days. These patients are critically ill.[AD]

Topic: PN Lipids

RefID **717**

Reference: (Kari et al. 1989)

Patient Population: Critically ill patients.

Study entry criteria: Patients admitted to the ICU because of severe injury, infection or respiratory insufficiency.

Study intervention/s: Patients were randomised to receive PN with : 1) soy bean oil-egg phosphatide fat emulsion (Emulsan) as the lipid source vs 2) Intralipid as the lipid source.

On study day 0 all patients received 5% dextrose (2gm/kg) and electrolytes in water.
From study day 1-3 both groups then received 0.27gm/kg nitrogen, 4.3gm/kg glucose and 1.4g/kg lipid (either as Emulsan or Intralipid as randomised). On study day 4 groups then received no nitrogen, 2g/kg glucose and 40g total of lipid/day (either as Emulsan or Intralipid as randomised). From study day 5-7 groups then returned to the regime given on days 1-3 (ie. 0.27gm/kg nitrogen, 4.3gm/kg glucose and 1.4g/kg Emulsan or Intralipid as randomised.

Total number of patients randomised: 20 patients were randomised: 10 to each group

Outcome by study arm:

Outcome Reporting
Outcomes are reported in all patients.

Intention to Treat Mortality
30 day mortality:
2/10 Group 1 (Emulsan) vs.
2/10 Group 2 (Intralipid)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):

Patients admitted to ICU with severe injury, infection or respiratory insufficiency. These patients are likely to be critically ill.[AD]

Topic: PN Lipids - Long chain (LC) and medium chain fatty acids (MCFA) vs long chain fatty acids (LCFA)

RefID **437**

Reference: (Nijveldt et al. 1998)

Patient Population: Surgical ICU patients.

Study entry criteria: Surgical ICU patients expected to require at least 5 days of mechanical ventilation and needed TPN on clinical grounds. Patients met at least 3 of the 4 Bone criteria for sepsis.

Study intervention/s: Patients were randomised to receive: 1) TPN with 50% medium (MCT) and 50% long chain triglycerides (LCT) vs. 2) TPN with 100% long chain triglycerides (LCT).

When patients were deemed to be eligible for the study they received 2.5% glucose and 0.45% NaCl for 24 hours. At the same time 24 hour energy expenditure was measured via indirect calorimetry (Datex Deltrac). Patients received MEE plus 10% throughout the study. For both groups TPN was given in bags containing lipid, amino acids and glucose combined and was run continuously over the 24 hour period. Two thirds of the non-protein calories were given as glucose 40% for both groups. One third of calories were then given as either long chain triglycerides (Intralipid 20%) in group 2 or 50% MCT and 50% LCT in group 1. Nitrogen calorie ratio was 1:140.

Total number of patients randomised: 20 patients were randomised: 12 to Group 1 and 8 to Group 2.

Outcome by study arm:

Outcome Reporting
Outcomes are reported on all patients.

Intention to Treat Mortality
Hospital outcome mortality:
2/12 Group 1 (MCT and LCT) vs
1/8 Group 2

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☒ No ☐
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
It is unclear as to the length of time patients were hospitalised for before TPN was commenced [FS]
Patients in a surgical ICU with 5 days of mechanical ventilation. Average APACHE II score was 22. These patients were critically ill.[AD]

Topic: PN Lipids - Long chain (LC) and medium chain fatty acids (MCFA) vs long chain fatty acids (LCFA)

RefID 41

Reference: (Garnacho-Montero et al. 2002)

Patient Population: ICU patients with sepsis.

Study entry criteria: Patients undergoing surgery with peritonitis that met the Bone criteria for sepsis and were likely to require TPN for at least 10 days.

Study intervention/s: Patients were randomised to: 1) TPN with 10% medium/long chain triglycerides (Lipofundin) vs. 2) TPN with 10% long chain triglycerides (Intralipid).

TPN was initiated 48 hours after admission when haemodynamically stable. Group 1 received their fat source as Lipofundin (10% MCT/LCT) and group 2 received their fat source as Intralipid (10% LCT). Both groups received the same 45% BCAA nitrogen solution (6.9%FreAmine) given at a rate of 1.4 +- 0.2 g amino acids/kg/day. Caloric intakes were also similar between groups, with a calorie: nitrogen ratio of 1:130. 60% of calories were given as glucose and 40% as fat.

Total number of patients randomised: 72 patients were included: 35 in Group 1 and 37 in Group 2.

Outcome by study arm:

Outcome Reporting
Outcomes are reported in all patients.

Intention to Treat Mortality
Hospital discharge mortality:
11/35 Group 1 (MCT and LCT) vs.
13/37 Group 2

Methodological issues:

Method of randomisation reported:	Yes ☐	No ☒	Allocation concealed:	Yes ☐	Unclear ☒
Consecutive pts enrolled:	Yes ☐	No ☒	Blinding employed:	Yes ☐	No ☒
100% follow-up:	Yes ☒	No ☐	Reporting of losses by study arm	Yes ☒	No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
Patients were in a medical and surgical ICU with sepsis. ICU LoS was about 16 days. These patients are critically ill.[AD]

Topic: PN Lipids (Liposyn vs. Intralipid)

RefID **680**

Reference: (Jarnberg 1991)

Patient Population: ICU patients

Study entry criteria: Mechanically ventilated ICU patients in need of TPN for at least 7 days.

Study intervention/s: Patients were randomised to receive: 1) TPN with 20% Liposyn or 2) TPN with 20% Intralipid

TPN was commenced when patients had been haemodynamically stable for 24 hours.
Energy expenditure was calculated using the Harris Benedict equation and injury factors as appropriate. Calories were supplied as glucose 60% and fat 40%. 0.2g nitrogen/kg was also given to both groups. Glucose and amino acids were given continuously over 24 hours. Fat emulsions were given at a rate of 50ml/hr, commenced in the morning.

Total number of patients randomised: 27 patients were randomised: 14 to Group 1 and 13 to Group 2.

Outcome by study arm:

Outcome Reporting
Outcomes are reported on all patients.

Intention to Treat Mortality
Hospital discharge mortality:
2/14 Group 1 (Liposyn) vs.
2/13 Group 2 (Intralipid)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
Average time to commencement of TPN for either group was not stated [FS]
Patients in an ICU on mechanical ventilation and needing TPN > 7 days. These patients are likely to be critically ill.[AD]

Topic: PN BCAA vs. standard PN vs. IV glucose

RefID **201**

Reference: (Reilly et al. 1990)

Patient Population: Liver transplant patients

Study entry criteria: Patients were enrolled either immediately before or after liver transplant. All patients met clinical criteria for transplant and were treated with the conventional immunosuppressive regimen of cyclosporine or steroids.

Study intervention/s: Patients were randomised to 1 of three groups: 1) TPN enriched with BCAA; 2) standard TPN or 3) IV glucose control.

Groups 1 and 2 received isocaloric, isonitrogenous TPN solutions that provided 35 nonprotein Cal/kg/day and 1.5 g protein/kg/day. Identical "standard" hospital TPN solutions were used for both groups excepting the protein solution. In group 1 "Branchamin" was added to a 3.5% crystalline amino acid base solution to provide a total protein concentration of 5%. In group 2, a 5% crystalline amino acid solution was given (in 25% dextrose).
Group 3 received a standard isotonic intravenous glucose solution as determined by hydration status.
All groups commenced TPN or IV dextrose (as randomised) on the first postoperative day.

Total number of patients randomised: 28 patients were randomised: 10 to Group 1, 8 to Group 2 and 10 to Group 3.

Outcome by study arm:

Outcome Reporting
Outcomes are reported in all patients.

Intention to Treat Mortality
Hospital discharge mortality:
1/10 Group 1 (BCAA) patients died vs
0/8 Group 2 and
2/10 Group 3 (IV dextrose)

Methodological issues:

Method of randomisation reported:	Yes ☐	No ☒	Allocation concealed:	Yes ☐	Unclear ☒
Consecutive pts enrolled:	Yes ☐	No ☒	Blinding employed:	Yes ☐	No ☒
100% follow-up:	Yes ☒	No ☐	Reporting of losses by study arm	Yes ☒	No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
Patients with liver transplant. Average days in ICU between 3.6 to 6. These patients are critically ill.[AD]

Topic: PN 50.2% BCAA vs. PN 15.6% BCAA

RefID 11

Reference: (Von Meyenfeldt et al. 1990)

Patient Population: Patients with sepsis and patients with trauma.

Study entry criteria: Patients with sepsis or who had suffered multiple trauma, undergone surgery for ruptured abdominal aortic aneurysm, severe non-septic pancreatitis, major GI surgery or non-septic enterocolitis.

Study intervention/s: Patients were randomised to receive: 1) PN enhanced with 50.2% BCAA or 2) standard PN with 15.6% BCAA.
Both solutions were isonitrogenous (0.17 g nitrogen/kg body weight/day) and provided 30Cal/kg body weight /day. 15% of calories came from fat. Caloric intake was determined using the Harris Benedict equation using documented stress factors and a 10% factor for food.

Total number of patients randomised: 101 patients were randomised: 49 to Group 1 and 52 to Group 2.

Outcome by study arm:

Outcome Reporting
Outcomes are reported in all patients.

Intention to Treat Mortality
Hospital discharge mortality:
17/49 in Group 1 (50.2% enhanced BCAA) vs.
16/52 Group 2 (standard 15.6% BCAA)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☒ Unclear ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☒ No ☐
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
60% of patients required treatment in the ICU.[GSD]
It is unclear as to when TPN commenced for both groups [FS]
These patients were septic and traumatized. 61/101 were treated in an ICU. Diagnosis included 19/101 pancreatitis, 24/101 perforated viscous, 13/101 enterocolitis and 15/101 interabdominal abscess. These patients are likely to be critically ill.[AD]

Topic: PN 50.2% BCAA vs. PN 15.6% BCAA

RefID 1172 – NOTE: same data as presented in RefID 11

Reference: (Vente et al. 1991)

Patient Population: Septic and 'traumatized' patients.

Study entry criteria: Patients with sepsis, multiple traumas, ruptured abdominal aortic aneurysm or acute non-septic fulminant pancreatitis.

Study intervention/s: Patients were randomised to: 1) PN enriched with 50.2% BCAA or 2) standard PN with 15.6% BCAA.

Both solutions contained 800Cal/L of glucose, 5g nitrogen/L, with differing amounts of BCAA as above. Intravenous fat infusions were given at least twice a week depending on energy requirements.
Nonprotein energy intake was determined using the Harris Benedict equation, documented stress factors and a 10% factor for food.

Total number of patients randomised: 101 patients were randomised: 49 to Group 1 and 52 to Group 2.

Outcome by study arm:

Outcome Reporting
Outcomes are reported in all patients.

Intention to Treat Mortality
Hospital discharge mortality:
17/49 in Group 1 (enhanced BCAA) vs.
16/52 Group 2

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☒ Unclear ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☒ No ☐
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
60% of patients required treatment in the ICU.[GSD]
It is unclear as to when TPN commenced for both groups [FS]
These patients were septic and traumatized. These patients are likely to be critically ill.[AD]
NOTE: This appears to be the same data as published in RefID 11. Can only be included once, so will use RefID 11, which is an earlier paper.

Topic: PN BCAA vs. PN BCAA : various concentrations

RefID **934**

Reference: (Cerra et al. 1983)

Patient Population: Multiple trauma or major general surgery.

Study entry criteria: Patients admitted to a surgical ICU within 24 hours of trauma or major surgery.

Study intervention/s: Patients were randomised to one of four groups: 1) PN enhanced with 0.7g/kg/day BCAA (~46% of total protein content); 2) PN enhanced with 0.5g/kg/day BCAA (50% of total protein content); 3) PN enhanced with 0.3g/kg/day BCAA (20% of total protein content) and; 4) PN enhanced with 0.15g/kg/day BCAA (15% of total protein content)

Glucose calories were fixed at 30Cal/kg/day for all groups. Intravenous lipid calories differed between groups with groups 1 and 3 receiving 7 Cal/kg/day and groups 2 and 4 receiving no lipid. Total amino acid content also differed with groups 1 and 3 receiving 1.5 g/kg/day and groups 2 and 4 receiving 1 g/kg/day.
PN feeding commenced within 24 hours of surgery/trauma.

Total number of patients randomised: 32 consecutive patients were randomised: 8 to each group.

Outcome by study arm:

Outcome Reporting
Outcomes are reported at day 7 only.

Intention to Treat Mortality
No deaths were reported during the 7 day study:
0/8 Group 1 (46% BCAA) vs
0/8 Group 2 (50% BCAA) vs.
0/8 Group 3 (20% BCAA) vs.
0/8 Group 4 (15% BCAA)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☒ No ☐	Blinding employed:	Yes ☒ No ☐
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):

Due to the short follow-up time (7 days) and the lack of any mortality events during that time, this study is 'uninformative'.[GSD]
Patients were enrolled in a surgical ICU. These patients are likely to be critically ill.[AD]

Topic: PN 45% BCAA vs. PN 23% BCAA and PN dose

RefID **514**

Reference: (Garcia-de-Lorenzo et al. 1997)

Patient Population: Septic patients

Study entry criteria: Septic patients admitted to an ICU who were in need of PN within the first three days of ICU admission and for at least 11 days.

Study intervention/s: Patients were randomised to receive: 1) PN with 23% BCAA (FreAmine [R]10%) and total protein intake of 1.5g/kg/day; 2) PN with 45% BCAA (FreAmine 6.9%) and total protein intake of 1.5 g/kg/day or 3) PN with 45% BCAA (FreAmine 6.9%) and total protein intake of 1.1g/kg/day.

All groups received isocaloric TPN (24 nonprotein calories/kg/day) given as 60% glucose and 40% Intralipid (1g/kg/day). Groups differed in the amount of total protein they received and the percentage of BCAA as above.

Total number of patients randomised: 69 patients were randomised: 22 in Group 1, 25 in Group 2 and 22 in Group 3

Outcome by study arm:

Outcome Reporting

3 patients in group 2 died after randomisation but before the onset of treatment. Outcomes are reported for these patients.

Intention to Treat Mortality

Hospital discharge mortality:
10/22 in Group 1 (23% BCAA and 1.5 g/kg/day protein) vs.
5/25 in Group 2 (45% BCAA and 1.5 g/kg/day protein) vs.
6/22 in Group 2 (45% BCAA and 1.1 g/kg/day protein)

Methodological issues:

Method of randomisation reported:	Yes ☐	No ☒	Allocation concealed:	Yes ☒	Unclear ☐
Consecutive pts enrolled:	Yes ☐	No ☒	Blinding employed:	Yes ☐	No ☒
100% follow-up:	Yes ☒	No ☐	Reporting of losses by study arm	Yes ☒	No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
Average time to TPN commencement for all groups was not stated [FS]
Patients were septic and in an ICU. Average APACHE II scores were 15.7-17.7. These patients are critically ill.[AD]

Topic: PN 45% BCAA vs. PN 25% BCAA

RefID 10

Reference: (Van, III et al. 1985)

Patient Population: Surgical ICU patients

Study entry criteria: Patients with a 'state of severe stress' (Geller criteria level > 4 which is defined as trauma and surgery or sepsis and surgery or trauma, sepsis and surgery) projected to need PN for at least 7 days with at least a 50% chance of survival.

Study intervention/s: Patients were randomised to: 1) PN with 45% BCAA or 2) PN with 25% BCAA.
TPN goals for both groups were 1-1.5g total protein/day and 30-45 Cal/kg body weight/day. Both groups also received 500mls of Intralipid twice a week.

Total number of patients randomised: 12 patients were randomised: 6 to each group

Outcome by study arm:

Outcome Reporting
Outcomes are reported on all patients.

Intention to Treat Mortality
Hospital mortality:
1/6 Group 1 (45%BCAA) vs
4/6 Group 2 (25% BCAA)

Methodological issues:

Method of randomisation reported:	Yes ☐	No ☒	Allocation concealed:	Yes ☒	Unclear ☐
Consecutive pts enrolled:	Yes ☐	No ☒	Blinding employed:	Yes ☒	No ☐
100% follow-up:	Yes ☒	No ☐	Reporting of losses by study arm	Yes ☒	No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
Average time to TPN commencement for both groups was not stated [FS]
Patients were in a surgical ICU. 5/12 had blunt trauma to multiple regions and 2/12 had gunshots. These patients are likely to be critically ill.[AD]

Topic: EN Selenium + EN antioxidants

RefID **1190**

Reference: (Berger et al. 2001)

Patient Population: Severely injured patients.

Study entry criteria: Patients 18 to 75 years old admitted to the ICU within 24 hours of injury involving at least 2 body systems with ISS > 15.

Study intervention/s: Patients were randomised to receive: 1) 500ug IV Selenium (Se)/day for 5 days or 2) 500ug IV Se/day plus 150mg α-tocopherol/day and 13 mg zinc/day or 3) placebo.

Supplementation with either selenium and/or vitamin E was commenced on the day of admission to the ICU. EN or TPN was commenced between study day 3 and 5.

Total number of patients randomised: 32 patients were entered: 9 to Group 1, 11 to Group 2 and 11 to Group 3

Outcome by study arm:

Outcome Reporting

1 patient who was 'entered' was excluded due to prior hypothyroidism. It is unclear if this patient was randomised and if so, to which group.

Intention to Treat Mortality

Hospital outcome mortality:
2/9 Group 1 (Se) vs.
0/11 Group 2 vs.
1/11 Group 3,

Methodological issues:

Method of randomisation reported:	Yes ☐	No ☒	Allocation concealed:	Yes ☐	Unclear ☒
Consecutive pts enrolled:	Yes ☐	No ☒	Blinding employed:	Yes ☒	No ☐
100% follow-up:	Yes ☐	No ☒	Reporting of losses by study arm	Yes ☐	No ☒

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):

There was a 3.1% loss to follow-up.[GSD]
No details are provided regarding the feeding protocols for any of the above groups. "Nutritional support was similar in all groups…the total amount of calories did not differ between groups". "Seventeen patients required artificial nutrition". 7/9 patients in the selenium group (group 1) were fed using EN and no TPN was used, 4/11 patients in group 2 (selenium plus vitamin E and zinc) were fed via EN and again no TPN was used, 5/11 patients in group 3 (placebo group) were fed using EN and 1/11 fed using TPN. It is unclear as to what the remaining patients were fed [FS]
Patients were severely injured. Average APACHE II 11 to 13, ISS 30. Ventilator days between 4 and 6 with ICU LoS around 6 days. These patients were critically ill.[AD]

Topic: EN Trace Elements:

RefID **1188**

Reference: (Berger et al. 1998)

Patient Population: Burns

Study entry criteria: Burns patients with > 30% TBSA

Study intervention/s: Patients were randomised to receive EN plus: 1) additional supplements of copper, selenium and zinc IV (in a 0.9% NaCl solution) or 2) placebo (0.9% saline solution).

The additional trace element or placebo infusions were commenced on day of ICU admission.
Both groups received daily IV vitamin supplementation (1 vial of Cernevit, and 500mg of ascorbic acid), plus standard amounts of trace elements (Addamel N, 1 vial/day) given as a separate infusion. EN was commenced in both groups within 12 hours of ICU admission via a nasojejunal tube using Fresubin MCT (no further details provided). Feeding rate was slowly upgraded over the first 5 days of admission. Resting energy expenditure was determined in both groups on day 2 of admission via indirect calorimetry.

Total number of patients randomised: 20 patients were randomised: 10 to each group

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
	Hospital outcome mortality: 1/10 Group 1 (supplemented) vs 0/10 Group 2

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☒ No ☐
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
Patients had thermal injury with average TBSA 48%. APACHE II 10 to 13 with mechanical ventilation between 9 to 12 days. These patients are critically ill.[AD]

Topic: PN delivery regime

RefID **1017**

Reference: (Forsberg et al. 1994)

Patient Population: Trauma or major surgery patients

Study entry criteria: Mechanically ventilated post-operative patients.

Study intervention/s: Patients were randomised to receive: 1) continuous TPN or 2) cyclic (12 h) TPN.
Both groups had their energy expenditure determined daily (study day 1) and then twice daily (study days 2 and 3) using indirect calorimetry (Engstrom Metabolic computer).
A continuous low-energy glucose infusion was given to both groups during study day 1 (5.2Cal/kg body weight/hr).
On study days 2 and 3, the cyclic TPN group (group 2) received its TPN over 12 hours (10am-10pm). From 10pm-10am the cyclic TPN group (group 2) then received the low-energy glucose infusion (5.2Cal/kg body weight/hr). Group 1 (continuous TPN) received their TPN (glucose, fat and amino acids) continuously over the 24 hour period.
Both groups received a total energy supply equal to 1.3 times their basal energy requirement.

Total number of patients randomised: 16 patients were randomised: 8 to each group

Outcome by study arm:

Outcome Reporting

Intention to Treat Mortality
ICU mortality:
1/8 Group 1 (continuous) vs.
3/8 Group 2
Hospital mortality:
1/8 Group 1 (continuous) vs.
5/8 Group 2

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
Prior to study commencement, TPN had been given for an average of 5 days [FS]
Patients were mechanically ventilated for pneumonia, sepsis, trauma or abdominal surgery. These patients are critically ill.[AD]

Topic: Tube Placement

RefID **131**

Reference: (Huerta and Puri 2000)

Patient Population: Critically ill patients.

Study entry criteria: ICU patients with a tracheostomy or endotracheal tube, a functional GI tract and a high likelihood that their ICU stay would require a minimum duration of EN for 2 days and a maximum of 5 days.

Study intervention/s: Patients were randomised to receive: 1) 8 French feeding tubes placed under fluoroscopic guidance with the aid of metoclopramide (maximum of 20mg) or 2) feeding tube placed at the bedside and confirmed by x-ray.

Group 1 began EN shortly after abdominal x-rays confirmed duodenal tube position. Group 2 began EN once abdominal x-ray confirmed the tube was in the duodenum. Follow-up x-rays were requested at 10hrs and 24 hours after tube insertion if the tube was still not in the duodenum. EN was initiated 24 hours after tube insertion in group 2 if gastric placement was achieved, regardless of duodenal tube placement.
For both groups, EN commenced at 50ml/hr (1/2 strength) Isocal and increased to 50ml/hr (full strength) EN on day 2. Rate of EN then increased by 25ml/hr/day to a goal rate of 100ml/hr by day 4.

Total number of patients randomised: 32 patients were randomised: 17 Group 1 and 15 Group 2

Outcome by study arm:

Outcome Reporting

Intention to Treat Mortality
ICU discharge mortality:
4/17 Group 1 (fluoroscopic guidance) vs.
3/15 Group 2

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☒ Unclear ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
Duodenal tube placement was successful in 88.2% of group 1 patients and 20% of group 2 patients ($p<0.001$). Feedings were initiated at 2.2 (group 1) and 29.6 (group 2) hours after tube insertion ($p<0.01$). It is unclear as to the amount of time patients were in ICU before EN was commenced [FS]
Patients had a tracheostomy or an ETT, were in the ICU and predicted to need feeding for at least 2 days. All patients were enrolled in the ICU. These patients are critically ill.[AD]

Topic: EN Probiotics: *Lacobacilli* (TPN vs. EN)

RefID 79

Reference: (Rayes et al. 2002a)

Patient Population: Major abdominal surgery.

Study entry criteria: Adult patients undergoing elective laparotomy and resection of the liver, stomach, colon or pancreas.

Study intervention/s: Patients were randomised to receive: 1) EN plus Lactobacillus planatarum 299 and 11.3 g/L oat fibre given twice a day (5.5 g/L soluble fibre and 5.7g/L insoluble fibre) or 2) EN with heat killed Lactobacillus plantarum 299 and 11.3 g/L oat fibre given twice a day or 3) TPN until oral intake was possible.

EN groups (groups 1 and 2) were fed via a nasojejunal feeding tube, which was placed at the time of surgery. EN formula used was Nutrison L.EN Fibre (750Cal/L, 30g protein/L, 92 g carbohydrate/L, 29g lipid/L), and was started within 24 hours of surgery. TPN (group 3) was commenced on postoperative day 2 when 2L of standard TPN was given and 500mls of crystalloid. On postoperative day 4 onwards patients received 2.5L of standard TPN containing 4% lipid, 1800Cal/day, 70g protein/day. Oral intake began on day 5.

Total number of patients randomised: 90 patients were randomised: 30 to each group

Outcome by study arm:

Outcome Reporting
Outcomes are reported in all patients.

Intention to Treat Mortality
Hospital discharge mortality:
0/30 Group 1
0/30 Group 2
0/30 Group 3

Methodological issues:

Method of randomisation reported:	Yes ☒ No ☐	Allocation concealed:	Yes ☒ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
It was reported that no deaths occurred. This study is therefore 'uninformative'.[GSD]
Patients requiring elective laparotomy for liver resection, gastrectomy, colectomy or pancreatic surgery. The mean ICU stay was 2 to 3 days. These patients are likely to be critically ill.[AD]

Topic: PN vs. EN

RefID **586**

Reference: (Borzotta et al. 1994)

Patient Population: Severe closed head injury.

Study entry criteria: GCS ≤ 8, with coma persisting for at least 24 hours. Enrollment and randomisation had to occur within 72 hours of injury.

Study intervention/s: Patients were randomised to: 1) Parenteral (TPN) or 2) Enteral nutrition (EN) via surgically placed jejunal tube. All patients were fed within 72 hours of injury. TPN (Travasol) commenced at 40% of target rate for 24 hrs and then increased by 20% every 12 hrs until goal rate achieved. Full strength EN (Vivonex TEN) commenced at 20% of target rate for 12 hours and then increased by 20% every 12 hours until goal rate achieved. The enteral and parenteral formulas were designed to be isonitrogenous and isocaloric. On day 5 of feeding, efforts were made to start to convert all TPN patients to EN feeding.

Total number of patients randomised: 59 patients were randomised: 23 to Group 1 and 36 to Group 2.

Outcome by study arm:

Outcome Reporting

Group 1 (TPN)
-1 patient died on day 4, 1 was lost to follow-up due to a protocol violation (delayed feeding)
Group 2 (EN)
- 5 patients died, 3 were lost to follow-up due to protocol violations and 1 failed gut feeding and was switched to PN (lost to follow-up)

Intention to Treat Mortality

Hospital mortality
2 (1+1 lost to follow-up)/23 Group 1 (TPN) patients died or were lost to follow-up vs
9 (5+4 lost to follow-up)/36 Group 2 (EN) patients

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients.

Reviewer comments (and initials):
This paper contains 8.5% loss to follow-up (5 / 59).[GSD]
Patients with severe head injury, GCS ≤ 8 for > 24 hours. Patients were critically ill.[AD]

RCTs excluded from the primary analysis

The RCTs in this section were: found to have major methodological flaws; or were not on topic; or not conducted in critically ill patients; or were duplicate publications; or contained excessive loss to follow-up. Papers with < 10% loss to follow-up reported by study group, but no other major flaws, were included in the a priori defined sensitivity analysis.
Topic: Lactobacillus and fiber vs. selective bowel decontamination

RefID 77

Reference: (Rayes et al. 2002b)

Patient Population: Liver transplant recipients.

Study entry criteria: Adult patients undergoing orthotopic liver transplantation with side to side anastomosis of the bile duct.

Study intervention/s: Patients were randomised to one of three groups: 1) Standard EN plus selective bowel contamination, 2) Fibre containing EN plus live Lactobacillus plantarum 299 or 3) Fibre containing EN plus heat killed Lactobacillus plantarum 299.
Group 1 commenced feeding on postoperative day 2 using Fresubin formula (1000Cal/L, 38g protein/L, 138g carbohydrate/L, 34g lipid/L). Feeding commenced at 25ml/hr for the first 24 hours and when tolerated increased up to a goal rate of 75 ml/hr by postoperative day 3. EN was given via a nasojejunal tube placed with the tip behind the ligament of Treitz.
Group 2 and 3 received Nutrison L.EN Fibre within 24 hours of surgery (1000Cal/L, 40g protein/L, 123g carbohydrate/L, 29g lipid/L and 15g/L fibre). During the first 12 days of the study both groups 2 and 3 also received L Plantarum 299 twice a day (in a dose of 10X9). Group 2 received the L Plantarum 299 live and group 3 received the L Plantarum dead.
Clear fluid diet was commenced on postoperative day 1 for all three groups and increased as tolerated.

Total number of patients randomised: 105 patients were randomised:

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
10 patients did not complete the study (4 Group 1, 4 in Group 2 and 2 in Group 3) due to severe early complications. Outcomes are not explicitly reported in these 10 patients.	Hospital mortality: **0 + 4 / 36** Group 1 vs. **0 + 4 / 35** Group 2 vs. **0 + 2 / 34** Group 3

Methodological issues:

Method of randomisation reported:	Yes ☒ No ☐	Allocation concealed:	Unclear ☒ No ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):
Due to 9.5% loss to follow-up, this study cannot be considered further. Due to long reported ICU LoS, these patients are likely critically ill.[GSD]

Topic: EN Composition – High fat low carbohydrate EN vs standard EN

RefID 213

Reference: (Al Saady et al. 1989)

Patient Population: Patients requiring artificial ventilation due to chronic obstructive airways disease, pneumonia, asthma, brain damage or surgery.

Study entry criteria: Patients with acute respiratory failure requiring artificial ventilation, who could be fed enterally. Patients were eligible to remain in the study if they tolerated 48 hours of EN which met their goal requirements whilst still ventilated.

Study intervention/s: Patients were randomised to receive either 1) High fat low carbohydrate EN (Pulmocare) or 2) Standard EN (Ensure Plus).
Pulmocare consisted of 62.5g protein/L, 92.1g fat/L, and 105.7g carbohydrate/L. Ensure Plus consisted of 62.6g protein/L, 50g fat/L, and 200g carbohydrate/L.
Feeding was commenced after a stable ventilatory state had been achieved. Water was given via nasogastric tube for 12 hours prior to EN commencement. EN was commenced at 20ml/hr (full strength) and if tolerated was increased q6hrs until goal rate achieved. Gastric aspirates were checked q4hrs for the first 72 hours of feeding. EN was ceased for 2 hours and then restarted at the previously tolerated rate if gastric aspirates exceeded that of the EN given in the last 2 hours.
Resting energy requirements were calculated on a daily basis using standards suggested by Fleisch and modified to reflect the impact of disease.

Total number of patients randomised: 40 patients were randomised: 21 to Hi fat low cho and 19 to standard EN.

Outcome by study arm:

Outcome Reporting

10 patients from each arm were 'excluded' from analysis. 3 early deaths in each group; 4 patients (3 in standard feed group) required a change to high frequency jet ventilation, surgery was required in 4 patients (3 in high fat group), 6 weaned from ventilator 48 hours after EN commencement (3 each group).

Apart from the six early deaths, outcomes are not reported in the remaining 14 patients.

Intention to Treat Mortality

Hospital mortality not explicitly reported. High loss to follow-up precluded ITT analysis.

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Unclear ☒ No ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):
EN was commenced after 64.3+-37.7 hrs (standard EN) vs 69.6 +- 47 hrs (high fat EN) of ventilation [FS]
Due to high loss to follow-up (14/40 = 35%), this study cannot be considered further.[GSD]

Topic: TPN vs. standard

RefID **1204**

Reference: (Abel et al. 1976)

Patient Population: Cardiac surgery patients

Study entry criteria: Malnourished as defined by: clinical history of recent weight loss > 4.5kg within the past 12 mths; absolute weight more than 15% below ideal body weight; clinical impression of malnutrition based on initial physical exam.

Study intervention/s: Once patients were stabilised they were randomised to receive: 1) early post-op parenteral nutrition or 2) control.
TPN contained 1.48kcal/ml and 5.1mg nitrogen/ml (no lipid) and was begun at 30ml/hr an increased 10ml/hr/day until max fluid tolerance was achieved (50-60ml/hr). Control solutions consisted of 5% dextrose in water with later commencement of TPN. Exact time to start of feedings post surgery was not provided.

Total number of patients randomised: 54 patients were identified as malnourished and randomised

Outcome by study arm:

Outcome Reporting

6 patients died in theatre prior to PN administration.

2 patients were lost to follow-up due to inability to safely administer TPN OR deemed need for TPN catheter use for drugs due to poor cardiovascular status
2 patients declined entry after randomisation

Intention to Treat Mortality

4 + ?? /?? early TPN (group 1)
3 + ?? /?? control (group 2)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Unclear ☒ No ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☐ No ☒

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):
Conservative ITT mortality cannot be calculated due to loss to follow-up of 10.5% of patients (4/48), not including deaths in OR *prior* to onset of treatment but *after* randomisation.[GSD]
Malnourished cardiac surgery patients with median of 4 days mechanical ventilation. These patients are critically ill.[AD]

Topic: TPN vs. standard

RefID **219**

Reference: (Woolfson and Smith 1989)

Patient Population: Major surgery

Study entry criteria: All patients receiving esophageal resection for carcinoma, thoraco-abdominal gastric resection for carcinoma, total cystectomy and conduit construction for carcinoma or pharyngo-laryngo-esophagectomy were eligible for entry.

Study intervention/s: Patients were allocated to receive 1) 6 days of post-op intravenous nutrition or 2) standard intravenous therapy (1L 0.9% saline and 2L 5% glucose).
Both groups started their feedings at 6pm following the day of surgery.
The intravenous nutrition was composed of glucose (35Cal/kg/day), amino-acids (FreAmine II), Intralipid 20% (500mls given on day 2 and 5) and electrolytes.

Total number of patients randomised: 122 patients were recruited: 62 into Group 1 (intravenous nutrition) and 60 Group 2 (controls)

Outcome by study arm:

Outcome Reporting
Mortality was reported on all recruited patients.

Intention to Treat Mortality
Hospital mortality:
8/62 intravenous fed patients (Group 1)
8/60 control (Group 2)

Methodological issues:

Method of randomisation reported:	Yes ☒ No ☐	Allocation concealed:	Unclear ☐ No ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☒ No ☐
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):
This study explicitly reports that a randomisation process was used that would VIOLATE allocation concealment. Study personnel recruiting patients for this study would KNOW which group every second patient would be allocated to prior to obtaining informed consent. Because there was some subjectivity with regards to the selection of every second patient, it is possible that the results of this trial are significantly biased.[GSD]
Major elective surgery patients. Acknowledgement is given to 'ITU Nurses'. These patients are likely to be critically ill.[AD]

Topic: TPN vs. standard

RefID **264**

Reference: (Leutenegger and Frutiger 1986)

Patient Population: Major trauma or major surgery patients requiring admission to a surgical ICU.

Study entry criteria: Need for intensive care and intravenous nutritional support.

Study intervention/s: Patients were randomised to one of three groups:
1) control group: received a 10% amino acid solution (Aminoplasma-L) and 30% glucose,
2) received a combined carbohydrate, fat and amino acid solution (Nutriplasma-G), 40g amino acids, 38 g fat and 120 g glucose per litre) and
3) received a combined carbohydrate, fat and amino acid solution (Nutriplasmol), 40g amino acids, 38 g fat, 75g sorbitol and 45g xylitol per litre.
All groups received their feedings within 7 days after major surgery/trauma.

Total number of patients randomised: 30 patients were 'randomised': 10 per group.

Outcome by study arm:

Outcome Reporting
Mortality was reported on all patients.

Intention to Treat Mortality
Hospital mortality
2/10 group 1
1/10 group 2
1/10 group 3

Methodological issues:

Method of randomisation reported:	Yes ☒ No ☐	Allocation concealed:	Unclear ☐ No ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):
"Randomisation was done by alternating the admission between groups 1 and 3, whereas group 2 was added following the first 20 patients owing to a delay in delivery of the solution." Since this study is pseudo-randomised, it does not qualify for further consideration.[GSD]
Surgical ICU patients for trauma or major surgery. These patients are critically ill.[AD]

Topic: PN vs. EN

RefID **586**

Reference: (Borzotta et al. 1994)

Patient Population: Severe closed head injury.

Study entry criteria: GCS ≤ 8, with coma persisting for at least 24 hours. Enrollment and randomisation had to occur within 72 hours of injury.

Study intervention/s: Patients were randomised to: 1) Parenteral (TPN) or 2) Enteral nutrition (EN) via surgically placed jejunal tube. All patients were fed within 72 hours of injury. TPN (Travasol) commenced at 40% of target rate for 24 hrs and then increased by 20% every 12 hrs until goal rate achieved. Full strength EN (Vivonex TEN) commenced at 20% of target rate for 12 hours and then increased by 20% every 12 hours until goal rate achieved. The enteral and parenteral formulas were designed to be isonitrogenous and isocaloric. On day 5 of feeding, efforts were made to start to convert all TPN patients to EN feeding.

Total number of patients randomised: 59 patients were randomised: 23 to Group 1 and 36 to Group 2.

Outcome by study arm:

Outcome Reporting

Group 1 (TPN)
-1 patient died on day 4, 1 was lost to follow-up due to a protocol violation (delayed feeding)
Group 2 (EN)
- 5 patients died, 3 were lost to follow-up due to protocol violations and 1 failed gut feeding and was switched to PN (lost to follow-up)

Intention to Treat Mortality

Hospital mortality
2 (1+1 lost to follow-up)/23 Group 1 (TPN) patients died or were lost to follow-up vs
9 (5+4 lost to follow-up)/36 Group 2 (EN) patients

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ No ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):
This paper contains 8.5% loss to follow-up (5 / 59).[GSD]
Patients with severe head injury, GCS ≤ 8 for > 24 hours. Patients were critically ill.[AD]

Topic: PN vs. EN

RefID **1181**

Reference: (Hadley et al. 1986)

Patient Population: Acute head injury.

Study entry criteria: Trauma patients with isolated head injury. GCS ≤ 10 6 hours post injury.

Study intervention/s: Patients were 'randomised' based on date of admission to 1) TPN or 2) enteral nutrition.

Total number of patients randomised: 45 patients: 24 to Group 1 and 21 to Group 2.

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**

Methodological issues:

Method of randomisation reported:	Yes ☒ No ☐	Allocation concealed:	Unclear ☐ No ☒
Consecutive pts enrolled:	Yes ☐ No ☐	Blinding employed:	Yes ☐ No ☐
100% follow-up:	Yes ☐ No ☐	Reporting of losses by study arm	Yes ☐ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):

Patients were 'randomised' based on 'date of admission'. Since this study is 'pseudo-randomised', and does not maintain allocation concealment, it cannot be considered further.[GSD]
Patients with GCS < 10 with isolated head injury. Avg GCS 5.8. Patients are critically ill.[AD]

Topic: PN vs. EN

RefID **1203**

Reference: (Young et al. 1987)

Patient Population: Severe head injury.

Study entry criteria: Primary site of injury was brain, GCS between 4 and 10 over first 24 hours after injury.

Study intervention/s: Patients were randomised to 1) TPN or 2) EN.
TPN was initiated within 48 hours of injury. EN was begun in the TPN group as soon as bowel sounds were present.
EN was commenced as soon as gastric tube placement was confirmed using either Traumacal (1.5Cal/ml, 22% protein, 40% fat and 38% carbohydrate) or Ensure Plus (1.5Cal/ml, 14.7% protein, 32% fat, 53.3% carbohydrate).
Energy requirements were calculated using the Harris Benedict equation.

Total number of patients randomised: 58 patients were enrolled and randomised.
23 patients (TPN) vs 28 patients (EN). 7 patients lost to follow-up (groups not specified).

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
7 patients (12%) were excluded from analysis due to - death / brain death within 4 days of enrollment (5 patients) and for withdrawal of consent from family (2 patients). Group not specified.	12 month mortality **7/23 + ??** (TPN group) **9/28 + ??** (EN group)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Unclear ☒ No ☐
Consecutive pts enrolled:	Yes ☒ No ☐	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☐ No ☒

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):
Since 12 % of all randomised patients were lost to follow-up (including 5 deaths) and could not be attributed to the group to which they were originally randomised, a conservative ITT analysis could not be conducted. [GSD]
Patients had GCS 4-10 within 24 hours. 78% had ICU monitoring. Patients are critically ill.[AD]

Topic: PN vs. EN

RefID 52

Reference: (Kudsk et al. 1992)

Patient Population: Blunt and penetrating abdominal trauma.

Study entry criteria: Intra-abdominal injury requiring laparotomy, with an abdominal trauma index > 15. Patients were enrolled and randomised within 8 hours of operation. Included patients with intestinal repairs or anastomosis.

Study intervention/s: Patients were randomised to: 1) TPN or 2) EN (jejunally fed).
Feeding was begun an average of 23 hours after surgery in both groups.
EN consisted of Vital HN (16.7% protein, 73.9% carbohydrate and 9.4% carbohydrate). PN consisted of 17% protein, 74% carbohydrate and 9% fat.
For both feeding groups a goal rate of 1.5-2g/kg/day protein and 30-35Cal/kg/day was set.

Total number of patients randomised: 98 patients were randomised: 46 to Group 1 and 52 to Group 2

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
2 patients died before day 4, (1 in each Group) and were thus 'excluded from further analysis.' Nil other deaths reported	**1 + ?? /46** (group 1) **1 + ?? /52** (group 2)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Unclear ☒ No ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):

Besides the 2 'early deaths' who were excluded from the study, I cannot find mortality outcomes explicitly reported for the patients who were 'on study'.[GSD]
Enteral feeding began 24 +-1.7 hours after surgery. TPN began 22.9 +-1.6 hours after surgery [FS]
Average ventilator days of approx 3, patients are likely to be critically ill.[AD]

Topic: PN vs. EN

RefID **259**

Reference: (Suchner et al. 1996)

Patient Population: Traumatic head injury or spontaneous cerebral lesion

Study entry criteria: Patients undergoing craniotomy for traumatic head injury or spontaneous cerebral lesion with a GCS ≤ 10 and deemed to require TPN or EN for the next 12 days.

Study intervention/s: Patients were randomised to 1) TPN or 2) EN.
Central lines and nasogastric tubes were placed in surgery (as randomised) and feeding begun on the first postoperative day. Group 1 received TPN consisting of glucose, amino acids (10%) and lipid (20%). Group 2 received Osmolite (1 Cal/ml, 16.7% protein, 30% lipid, 53.3% carbohyrate). Energy requirements were calculated daily using indirect calorimetry.

Total number of patients randomised: 49 patients were enrolled and randomised: 24 to Group 1 and 25 to Group 2

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
2 Group 1 (TPN) patients were lost to follow-up due to 'early recovery' and 5 Group 1 patients were lost due to hemodynamic instability and sepsis. 4 Group 2 (EN) patients were lost to follow-up due to 'early recovery' and 4 Group 2 patients were lost due to hemodynamic instability and sepsis.	

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Unclear ☒ No ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):
31% (15/49) of all enrolled patients were excluded from follow-up. Of the remaining 34 patients 'who completed the study', outcomes were not explicitly reported.[GSD]
These patients are likely to be critically ill.[AD]

Topic: PN vs. EN

RefID **615**

Reference: (Moore et al. 1989)

Patient Population: Major abdominal trauma.

Study entry criteria: Patients undergoing emergency celiotomy with an abdominal trauma index > 15 and < 40. After regaining consciousness post-op, each patient was approached for informed consent.

Study intervention/s: Patients were randomised to: 1) TPN or 2) EN via needle catheter jejunostomy.
TPN (group 1) was designed to be similar to the EN in terms of composition and consisted of 33% branched chain amino acids, 2.2% fat and 85% carbohydrate. EN (group 2) consisted of Vivonex TEN (33% branched chain amino acids, 2.5% fat, 82% carbohydrates) and was begun at one-quarter strength and increased q8hrs to three-quarter strength within 72 hours. TPN and EN was begun within 12 hours of surgery. Energy requirements were initially calculated using the Harris Benedict equation and a stress factor of 1.5 and confirmed using indirect calorimetry.

Total number of patients randomised: 75 patients were randomised: 36 to Group 1 and 39 to Group 2

Outcome by study arm:

Outcome Reporting

4 patients were 'excluded' due to early death. The group to which these patients were randomised to was not stated.
3 excluded due to re-operation.
3 due to significant chronic medical disease
2 due to ATI > 40
2 due to presence of head injury, mechanical failure of EN delivery (1) and early transfer (1).
Total of 16 patients lost to follow-up were not identified as to which group they were randomised to.

Intention to Treat Mortality

Methodological issues:

Method of randomisation reported:	Yes ☒ No ☐	Allocation concealed:	Unclear ☒ No ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):
Due to the failure to report loss to follow-up by study arm in 16 of 75 patients (21%), a conservative ITT analysis cannot be calculated. This paper cannot be considered further. [GSD]
Patients are likely to be critically ill.[AD]

Topic: Timing of EN (early vs late feeding) + site of feeding

RefID **137**

Reference: (Minard et al. 2000)

Patient Population: Patients with severe closed head injury, managed in ICU

Study entry criteria: GCS <11 within the first 6 hours of injury

Study intervention/s: Patients were randomised to either 1) early enteral nutrition (EN) or 2) delayed EN (nasogastric feeding after the resolution of gastroparesis)

The early feeding group was fed within 60 hrs of injury using an endoscopically placed nasoenteric tube. The standard feeding group was fed by NGT when gastroparesis resolved (decreased NG output to <500mls/d, no abdominal distension or vomiting for 24 hrs).
Both groups received Impact with fibre (an immuno-enhanced formula) for 15 days and then changed to standard formula if required. Goal rate of feeding was 21 nonprotein calories/kg/d and 0.3 g nitrogen/kg/d. No patients required supplemental TPN.

Total number of patients randomised: 30 patients were randomised – 14 to early EN (group 1) and 16 to standard EN (group 2)

Outcome by study arm:

Outcome Reporting

2 patients in group 1 were excluded from analysis due to inability to place nasoenteric tube (no mortality reported)
1 patient in group 2 was excluded post randomisation as they died within 72 hrs of injury

Intention to Treat Mortality

Hospital mortality:
2 +1/14 early nasoenteric group (group 1) vs.
1+ 4/16 (group 2) gastric

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Unclear ☒ No ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):
This paper contains 6% loss to follow-up. [GSD]
Time to initiation of enteral feeding was 33 hrs (group 1) vs 84 hrs (group 2). Group 1 received 13 days of feeding vs 8 days in group 2. [FS]
Moderate/severe head injury. Managed in ICU with significant ventilator days and ICU days. Patients are critically ill adults.[AD]

Topic: Timing of EN (early vs late feeding)

RefID **566**

Reference: (Eyer et al. 1993)

Patient Population: Intensive care trauma patients

Study entry criteria: Blunt trauma patients admitted to ICU, age>17, ISS >13, feeding anticipated for at least 7 days, ability to start jejunal EN within 24 hrs post ICU admission.

Study intervention/s: Patients were randomised to either 1) early EN (fed <24 hrs after intensive care admission) or 2) late EN (fed >72 hrs after intensive care admission).

Both groups were fed using 10Fr nasoduodenal feeding tubes. Target rates for both groups was 1.5g protein/kg/d (nil other feeding goals specified). Both groups used Reabilan HN formula (1.33Cal/ml, 58g protein/L, 52 g fat/L, 158g carbohydrate/L). Feeding started at 25ml/hr and increased by 25ml q4hrs until goal rate achieved.

Total number of patients randomised: 52 patients were randomised: 26 to each group

Outcome by study arm:

Outcome Reporting

14 patients were excluded from analysis (7 in each group) due to various reasons = 3 commenced oral diet, 3 received steroids, 2 pulled out feeding tubes which were not replaced, 1 had an enterorrhaphy, 1 had a duodenal perforation (day 4), 1 had severe hypernatremia, 1 could not have a feeding tube placed, 1 had physician withdrawal consent, 1 patient refused to have a feeding tube placed.
Outcomes were not reported for these patients.

Intention to Treat Mortality

Hospital mortality:
2 + 7/26 Group 1 (early EN) vs
2 + 7/26 Group 2 (delayed EN)
- includes 2 reported deaths in each group plus 14 pts lost to follow-up

Methodological issues:

Method of randomisation reported:	Yes ☒ No ☐	Allocation concealed:	Unclear ☒ No ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):

27% loss to follow-up. This could have lead to a significant bias.[GSD]
On average the early feeding group (group 1) was fed 31 hrs after ITU admission and the late fed group (group 2) was fed 82 hrs after admission. On average group 1 spent 11.8 days in ITU and group 2 spent 9.9 days [FS]
Blunt trauma patients admitted to the Trauma ICU. These patients were critically ill.[AD]

Topic: Timing of EN (early vs late feeding) + EN vs. standard

RefID **634**

Reference: (Moore and Jones 1986)

Patient Population: Severe trauma.

Study entry criteria: Patients undergoing emergency celiotomy with abdominal trauma index > 15.

Study intervention/s: Patients were randomised to: 1) Early EN via jejunostomy vs. 2) standard care.
Standard care patients (group 2) received D_5W IV for first 5 days post-op followed by TPN (composition not specified) if they could not tolerate an oral diet.
In Group 1, elemental diet (Vivonex HN) was begun at 12 to 18 hours post-op. Vivonex was begun at 0.25Cal/ml at 50ml/hr and was increased q8hrs to a goal rate of 125ml/hr full strength feeding within 72hrs. Feeding was continued in both groups until an adequate oral diet was tolerated.

Total number of patients randomised: 75 patients were randomised – 32 early EN and 31 control (and 12 lost to follow-up, groups not specified)

Outcome by study arm:

Outcome Reporting

12 patients were lost to follow-up within the first 72 hours post-randomisation due to: reoperation (6 pts), death (4 pts), transfer to another hospital (2 pts). It is not clear as to which group these patients were randomised.

Intention to Treat Mortality

?? + **1/32** early EN (group 1)
?? + **2/31** control (group 2)

Methodological issues:

Method of randomisation reported:	Yes ☒ No ☐	Allocation concealed:	Unclear ☒ No ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☐ No ☒

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):
Due to loss to follow-up of 12 of 75 (16%) randomised patients, and incomplete reporting of loss to follow-up by study arm, this paper cannot be considered.[GSD]
Trauma patients requiring laparotomy (ATI > 15). These patients are critically ill.[AD]

Topic: Site of EN feeding (post-pyloric vs. gastric)

RefID **664**

Reference: (Montecalvo et al. 1992)

Patient Population: Medical and surgical ICU patients.

Study entry criteria: If the attending physician anticipated that patients would require tube feeding for at least 3 days, patients had no contraindications to tube feeding and no evidence of GI bleeding.

Study intervention/s: Patients were randomised to: 1) endoscopically placed 12-Fr jejunal tube feeding or 2) 12-Fr gastric tube feeding.
Group 1 had their jejunal tubes placed endoscopically (maximum of two attempts) over a guidewire and verified via abdominal roentgenogram. If jejunal tube placement was unsuccessful patients were fed gastrically and excluded from further analysis. In most cases both groups 1 and 2 used Newtrition Isofiber enteral formula which was begun at 25ml/hr for the first 24 hours and then increased 25ml/hr/day until goal rate was achieved.

Total number of patients randomised: 69 patients were randomised but results are given on only 38 patients (19 each group)

Outcome by study arm:

Outcome Reporting

31 patients were 'excluded' due to - 11/31 were not consented, 13/31 had a change in clinical condition preventing enteral feeding, 7/31were unable to have a feeding tube placed successfully. Based on reporting, it is possible that 13 + 7 of these 'excluded' patients were excluded *after* randomisation.

Intention to Treat Mortality

5 deaths in jejunal group (group 1)
5 deaths in gastric group (group 2)

38/69 patients completed the study (55%).

Methodological issues:

Method of randomisation reported:	Yes ☒ No ☐	Allocation concealed:	Unclear ☒ No ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☐ No ☒

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):
The authors report that "38 of 69 eligible patients were randomised and completed the study." The authors then go on to report that 7 of the 31 eligible patients who did not complete the study "could not have their feeding tubes placed." With regards to failure to place a jejunal feeding tube, the methods section states that "If a second endoscopy could not be performed, patients were fed gastrically and excluded from analysis." At the very least, it is clear that these 7 patients had been randomised to the jejunal feeding group. As such, since outcomes are not reported for these 7 patients, a true intention to treat analysis cannot be performed. Due to the significant potential for bias resulting from this minimum of 18% differential loss to follow-up, this study cannot be considered further. (GSD)
Study conducted in the medical and surgical ICU. These patients were critically ill.[AD]

Topic: Role of Prokinetics in enteral feeding.

RefID 83

Reference: (Reignier et al. 2002)

Patient Population: Intensive care patients.

Study entry criteria: All patients who were expected to require invasive mechanical ventilation (InvMV) and early nutrition support for greater than 5 days. Patients were included within 24hrs of initiation of InvMV.

Study intervention/s: Patients were randomised to receive either –
1) Erythromycin lactobionate (250mg in 50ml of 5% dextrose) or
2) Intravenous injections of placebo (50ml of 5% dextrose)

Both injections were initiated at 8am on the day after InvMV initiation then q 6 hours for 5 days. Enteral nutrition (Enterodrip) was provided for both groups via a 14-Fr intragastric tube, and increased by 500mls daily to a goal volume of 2000mls.

Total number of patients randomised: 48 (25 randomised to erythromycin vs 23 to placebo).

Outcome by study arm:

Outcome Reporting

- 5 patients from the erythromycin group (group 1) and 3 from the placebo group (group 2) were excluded from analysis and reporting due to InvMV lasting less than 5 days

Intention to Treat Mortality

Day 5 Mortality?

- **5+ 6/25** (erythromycin group, group 1)
- **3+ 8/23** (placebo group, group 2)

Methodological issues:

Method of randomisation reported:	Yes ☒ No ☐	Allocation concealed:	Unclear ☒ No ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☒ No ☐
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):

It is difficult to determine the exact time of mortality follow-up. Lack of outcome reporting in 16% of randomised patients is concerning [GSD]

Enteral feeding was discontinued in 7 patients (28% intention to treat) in the erythromycin group (group 1) and 14 patients (61% intention to treat) in the placebo group (group 2) [FS]

All patients were receiving invasive mechanical ventilation. These patients were critically ill.[AD]

Topic: EN vs. Standard

RefID 5

Reference: (Swails et al. 1995)

Patient Population: Elective esophagogastrectomy patients.

Study entry criteria: Patients with a preoperative diagnosis of cancer of the esophagus or gastric cardia who presented for elective esophagogastrectomy.

Study intervention/s: Patients were randomised pre-op to receive: 1) a feeding jejunostomy at completion of surgery with feeds started < 24 hours post-op or 2) no feeding jejunostomy, oral feeds at post-op day 4 or 5.

Group 1 patients received either a full strength elemental (Vivonex TEN, 1 Cal/ml, 206 g carbohydrate/L, 38 g protein/L, 3 g fat/L) or polymeric formula (Formula 9119, 1.06 Cal/ml, 141 g carbohydrate/L, 44 g protein/L, 37 g fat/L) within 24 hours of surgery. Formulas were chosen at the discretion of the nutrition support service. Enteral feeding was commenced at 10ml/hr and increased 10ml q12-24hrs until goals achieved. Once an intact anastomosis was demonstrated oral diet was commenced.
Group 2 patients received IV fluid and electrolyte replacement until post-op day 4 or 5, when an oral diet was initiated. If an anastomotic leak was demonstrated at day 4 or 5 TPN (no further details provided) was commenced. Feeding goals for both groups were estimated by using 25-30Cal/kg body weight and 1.2-1.5g protein/kg body weight.

Total number of patients randomised: 25 patients were randomised: 13 to Group 1, 12 to Group 2.

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ No ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☐	Reporting of losses by study arm	Yes ☐ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):
ICU LoS was reported but mortality was not explicitly reported. Given the small study size, if no mortality events were experienced in either arm, the study would be considered 'uninformative' at best.[GSD]
2/13 (15%) group 1 and 5/12 (42%) group 2 patients required TPN during their hospital stay [FS]
The patients were undergoing elective oesophagogastrectomy, with an average ICU stay of 1 day. These patients are likely to be critically ill.[AD]

Topic: EN vs. Standard

RefID **134**

Reference: (Powell et al. 2000)

Patient Population: Severe acute pancreatitis

Study entry criteria: Patients admitted within 72 hours of onset of prognostically severe pancreatitis as defined by GCS ≥ 3 (sic) or an APACHE II score ≥ 7.

Study intervention/s: Patients were randomised to 1) enteral nutrition or 2) control (NPO).

Group 1 patients received EN (Jevity, 1.06 Cal/ml, 44 g protein/L, 35 g fat/L) via a 8-Fr N-J tube. EN was commenced at 25ml/hr and increased daily by 25ml until goal rate achieved.

Total number of patients randomised: 28 patients were randomised: 13 to Group 1 and 14 to Group 2.

Outcome by study arm:

Outcome Reporting

1 patient was found to have an acute mesenteric infarction at laparotomy and was therefore excluded from follow-up (3.4% loss to follow-up).
1 patient who was randomised to Group 1 (EN) refused tube placement and was re-allocated to Group 2.

Intention to Treat Mortality

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Unclear ☒ No ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☐ No ☒

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):

Mortality was not explicitly reported. Study duration was 4 days. This study cannot be considered further.[GSD]
Patients had severe acute pancreatitis. They are likely to be critically ill.[AD]

Topic: EN Glutamine vs. EN

RefID **1187**

Reference: (Houdijk et al. 1998)

Patient Population: Multiple trauma.

Study entry criteria: Multiple trauma patients with age ≥ 18 and ≤ 65, ISS ≥ 20 and expected to survive longer than 48 hours (defined as GCS ≤ 8 AND ISS ≥ 50).

Study intervention/s: Patients were randomised to receive: 1) glutamine-supplemented enteral nutrition (Alitra Q) or 2) balanced isocaloric, isonitrogenous EN.
Alitra Q contained 1000Cal/L, 52 g protein/L, 165 g carbohydrate/L, 15 g fat/L and 30.5 g glutamine/100g protein. The control formula contained 3.5 g glutamine/100g protein. A nasoduodenal tube was inserted endoscopically and feeding was begun within 48 hours of ICU admission.
Feeding aimed to meet 75% of calculated basal energy expenditure within 72 hrs of admission. Indirect calorimetry was undertaken on each patient to determine caloric requirements.

Total number of patients randomised: 80 patients were randomised: 41 to Group 1 (glutamine supplemented EN) and 39 to Group 2 (control EN)

Outcome by study arm:

Outcome Reporting

4 patients were lost to follow-up Group 1 due to: age ≥ 65 (2 pts), HIV infection (1 pt) and transfer (1 pt).
1 patient was lost-to follow-up in Group 2 due to transfer.

Intention to Treat Mortality

15 day study follow-up mortality:
8 (4 deaths+4 loss to follow-up) / 41 in Group 1 vs
4 (3 deaths+1 loss to follow-up) / 39 pts in Group 2

Methodological issues:

Method of randomisation reported:	Yes ☒ No ☐	Allocation concealed:	Yes ☒ No ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☒ No ☐
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):

Differential loss to follow-up of 6.25% (5 / 80) creates potential for bias in calculation of conservative ITT analysis.[GSD]
Trauma patients with ISS > 20 expected to survive > 48 hours. APACHE II 15 to 16 and GCS 8 on admission. These patients ARE critically ill.[AD]

Topic: EN Glutamine vs. EN

RefID **965**

Reference: (Conejero et al. 2002)

Patient Population: ICU patients with SIRS (systemic inflammatory reponse syndrome).

Study entry criteria: ICU patients who develop SIRS after an acute event and who are expected to require EN for at least 7 days.

Study intervention/s: Patients were randomised to receive: 1) glutamine supplemented EN or 2) control EN diet (no glutamine).
Group 1 formula consisted of 1000Cal/L, 52.5g protein/L, 15.5g fat/L, 165g carbohydrate/L, and 30.5g glutamine/100g. Group 2 formula consisted of 1200Cal/L, 66.2 g protein/L, 40.2 g fat/L, 148 g carbohydrate/L. Site of feeding and route of access was determined by each investigator. Feeding was begun at full strength for both groups at 42ml/hr on the first day of feeding and increased 20ml every 12 hours to goal rate. Estimated requirements were determined using the Harris Benedict equation and applying a fixed stress factor of 1.3. Feeding goals were to achieve calculated requirements within 72hrs of EN commencement.

Total number of patients randomised: 84 patients were randomised: 47 to Group 1 and 37 to Group 2.

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
8 patients were 'excluded' from follow-up during the first 48 hours: 2 in each Group due to 'death or transfer' and 2 in each Group due to 'feeding problems'	28 day mortality: **18 (14 deaths + 4 lost to follow-up) / 47** in Group 1 vs **13 (9 deaths +4 lost to follow-up) / 37** in Group 2

Methodological issues:

Method of randomisation reported:	Yes ☒ No ☐	Allocation concealed:	Yes ☒ No ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):
Incomplete follow-up on 9.24% of all randomised patients (8 / 84) could result in significant bias in calculation of ITT analysis.[GSD]
Average length of time in ICU before study randomisation and hence EN commencement was not stated for either group [FS].
Patients were admitted to an ICU. Average APACHE II score was 18 to 20 on admission. Large percentage were mechanically ventilated. These patients ARE critically ill. [AD]

Topic: EN Glutamine vs. EN

RefID **182**

Reference: (Jones et al. 1999)

Patient Population: Patients admitted as emergencies to a general ICU.

Study entry criteria: APACHE II ≥ 11, malnourished or likely to become malnourished due to inability to resume normal diet within 5 days.

Study intervention/s: Patients were randomised to receive: 1) glutamine enhanced EN vs. 2) control EN via NGT.
Formula consisted of Protina MP (0.88 Cal/ml, 8 g nitrogen/L) with added glutamine (10g glutamine/L for group 1) or glycine (10g/L for group 2). Both groups received a total of 20g nitrogen/day and 1760Cal/day with feeding given over 18hrs. If required, Group 1 patients could also receive glutamine enhanced PN whereas Group 2 patients would receive regular PN.

Total number of patients randomised: 78 patients were randomised and clinically considered appropriate for enteral nutrition.

Outcome by study arm:

Outcome Reporting

18 patients were lost to follow-up because they were randomised but received 'no effective feeds' due to death or early transfer.
10 patients were lost to follow-up because they did not tolerate EN (< 1500ml over 48 hrs).
Loss to follow-up was not reported by study arm.

Intention to Treat Mortality

Methodological issues:

Method of randomisation reported:	Yes ☒ No ☐	Allocation concealed:	Yes ☒ No ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☒ No ☐
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☐ No ☒

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):
Not considering the 18 patients who were randomised but *did not receive 'any effective feeds'*, 10 of the remaining 60 patients were randomised and DID receive feeds but were lost to follow-up after 48 hours (16.6%). The groups to which these patients were initially randomised were not reported, making a conservative ITT analysis impossible.[GSD]
EN was "normally" stated to start ~48hrs post admission for all ICU patients excepting burns patients where EN started ~24 hrs post ICU admission. No averages were provided however for either group on time to feeding commencement for this study [FS]
Patients admitted as emergencies to ICU. APACHE ≥ 11 (average 17). Large percent were mechanically ventilated. These patients ARE critically ill.[AD]

Topic: EN Glutamine vs. EN

RefID **536**

Reference: (Jensen et al. 1996)

Patient Population: Mixed medical-surgical ICU patients

Study entry criteria: Candidates for enteral feeding within 48 h of admission, APACHE II > 10 and age between 18 and 75 and expected to require enteral support for at least 5 days.

Study intervention/s: Patients were randomised to receive: 1) glutamine enhanced EN or 2) isonitrogenous, isoenergetic EN.

Full strength nasojejunal feeds were started within 48 hours of ICU admission using nutritionally complete formulas, which were identical except for their amino acid content. One litre of formula provided 1Cal/ml, 52g protein/L, 15.5 g fat/L, and 165 g carbohydrate/L. The glutamine enhanced feed contained 289g glutamine/kg protein. Control EN contained 50g glutamine/kg protein.
Full strength feeding was begun on day 0 at 25ml/hr and increased to 30-35Cal/kg/day within 72 hrs of feeding commencement.

Total number of patients randomised: 28 patients were randomised: 14 to each Group

Outcome by study arm:

Outcome Reporting

9 patients were excluded from follow-up due to: 2 early deaths (one in each Group); 3 early progression to oral diet (1 Group 1, 2 Group 2); 4 switched to PN (2 Group 1 and 2 Group 2).
Except for the early deaths, outcomes are not reported on the remaining 7 excluded patients.
Mortality is not explicitly reported in the remaining 19 patients.

Intention to Treat Mortality

3+ ?+2/14 Group 1 (glutamine enriched EN)
4+ ?+2/14 Group 2 (control EN)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☐	Allocation concealed:	Yes ☐ No ☐
Consecutive pts enrolled:	Yes ☐ No ☐	Blinding employed:	Yes ☐ No ☐
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☐ No ☒

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):

Incomplete follow-up on 25% of all randomised patients (7 / 28) who were fed less than 5 days (for any reason) could result in significant bias in calculation of conservative ITT analysis. Mortality outcome is not explicitly reported in the remaining 19 patients who were fed more than 5 days.[GSD]
These patients were ICU patients. APACHE > 10 (average was 17-19). These patients are likely to be critically ill.[AD]

Topic: EN Glutamine vs. EN

RefID 45

Reference: (Velasco et al. 2001)

Patient Population: Surgical ICU patients

Study entry criteria: Surgical ICU patients who were critically ill, with at least 4 days of enteral feeding.

Study intervention/s: Patients were randomised to: 1) EN supplemented with 0.3 g/kg per day glutamine or 2) EN supplemented with 0.15 g/kg per day glutamine plus 0.2 g/kg per day casein or 3) EN supplemented with 0.4 g/kg per day casein.
All groups received the polymeric formula ADN Nutricomp, which contains 1Cal/ml,35.6 g casein/L, 131.6 g carbohydrate/L, and 39.6 g lipid/L with the above additions. All groups reached their feeding goals within 72 hrs.

Total number of patients randomised: 23 patients were randomised: 8 to Group 1, 7 to Group 2 and 8 to Group 3

Outcome by study arm:

Outcome Reporting **Intention to Treat Mortality**

Clinical outcomes are not explicitly reported.

Methodological issues:

Method of randomisation reported:	Yes ☐	No ☐	Allocation concealed:	Yes ☐	No ☐
Consecutive pts enrolled:	Yes ☐	No ☐	Blinding employed:	Yes ☐	No ☐
100% follow-up:	Yes ☐	No ☐	Reporting of losses by study arm	Yes ☐	No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):
Clinical outcomes (mortality) are not explicitly reported. Due to the very short follow-up time (8 days), lack of explicit reporting of clinical outcomes, this study becomes 'uninformative' at best and cannot not be considered further.[GSD]
Group 1 was fasted for an average of 9.1 days, group 2 for an average of 6.1 days and group 3 for an average of 8.3 days before EN commencement [FS].
Patients admitted to surgical ICU. Average APACHE II was 10. Diagnoses were consistent with ICU admission. These patients were critically ill.[AD]

Topic: EN Arginine vs. Standard EN

RefID **972**

Reference: (Brown et al. 1994)

Patient Population: Trauma patients.

Study entry criteria: Age 18 to 75 years old, who sustained multiple trauma and required EN (could not take oral diet and had functioning and accessible GI tract).

Study intervention/s: Patients were randomised to: 1) arginine enhanced EN or 2) standard formula (Osmolite HN) supplemented with protein powder.
Group 1 formula consisted of 1.3Cal/ml, 66.6 g protein/L of which 10% was L-arginine, 37.4 g fat/L. Group 2 formula (Osmolite HN supplemented with promod protein powder) consisted of 1.14 Cal/ml, 63 g protein/L, and 36.8 g fat/L. Both groups were fed by NGT, gastrostomies or jejunostomies. EN commenced at 25-50ml.hr and increased 25ml/hr to provide a goal rate of 35Cal/kg/d and 1.5g protein/kg/d.

Total number of patients randomised: 41 patients were randomised

Outcome by study arm:

Outcome Reporting

4 patients were lost to follow-up due to not receiving EN within 7 days (original group allocation not reported). Average time to feeding for the control group was 5 days, which suggests that there could have been a differential loss to follow-up.
No mortality events are reported.

Intention to Treat Mortality

Methodological issues:

Method of randomisation reported:	Yes ☒ No ☐	Allocation concealed:	Unclear ☒ No ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☐ No ☒

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):
Due to 9.8% loss to follow-up, conservative ITT cannot be calculated. Also due to small group size, and no explicit reporting of subsequent mortality events, the study cannot be considered further.[GSD]
Group 1 was fed on average 3.5 days after admission, group 2 (control) was fed on average 5 days after admission (P<0.05). Group 2 uses a commercially modified formula (Osmolite HN with added protein powder) [FS].
The patients were trauma patients admitted to the trauma ICU or the neurosurgery ICU. The patients are likely to be critically ill.[AD]

Topic: EN Arginine vs. Standard EN

RefID 16

Reference: (Bower et al. 1995)

Patient Population: ICU patients

Study entry criteria: New event (trauma, operation or new infection) requiring ICU care. APACHE II score ≥ 10, TISS ≥ 20 and appropriate candidates for EN for at least 7 days and less than 48 hours since ICU admission.

Study intervention/s: Patients were randomised to receive: 1) EN supplemented with arginine (Impact) or 2) Standard EN (Osmolite HN)
Group 1 formula (Impact) consisted of 1.0Cal/ml, 134 g carbohydrate/L, 55.8 g protein/L (of which 12.5 g/L was L-arginine), and 27.8 g fat/L. Group 2 (Osmolite HN) consisted of 1.06 Cal/ml, 141 g carbohydrate/L, 44 g protein/L, and 37 g fat/L.
Both groups were stated to receive enteral formula within 48hrs of injury and reach 60ml/hr within 96 hrs of injury. Once 60ml/hr was achieved, the rate of formula was upgraded to meet up to 1.25 times the resting energy expenditure as measured by indirect calorimetry. Route of administration was as per the physicians discretion. EN continued until day 7 for both groups, after this the physician was able to direct nutritional care as desired.

Total number of patients randomised: 326 patients were randomised into the trial: 167 to Group 1 and 159 to Group 2

Outcome by study arm:

Outcome Reporting

14 patients randomised to Group 1 and 16 patients randomised to Group 2 were lost to follow-up because 'entrance criteria were not met'. Outcomes, or whether these patients ever received feeds, are not reported.
In addition, follow-up is not reported in 6 patients randomised to Group 1 and 11 Group 2 patients due to 'not receiving enteral feeding'.

Intention to Treat Mortality

Hospital mortality:
(14+6) +23/167 Group 1 (Impact) vs
(16+11) +10/159 Group 2

Methodological issues:

Method of randomisation reported:	Yes ☒ No ☐	Allocation concealed:	Unclear ☒ No ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☒ No ☐
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):

By conservative estimates, there was 9.2 % loss to follow-up (14+16 / 326). Based on the definition of an intention to treat analysis (ALL patients randomised), there was 14.4% loss to follow-up (14+6+16+11/326). This degree of loss to follow-up could result in significantly biased interpretations based on the remaining patients [GSD].
Average time to commencement of EN from time of injury causing ICU admission is 0.9-1.4 days (group 1, Impact) and 1.0-1.5 days (group 2, Osmolite HN) [FS]
All patients were treated in an ICU. Average APACHE II was 15 to 17. These patients are critically ill.[AD]

Topic: EN Arginine vs. Standard EN

RefID **304**

Reference: (Caparros et al. 2001)

Patient Population: Critically ill patients.

Study entry criteria: ICU patients were enrolled if it was predicted that they would require enteral nutrition for at least 7 days.

Study intervention/s: Patients were randomised to: 1) EN enhanced with arginine (Stresson) or 2) standard EN (Nutrison Protein Plus).

Stresson provided 1.25 Cal/ml, 75g protein/L (of which 6.7 g/L is L-arginine and 13 g/L is glutamine), 145 g carbohydrate/L, 41.7 g fat/L. Nutrison Protein Plus provided 1.25 Cal/ml, 62.5 g protein/L, 141.1 g carbohydrate/L and 48.6 g fat/L. Caloric requirements were calculated at 25Cal/kg/day, with an aim to achieve goal rate within 72hrs of EN commencement. Feeding commenced at 42ml/hr on day 1 and increased on day 2 by 20ml q12hrs to goal rate. Site of feeding tube was decided by the local investigator.

Total number of patients randomised: 237 patients were randomised

Outcome by study arm:

Outcome Reporting

17 patients were excluded from follow-up because they did not receive any intervention. It is not reported to which Group these patients were randomised to.

Intention to Treat Mortality

Due to the 17 pts lost to follow-up, **conservative ITT cannot be calculated.** Reported Hospital mort was:
25 / 122 Group 1 (Stresson) vs.
29 / 98 Group 2
Reported 6 mth mortality was
30 / 122 Group 1 (Stresson) vs.
31 / 98 Group 2

Methodological issues:

Method of randomisation reported:	Yes ☒	No ☐	Allocation concealed:	Yes ☒	No ☐
Consecutive pts enrolled:	Yes ☐	No ☒	Blinding employed:	Yes ☒	No ☐
100% follow-up:	Yes ☐	No ☒	Reporting of losses by study arm	Yes ☐	No ☒

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):

7.17% (17/237) differential loss to follow-up. Although it is reported that the 'investigators' remained blind to treatment for the diagnosis of nosocomial pneumonia and to the statistical analysis until after the 6mth follow-up, the healthcare team was not reported as being blinded. Because the subjective decision to feed was made by the healthcare team in an unblinded manner, it is possible that a significant amount of bias could have been introduced by the failure to report allocation of the 17 patients lost to follow-up.[GSD]
Of the 220 patients which had outcomes reported, time to EN commencement was 27 hours (group 1) and 30hrs (group 2) [FS].
These patients were in ICU. Average APACHE II 16-17. 95% were mechanically ventilated. These patients were critically ill.[AD]

Topic: EN Arginine vs. Standard EN

RefID **953**

Reference: (Weimann et al. 1998)

Patient Population: Multiple trauma patients.

Study entry criteria: ISS > 20, age between 18 and 64 admitted to the ICU.

Study intervention/s: Patients were randomised to: 1) EN supplemented with arginine (Impact) or 2) isonitrogenous, isocaloric control EN.
Group 1 formula (Impact) consisted of 1.0 Cal/ml, 134 g carbohydrate/L, 56 g protein/L (of which 12.5 g/L was L-arginine), 28 g fat/L. Group 2 formula was identical to group 1 excepting there was no L-arginine. EN was commenced on day 2 after trauma via an endoscopically placed nasoduodenal or nasojejunal tube. Full strength EN was commenced at 25ml/hr and increased by 25ml/hr each day to a final rate of 150ml/hr over 18hrs. PN was also utilised to meet requirements whilst grading up to goal rate (aiming to provide 35-40 Cal/kg/day).

Total number of patients randomised: 32 patients were randomised:

Outcome by study arm:

Outcome Reporting
3 patients were lost to follow-up:
2 because they had an 'uneventful course' and could be transferred to the surgical ward on day 4 and 5 to begin oral diets and 1 due to technical problems placing the feeding tube. The groups to which these patients were allocated were not stated nor were their outcomes.

Intention to Treat Mortality
Conservative ITT cannot be calculated.
Reported mort:
?? + 2/16 Group 1 (Impact) vs.
?? + 4/13 Group 2 (control EN)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Unclear ☒ No ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☐ No ☒

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):
9.3% (3/32) differential loss to follow-up for subjective reasons. Although it is implied that the loss to follow-up occurred in the control group (Group 2), this is not explicitly stated and cannot be assumed. Conservative ITT cannot be calculated.[GSD]
Abstract states that the study was "double blind" but there is no mention in the body of the paper as to how this was achieved [FS]
Patients had suffered from multi-trauma. All patients were admitted to an ICU. All were mechanically ventilated. These patients are critically ill.[AD]

Topic: EN Arginine vs. Standard EN

RefID **472**

Reference: (Mendez et al. 1997)

Patient Population: Multiple trauma patients

Study entry criteria: Trauma patients (ISS > 13) admitted to the surgical ICU.

Study intervention/s: Patients were randomised to: 1) EN supplemented with arginine (experimental diet) or 2) isonitrogenous standard diet (Osmolite HN plus added Promod protein powder).
Group 1 formula consisted of 1.3Cal/ml, 66.6 g protein/L (of which 6.6 g/L was arginine), 37.4 g fat/L. Group 2 formula (Osmolite HN supplemented with promod protein powder) consisted of 1.17 Cal/ml, 64.4 g protein/L (of which 3.5 g is arginine), and 39.2 g fat/L. EN was delivered via needle catheter jejunostomy or nasoduodenal tube and began within 3 days of hospital admission. Goal feeding rate was 30Cal/kg/day and 1.5 g protein/kg/day.

Total number of patients randomised: 59 patients were enrolled and randomised:

Outcome by study arm:

Outcome Reporting
16 patients were 'eliminated' from the study: 1 due to 'inadequate data collection' and 15 because they received less than 5 days of EN. Neither randomisation group nor outcomes were reported for these 16 patients.

Intention to Treat Mortality
Conservative ITT cannot be calculated.

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Unclear ☒ No ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☒ No ☐
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☐ No ☒

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):

27% differential loss to follow-up. Conservative ITT cannot be calculated due to high loss to follow-up. This paper cannot be considered further.[GSD]
Group 1 was fed within 2.5 days and Group 2 within 2.6 days. The formulas used are not commercially available (experimental formula) or are available but have been manipulated (Osmolite HN with added protein) [FS].
Patients were adult trauma patients admitted to a surgical ICU. Avg ICU LoS and a days ventilated were > 10. These patients are critically ill.[AD]

Topic: EN Arginine vs. Standard EN

RefID **321**

Reference: (Preiser et al. 2001)

Patient Population: Critically ill (ICU) patients

Study entry criteria: Patients admitted to a mixed medical and surgical ICU over 18 yo who required EN.

Study intervention/s: Patients were randomised to: 1) EN enriched with arginine or 2) standard EN.
The group 1 formula contained 1.25 Cal/ml, 68.5 g protein/L (8.7 g came from arginine), 136 g carbohydrate/L, 49 g lipid/L. The group 2 formula was identical to group 1 in terms of above content excepting that group 2 formula was lower in arginine content (2.4 g from arginine).
EN commenced at 30ml/hr continuously at study day 0 and increased to 60ml/hr over 24 hrs on study day 1 and for the duration of the study.

Total number of patients randomised: 51 patients were randomised:

Outcome by study arm:

Outcome Reporting
14 patients were 'dropped' from the study. 8 patients were 'dropped' due to death before study day 7, 6 patients were 'dropped' due to ability to consume an oral diet before study day 7. The Group to which each of these 14 patients was randomised was not reported. Outcomes for the patients who were able to convert to oral intake early were not reported.

Intention to Treat Mortality
Conservative ITT cannot be calculated due to loss to follow-up / incomplete reporting.

Methodological issues:

Method of randomisation reported:	Yes ☒ No ☐	Allocation concealed:	Unclear ☒ No ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☐ No ☒

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):
Due to 27% loss to follow-up/incomplete reporting of loss by study arm, a conservative ITT cannot be calculated. This study cannot be considered further.[GSD]
These patients were enrolled while in the ICU. Likely to be critically ill.[AD]

Topic: EN Arginine vs. standard EN

RefID **465**

Reference: (Senkal et al. 1997)

Patient Population: Surgical ICU patients.

Study entry criteria: Patients who underwent major GI surgery for upper GI cancer.

Study intervention/s: Patients were randomised to receive: 1) arginine enhanced EN (Impact) or 2) isocaloric, isonitrogenous placebo diet.
Group 1 formula (Impact) consisted of 1.0Cal/ml, 134 g carbohydrate/L, 55.8 g protein/L (of which 12.5 g/L was L-arginine), 27.8 g fat/L. Group 2 formula consisted of 1.0Cal/ml, 119.8 g carbohydrate/L, 70g protein/L (no arginine) 27.8 g fat/L.
Feeding for both groups were commenced 12-hrs post surgery via an intraoperatively placed needle-catheter jejunostomy tube. Enteral feeding commenced at 20ml/hr and aimed to increase to a goal rate of approximately 25Cal/kg/day by postoperative day 5.

Total number of patients randomised: 164 patients were randomised: 82 to Group 1 and 82 to Group 2.

Outcome by study arm:

Outcome Reporting

"On review of the eligibility criteria, 10 patients had to be excluded from the study." 2 due to withdrawn consent and 8 due to insufficient diet intake. 5 were withdrawn from each group. Outcomes (mortality) are not reported in these patients.

Intention to Treat Mortality

Reported in-hospital mortality:
5+ 3/ 82 Group 1 (Impact) vs.
5+ 2/ 82 Group 2

Methodological issues:

Method of randomisation reported:	Yes ☒ No ☐	Allocation concealed:	Unclear ☒ No ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☒ No ☐
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☐ No ☒

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):

6% (10/164) overall loss to follow-up. Since patients were excluded from follow-up due to poor intake, and it is possible that patients who do not tolerate an EN diet may have a higher risk of poor outcome, this lack of follow-up could represent a source of bias.[GSD]
Patients were having major abdominal surgery for upper GIT cancer. Long ICU stay (5-6.8 days), long hospital stays (27-30 days) and APACHE II score of approx 10. These patients are likely to be critically ill.[AD]

Topic: EN Composition: Carbohydrate/Fats Fish Oils

RefID **258**

Reference: (Kenler et al. 1996)

Patient Population: Patients with upper GI cancer.

Study entry criteria: Patients scheduled for major abdominal surgery for upper GI cancer.

Study intervention/s: Patients were randomised to: 1) fish-oil based EN or 2) standard EN (Osmolite HN).
The two formulas were identical in terms of percentage of total calories from carbohydrate (53.3%), fat (30%) and protein (16.7%). They only differed in their individual lipid compositions. Both solutions were 1.06Cal/ml. Group 1 (fish-oil EN) received 70% of their total fat content as fish oils and MCT oil (and the remainder consisted of 20% canola oil, 6.8% soybean oil and 3.2% soy lecithin). Group 2 received 48.4% of their total fat as MCT oil (and the remainder consisted of 38.7% corn oil, 9.7% soybean oil and 3.2% soy lecithin).
All patients had a jejunostomy tube placed at the time of abdominal surgery and feeding began within 48 hours of surgery. EN was commenced at 10ml/hr (full strength) and increased by 10mls q12hrs, to reach goal rate 3-4 days postoperatively. Both groups aimed for 25-30Cal/kg body weight/day and 1.2-1.5g protein/kg/day.
Oral diets were advanced as per the surgeon and the enteral feeding rate was gradually reduced. Dietary fat was restricted and measured.

Total number of patients randomised: 50 patients were randomised: 25 to each Group

Outcome by study arm:

Outcome Reporting

Outcomes are not reported on 15 patients (7 from Group 1 and 8 from Group 2) because they did not reach ≥ 40 mls/hr of enteral intake.

Intention to Treat Mortality

A conservative ITT cannot be calculated. Reported mortality:
?? + 0/17 Group 1 (added fish oils) vs.
?? + 1/18 Group 2

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Unclear ☒ No ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☒ No ☐
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☐ No ☒

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):

30% (15/50) loss to follow-up yields this study potentially unreliable. Conservative ITT cannot be calculated. This study cannot be considered further.[GSD]
The fish oil fortified formula was made especially for this experiment [FS]
Patients having major abdominal surgery for upper GIT malignancy. Oesophagectomy 13/35, whipple 13/35. APACHE II of approx 8 at admission. These patients are likely to be critically ill.[AD]

Topic: EN + IV Glutamine vs. **EN + IV** amino acids

RefID **293**

Reference: (Wischmeyer et al. 2001)

Patient Population: Severe burns

Study entry criteria: Patients with burns > 25% BSA, > 2 years old admitted within 72 hours of burn injury.

Study intervention/s: Patients were randomised to: 1) EN plus IV glutamine or 2) EN plus isonitrogenous control amino acid solution.
EN formula (Pro-Balance) was used in both groups (contained no added glutamine or other immunonutrients, composition not provided). TPN was also used if EN was unable to be tolerated.
All patients received EN feeding + IV supplement within 48 hours of injury. IV glutamine (0.57g/kg/day L-Glutamine) or isonitrogenous control solution (0.57g/kg/day mixed amino acids but containing no glutamine) were not taken into account with regards to the calculation of nutritional goals. A caloric goal of 30Cal/kg/day was set for both groups.

Total number of patients randomised: 31 patients were randomised: 15 to Group 1 and 16 to Group 2.

Outcome by study arm:

Outcome Reporting

3 patients in Group 1 were 'excluded': 1 death < 72 hrs, and 2 patients due to age < 2. Outcomes were not reported for these 2 patients.
2 patients in Group 2 were 'excluded': 1 death < 72 hrs, 1 failure to obtain consent.

Intention to Treat Mortality

Hospital discharge mortality:
2 loss to follow-up + 2/ 15 Group 1 (IV glutamine) vs
1 loss to follow-up + 5/ 16 Group 2 (IV amino acids)

Methodological issues:

Method of randomisation reported:	Yes ☒ No ☐	Allocation concealed:	Yes ☒ No ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☒ No ☐
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):

There were 3 of 31 patients (9.7%) on whom outcomes were not reported. This could lead to bias in the interpretation of the conservative ITT.[GSD]
Group 1 had 5.2 days of TPN and group 2 had 7 days [FS]
Patients with burns. TBSA around 50%. 70% required mechanical ventilation. These patients are critically ill.[AD]

Topic: PN L-alanyl-L-Glutamine vs. PN

RefID **240**

Reference: (Goeters et al. 2002)

Patient Population: Surgical ICU patients.

Study entry criteria: Patients were eligible for randomisation within 3 days of ICU admission and before the start of balanced nutrition. Patients must have failed EN or have a contraindication to EN and be expected to stay in ICU for at least 5 more days.

Study intervention/s: Patients were randomised to: 1) PN supplemented with L-alanyl-L-Glutamine or 2) standard PN.
Group 2 (control) received 1.5 g amino acids/kg body weight/day, group 2 received 1.2 g amino acids/kg body weight/day and 0.3 g/kg body weight/day alanyl-glutamine (Dipeptiven). Target goals for daily fat and protein intakes were 1 g/kg body weight/day and 3 g/kg body weight/day respectively for both groups.

Glutamine free enteral nutrition (EN) was begun as soon as possible, with PN being reduced only when 700mls of EN were tolerated. Group 1 continued to receive glutamine supplementation as long as central venous access was required for other reasons.

Total number of patients randomised: 144 patients were randomised.

Outcome by study arm:

Outcome Reporting

34 randomised patients were discharged from the ICU prior to receiving 5 days of feeding and **15** randomised patients died prior to receiving 5 days of feeding. Group allocation is not reported for any of these 49 patients. Outcomes are not reported for the 34 early discharge patients.

Intention to Treat Mortality

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Unclear ☒ No ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☐ No ☒

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):

Due to 34% loss to follow-up a conservative ITT analysis cannot be conducted. This paper cannot be considered further.[GSD]
Average time to feeding commencement was not provided for both groups. Mortality does not seem to be provided for those staying >=5 days only for those staying >= 9 days [FS]
Patients were randomised in the ICU. These patients are critically ill.[AD]

Topic: PN Glutamine vs. PN

RefID **1152**

Reference: (De Beaux et al. 1998)

Patient Population: Acute pancreatitis

Study entry criteria: Patients with severe acute pancreatitis, defined as a modified Glasgow score ≥ 3 in a patient requiring TPN because of persistent failure of GI tract 7 d after the onset of illness.

Study intervention/s: Patients were randomised to: 1) PN supplemented with glutamine or 2) isocaloric, isonitrogenous, isovolumetric control PN.

All 14 patients were commenced on PN for a minimum of 3 days prior to randomisation.
Both groups received 0.25 g nitrogen/kg body weight/day ("Glamin" in group 1 or "Vamin 18 EF" in group 2) with lipid emulsion (20% Intralipid) and glucose (concentration unspecified). Group 2 therefore received an additional 0.22 g glutamine/kg body weight/day in comparison to group 1. Both groups received 29.4 Cal/kg body weight/day.

Total number of patients randomised: 14 patients were randomised: 7 in Group 1 and 7 in Group 2.

Outcome by study arm:

Outcome Reporting
1 patient from Group 1 was lost to follow-up due to central line sepsis on day 3 of study protocol.

Intention to Treat Mortality
1+ 0/14 Group 1 (PN plus glutamine)
0/14 Group 2 (control PN)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Unclear ☒ No ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):

It is reported that no patient died from the disease during the 'index admission'. Due to zero reported mortality events and the small sample size, this study becomes 'uninformative'. Due to the 7.1% (1/14) differential loss to follow-up, interpretation of the presented results could be biased[GSD].
Patients had severe acute pancreatitis. Modified Glasgow score ≥ 3. No overt measure of severity (ie. Ranson's, CT etc) reported. These patients are likely to be critically ill.[AD]

Topic: PN Glutamine vs. PN

RefID **958**

Reference: (Jackson et al. 2000)

Patient Population: ICU patients

Study entry criteria: ICU admission.

Study intervention/s: Patients were randomised to receive: 1) PN supplemented with glutamine (0.4 g/kg/day); 2) standard PN or 3) PN supplemented with glutamine (0.4 g/kg/day) and growth hormone (0.2 IU/kg/day).
A standard TPN solution was used for all groups and consisted of 50% dextrose, 20% Intralipid (Kabivitrum), and a mixed amino acid solution (Vamin 14). Groups 1 and 3 also received additional nitrogen to group 2 due to the addition of glutamine (~0.06 g nitrogen/kg/day).

Total number of patients randomised: 19 patients were initially studied

Outcome by study arm:

Outcome Reporting
2 of the 19 patients initially studied 'died before completion of the second study'. It is not reported to which group these patients were randomised. Of the remaining 17 patients, no mortality events are reported for Group 1 or Group 2.

Intention to Treat Mortality
Conservative ITT cannot be calculated.
Reported 28-day mortality
?? + 0/6 Group 1 (PN glutamine)
?? + 0/6 Group 2 (standard PN)
?? + 1/5 Group 3 (PN glutamine and growth hormone)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Unclear ☒ No ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☐ No ☒

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):

With 10.5% (2/19) differential loss to follow-up (two mortality events) and no additional mortality events reported in Group 1 or Group 2, this study becomes 'uninformative'.[GSD]
Patients were randomised in the ICU. Avg APACHE II was 16. These patients are likely to be critically ill.[AD]

Topic: PN Dose, hypocaloric vs. standard + lipids

RefID **355**

Reference: (McCowen et al. 2000)

Patient Population: Hospitalised patients requiring PN.

Study entry criteria: Requirement for PN according to 'standard hospital criteria'.

Study intervention/s: Patients were randomised to: 1) Hypocaloric PN or 2) standard PN.

Group 1 (hypocaloric group) received 1 litre of TPN solution/day (providing 70g protein/day and 1000Cal/day, no lipid).
Group 2 (standard TPN) aimed for a goal rate of 25Cal/kg body weight/day and 1.5 g protein/kg body weight. Fat was provided as part of the 3-in-1 solution and could account for up to 30% of calories for group 2.

Total number of patients randomised: 48 patients were randomised: 25 to Group 1 (hypocaloric PN) and 23 to Group 2 (control PN).

Outcome by study arm:

Outcome Reporting
4 patients in each group (total of 8 patients) were excluded from data analysis due to a PN duration of ≤ 4 days. Outcomes are not reported for these patients.

Intention to Treat Mortality
Conservative ITT cannot be calculated.
Reported mortality:
?? + 2/21 Group 1 (hypocaloric) vs.
?? + 3/19 Group 2 (control PN)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Unclear ☒ No ☐
Consecutive pts enrolled:	Yes ☒ No ☐	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☐ No ☒

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):

Due to 16% (8/48) loss to follow-up, interpretation of the reported outcomes may be significantly biased.[GSD]
Average time to commencement of TPN was not stated for either group [FS]
Patients requiring TPN. 17/48 required TPN and 13/48 required vasopressors. These patients are likely to be critically ill.[AD]

Topic: EN + bolus OKG vs. EN + continuous OKG vs. control EN

RefID **748**

Reference: (Le Bricon et al. 1997)

Patient Population: Burns patients

Study entry criteria: Consecutively admitted burns patients with TBSA > 20% but < 50%.

Study intervention/s: Patients were randomised to: 1) 10g ornithine α-ketoglutarate (OKG) delivered as a bolus before the start of EN, 2) OKG delivered continuously (10, 20 or 30g/day over 21 days) during the delivery of EN or 3) standard EN.

All groups received continuous nasogastric EN using a polymeric commercial formula (Dripsol 81, no further details provided). Individual nutritional requirements were calculated using the Harris Benedict equation. Enteral feeding commenced at approximately 500Cal/day and 4g protein/day (on day 1 or 2 post injury) and increased to an average of 2990Cal/day and 24g protein/day by study day 7.

Total number of patients randomised: 54 consecutive patients were scheduled to be included:

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
OKG kinetic studies were performed on day 7 post injury. 12 patients with septicaemia or who were intolerant to EN at the time kinetic studies were performed were excluded to follow-up.	

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Unclear ☒ No ☐
Consecutive pts enrolled:	Yes ☒ No ☐	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☐ No ☒

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):

Glutamine and arginine are metabolites of OKG. Due to 22% (12/54) loss to follow-up by day 7, and a lack of outcome reporting beyond day 7, this paper cannot be considered further.[GSD]
Burns patients admitted to a burns ICU. Avg TBSA 25 to 35%. These patients are likely to be critically ill.[AD]

Topic: PN Timing: early PN vs. delayed PN

RefID 2

Reference: (Sacks et al. 1995)

Patient Population: Severe head trauma

Study entry criteria: Patients with head trauma and a Glasgow Coma Scale score between 3 to 12.

Study intervention/s: Patients were randomised to receive: 1) early PN (day 1) or 2) delayed PN (day 5).

Goals for PN administration in both groups were 2 g protein/kg/day and 40 nonprotein Cal/kg/day (Aminosyn II 10% or Novamine 15%, Liposyn II 20%, hydrated dextrose 70%). Maximum glucose administration was 6 mg/kg/minute. IV lipid was given to all patients and constituted 15-30% of nonprotein calories. EN was commenced as early as the GI tract became functional and accessible using either a 1 or 2 Cal/ml solution (products and composition not specified).

Total number of patients randomised: 17 patients were randomised: 8 (group 1) and 9 (group 2).

Outcome by study arm:

Outcome Reporting

8 randomised patients were excluded from follow-up. 4 from each group. 5 because they regained consciousness and tolerated an oral diet within the first week (2 group 1 and 3 group 2). 3 because they died before receiving 7 days of PN (2 in group 1 and 1 in group 2).

Intention to Treat Mortality

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Unclear ☒ No ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☐ No ☒

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):

Other than the 3 patients who died before receiving 7 days of PN, mortality is not explicitly reported. A conservative ITT cannot be calculated. This paper cannot be considered further.[GSD]
Patients with closed head injury, GCS 3 to 12. Avg admission GCS 7 to 8. These patients are likely to be critically ill.[AD]

Topic: EN Composition: Lactobacillus and fibre

RefID 18

Reference: (Olah et al. 2002)

Patient Population: Acute pancreatitis

Study entry criteria: Typical clinical picture including abdominal pain, laboratory signs of pancreatitis (plasma amylase > 200 units/l) and a short duration of symptoms (admitted within 48 hours of onset).

Study intervention/s: Patients were randomised to receive: 1) EN (Nutrison Fibre) with added live lactobacillus and oat fibre vs. 2) EN (Nutrison Fibre) with added dead lactobacillus and oat fibre .

Both groups were fed using a 14F nasojejunal feeding tube, which was inserted on the day of admission. Feeding goals (30Cal/kg body weight) aimed to be met within 2-3 days of admission.
Group 2 was fed Nutrison Fibre via continuous gravity feeding for at least 7 days. Twice daily they also received heat-killed L-plantarum 299 and 10g oat fibre via feeding tube.
Group 1 received the same feeding protocol as group 2 above except that they received live L-plantarum 299 instead of dead.

Total number of patients randomised: 50 patients were randomised, 45 patients completed the study: 22 in Group 1 and 23 in Group 2.

Outcome by study arm:

Outcome Reporting

5 patients were 'excluded'. Three due to intolerance of the feeding tube (self-removed) and 2 due to intolerance of EN due to 'severe ileus'. Group of randomisation or outcome are not reported for these 5 patients.

Intention to Treat Mortality

Conservative ITT cannot be calculated.
Reported mortality:
?? + 1/22 Group 1 (lactobacillus) vs.
?? + 2/23 Group 2

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Unclear ☒ No ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☒ No ☐
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☐ No ☒

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):

10% (5/50) loss to follow-up precludes calculation of conservative ITT.[GSD]
Patients with acute pancreatitis. Average CRP 189-207. Severe in 32/45. Glasgow score > 3. These patients are likely to be critically ill.[AD]

Topic: EN Composition: Fibre

RefID **314**

Reference: (Spapen et al. 2001)

Patient Population: Patients with sepsis.

Study entry criteria: ICU patients in whom severe sepsis or septic shock was diagnosed within 4 hours of clinical onset. Severe sepsis was defined as sepsis with organ dysfunction, hypotension or hypoperfusion. Septic shock was considered present if systolic BP < 90 mmHg or decreased by > 40 mmHg from baseline.

Study intervention/s: Patients were randomised to: 1) EN supplemented with 22g/L of partially hydrolyzed guar (Benefibre) or 2) isonitrogenous, isocaloric control EN with no added fibre.

All patients were fed via a 16 French nasogastric tube within 24 hours of randomisation. Energy expenditure was estimated using an equation specifically designed for septic, ventilated patients. Both groups received a lactose free, 1Cal/ml formula consisting of 54% carbohydrate, 16% protein and 30% fat. Feeding started at 25ml/hr for the first 24 hours and then was increased by 25-35ml/hr to ultimately meet at least 80% of individual goals. No TPN was used.

Total number of patients randomised: 35 patients were randomised: 19 to Group 1 and 16 to Group 2.

Outcome by study arm:

Outcome Reporting

10 patients were excluded from final analysis (6 Group 1 and 4 Group 2) due to inadequate duration of enteral feeding as a result of: death within 6 days (n=4), intractable vomiting (n=2), gastric stasis with regurg. (n=3) and urgent abdominal surgery (n=1).
Reasons for loss to follow-up were not reported by group.

Intention to Treat Mortality

Conservative ITT cannot be calculated.
Reported mortality:
?? + 1/13 Group 1 (fibre) vs.
?? + 4/12 Group 2

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Unclear ☒ No ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☒ No ☐
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☐ No ☒

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):
29% (10/35) loss to follow-up precludes calculation of conservative ITT. This paper cannot be considered further.[GSD]
Patients with sepsis. Patients were enrolled in an ICU. APACHE II scores avg 24-26. These patients are critically ill.[AD]

Topic: EN Composition: Protein source

RefID **676**

Reference: (Borlase et al. 1992)

Patient Population: Hypoalbuminemic critically ill patients.

Study entry criteria: Patients with a compromised GI tract (non-use for more than a week, surgery or GI tract disease) anticipated to required EN for more than 7 days.

Study intervention/s: Patients were randomised to receive: 1) EN with hydrolyzed whey as a protein source (Peptamen) or 2) EN with free amino acids (Vivonex TEN).

Group 1 (Peptamen) consisted of 1.0 Cal/ml, 40g/L protein (hydrolysed whey), 127 g/L carbohydrate, 39 g/L fat (70% MCT, 30% LCT). Group 2 (Vivonex TEN) consisted of 1.0 Cal/ml, 38g/L protein (free amino acids), 206 g/L carbohydrate, 3g/L fat (sunflower oil).
Individual energy requirements were calculated for both groups using the Harris Benedict equation. Protein requirements were estimated at between 1 and 1.2g/kg body weight/day for both groups. EN commenced on study day 1 at 20-30ml/hr and increased by 10ml/hr each day until goal rate achieved.

Total number of patients randomised: 20 patients were randomised: 10 to each group

Outcome by study arm:

Outcome Reporting
4 patients (2 each group) were fed for less than 7 days and were thus excluded from analysis. Including one patient (Group 2) who died on day 6. Mortality for the 3 other 'exclusions' was not explicitly reported.

Intention to Treat Mortality
Conservative ITT cannot be calculated.
Reported deaths.
2 /10 Group 1 (Peptamen) vs
2 /10 Group 2 (Vivonex TEN)

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Unclear ☒ No ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):

Outcomes are not explicitly reported in 3/20 (15%) of randomised patients. Calculation of ITT may be unreliable.[GSD]
Patients wre thought to need tube feeding for > 7 days. 16/20 had GIT disease as primary diagnosis. ICU + mechanical ventilation of avg 23 to 28 days. These patients are likely to be critically ill.[AD]

Topic: EN Composition: peptide based EN

RefID **1194**

Reference: (Mowatt-Larssen et al. 1992)

Patient Population: Hypoalbuminemic critically ill patients

Study entry criteria: Acutely injured, critically ill patients with serum albumin < 3.0 g/dl at initiation of enteral feeding.

Study intervention/s: Patients were randomised to: 1) peptide based EN (Reabilan HN) or 2) isonitrogenous standard EN (Isocal HN).

15 g/L of whey protein (Promod) was added to the standard feed to make the formulas similar in nitrogen content. Full strength feedings were initiated at 25-50ml/hr, increasing by 25ml/day to a goal rate of 35Cal/kg body weight/day. Both groups were allowed to eat ad libitum if an oral diet was prescribed. Energy expenditure was calculated using the Harris Benedict equation.

Total number of patients randomised: 54 patients were randomised: 27 to each group.

Outcome by study arm:

Outcome Reporting

13 patients were lost to follow-up because they did not receive 5 consecutive days of EN (6 Group 1 and 7 Group 2). Of these 13 patients, one patient (Group 2) died within 5 days. Outcomes are not reported for the remaining 12 patients.

Intention to Treat Mortality

Conservative ITT cannot be calculated.
Outcomes not reported.

Methodological issues:

Method of randomisation reported:	Yes ☒ No ☐	Allocation concealed:	Unclear ☒ No ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):

22% (12/54) of patients are lost to follow-up. Clinical outcomes are not explicitly reported on the remaining 41 patients. This paper cannot be considered further.[GSD]
The number of days between hospital admission and study entrance was 5.9 days +- 4.6 days for all patients in the study [FS]
Patients were acutely injured. All were in ICU at study entry. APACHE II avg 9, ISS avg 28. These patients are likely to be critically ill.[AD]

Topic: EN Composition: Immune-enhancing diet (Immun-Aid)

RefID 20

Reference: (Moore et al. 1994)

Patient Population: Trauma patients.

Study entry criteria: Trauma patients with ISS from 16 to 45, and ATI from 18 to 40.

Study intervention/s: Patients were randomised to: 1) EN enhanced with glutamine, arginine, nucleic acids and omega-3 fatty acids (Immun-Aid) vs. 2) standard EN (Vivonex T.E.N).

Continuous enteral nutrition was commenced within 24hrs of injury via a needle catheter jejunostomy, transpyloric gastrojejunostomy or a nasally inserted post pyloric feeding tube. Immun-Aid was commenced at 25ml/hr (full strength), whereas Vivonex TEN was commenced at either full or half strength. Target goal rate by 72 hours was 35Cal/kg body weight/day for both groups.
Group 1 (Immun-Aid) consisted of 1Cal/ml, 80g total protein/L (29g BCAA, 12.5 g glutamine, 15.4 g arginine), 22g/L fat (1.1g omega 3 fats), 120g carbohydrate/L. Group 2 (Vivonex TEN) consisted of 1Cal/ml, 38g total protein/L (12.5g BCAA, 4.9g glutamine, 2g arginine), 3g/L fat, 206g carbohydrate/L.

Total number of patients randomised: 114 patients were randomised: 59 to Group 1 and 55 to Group 2.

Outcome by study arm:

Outcome Reporting

On examination of randomised patients, 9 were found not to meet inclusion/exclusion criteria (6 Group 1 and 3 Group 2). Of the remaining 105 patients, 7 were subsequently excluded (2 Group 1, 5 Group 2) because they did not receive enteral diet for 72 hours. Of these 7, one patient was reported as dead on day 3.

Intention to Treat Mortality

Conservative ITT cannot be calculated.
Reported mortality:
1+7 lost/ 51 Group 1 (Immun-Aid) vs
2 +8 lost / 47 Group 2 +8 lost

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Unclear ☒ No ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):

15 of 114 randomised patients (13%) were lost to follow-up and did not have outcomes reported. This amount of loss to follow-up could introduce significant bias.[GSD]
Patients with major torso trauma. ISS avg 20-21, 5.3 to 8.6 ICU days and 1.9 to 5.3 ventilator days. These patients are likely to be critically ill.[AD]

Topic: PN Lipids - Long chain (LC) and medium chain fatty acids (MCFA) vs long chain fatty acids (LCFA)

RefID **348**

Reference: (Lindgren et al. 2001)

Patient Population: Critically ill patients.

Study entry criteria: ICU patients between 18 and 80 suffering from multi-trauma and/or post-operative or septic patients who were anticipated to require TPN for at least 5 days.

Study intervention/s: Patients were randomised to receive: 1) TPN with MCFAs and LCFAs (Structolipid) vs. 2) TPN with LCFAs (Intralipid 20%).

Fat (Structolipid or Intralipid as randomised) was given starting on study day 1 at 1.5g triglycerides/kg body weight/day. The fat was administered over 12 hours (12am-12pm) as a separate infusion. Amino acids (Vamin 9 or 14) were infused at a dose of 0.2g nitrogen/kg body weight/day. Resting energy needs were determined daily by indirect calorimetry and glucose was used to make up the balance of energy requirements for both groups.

Total number of patients randomised: 30 patients were randomised: 15 to each Group

Outcome by study arm:

Outcome Reporting

6 patients in Group 1 were excluded from follow-up due to 1 early death (< 72 hours), lack of day 3 urinary N (n=4) or 'wrong stratification' (n=1). 4 Group 2 patients were excluded from follow-up due to: 2 early deaths (< 72 hrs), lack of day 3 urinary N (n=1) and raising serum creatinine (n=1). Hospital outcome is not explicitly reported in 5 Group 1 patients and 2 Group 2 patients.

Intention to Treat Mortality

Conservative ITT cannot be calculated.
Reported hospital mortality:
1 early death + 5 loss to follow-up+ 4/ 15 Group 1 vs
2 early deaths + 2 loss to follow-up+ 5/ 15 Group 2

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Unclear ☒ No ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☒ No ☐
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☐ No ☒

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):
Hospital outcome is not explicitly reported in 7 / 30 patients. 23% loss to follow-up could result in significant bias.[GSD]
It is unclear as to the length of time patients were hospitalised for before TPN was commenced [FS]
All patients were enrolled in the ICU and were thought to need TPN for > 5 days. Average APACHE II score was 16, average ICU LoS was 20 days. These patients are critically ill.[AD]

Topic: PN Lipids - Long chain (LC) and medium chain fatty acids (MCFA) vs long chain fatty acids (LCFA)

RefID **603**

Reference: (Porta et al. 1994)

Patient Population: ICU patients

Study entry criteria: ICU patients in need of TPN for at least 7 days.

Study intervention/s: Patients were randomised to receive: 1) TPN with 10% of medium chain and long chain triglycerides (20% Lipofundin) vs. 2) TPN with long chain triglycerides (20% Intralipid).

The two TPN solutions were isonitrogenous and isocaloric, differing only in the composition of lipid emulsions as above. Both formulas provided 0.25g nitrogen/kg/day (PT20 Pharmacia) and 35 Cal/kg/day. 57% of total calories were provided as glucose (5g glucose/kg/day) and 43% as lipid emulsion (1.7g/kg/day). Lipid emulsions were infused over 12 hours.

Total number of patients randomised: 23 patients were randomised: 12 to Group 1 and 11 to Group 2.

Outcome by study arm:

Outcome Reporting

7 patients were lost to follow-up. 4 due to death (group not reported) and 3 due to receiving ASA before the final day 7 platelet function test.

Intention to Treat Mortality

Conservative ITT cannot be calculated.

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Unclear ☒ No ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☐ No ☒

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):

Due to 23% loss to follow-up, this study cannot be considered further.[GSD]
Patients in general ICU who needed TPN for > 7 days. Average APACHE II score was 14.3. These patients are likely to be critically ill.[AD]

Topic: PN Lipids - Long chain (LC) and medium chain fatty acids (MCFA) vs long chain fatty acids (LCFA)

RefID **659**

Reference: (Ball 1993)

Patient Population: ICU patients

Study entry criteria: ICU patients who were likely to require TPN for at least 6 days.

Study intervention/s: Patients were allocated to: 1) TPN with 500mls of 20% medium and long chain triglycerides/day (Lipofundin) vs. 2) TPN with 500mls of long chain triglycerides/day (Lipofundin S).

Both groups of patients received 14g nitrogen/day (Synthamin 14), 250g glucose/day and 100g lipid/day (ie. 500mls of emulsion) except for those with multiple trauma who received 16g nitrogen/day, 350g glucose/day and 100g lipid/day. Lipid (as randomised) was infused over 8 hours in the evening.

Total number of patients randomised:

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**

Methodological issues:

Method of randomisation reported:	Yes ☒ No ☐	Allocation concealed:	Unclear ☐ No ☒
Consecutive pts enrolled:	Yes ☐ No ☐	Blinding employed:	Yes ☐ No ☐
100% follow-up:	Yes ☐ No ☐	Reporting of losses by study arm	Yes ☐ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):

This paper is a pseudo-randomised trial. Patients were allocated to treatment based on an alternating process. This paper cannot be considered further.[GSD]
Patients in an ICU requiring mechanical ventilation and at least 6 days of TPN. These patients are likely to be critically ill.[AD]

Topic: PN 46% BCAA vs. PN 21% BCAA

RefID **206**

Reference: (Kuhl et al. 1990)

Patient Population: Injured ICU patients.

Study entry criteria: Consecutive patients requiring PN for at least 7 days admitted to the ICU at a level 1 trauma centre due to injury.

Study intervention/s: Patients were randomised to receive: 1) PN with 46% BCAA or 2) PN with 21% BCAA.

Regimens were designed to be isocaloric, isonitrogenous and isovolemic and aimed to initially provide 30 nonprotein Cal/kg body weight/day and 0.25g/kg/day nitrogen. Approximately 40% of the nonprotein calories were given as lipid. Adjustments to infusion rate were made in an attempt to obtain nitrogen balance. Patients were allowed to eat ad libitum if clinically indicated.

Total number of patients randomised: 22 patients were enrolled: 11 to Group 1 and 11 to Group 2.

Outcome by study arm:

Outcome Reporting

2 patients (one from each group) were randomised but excluded from follow-up because they did not receive PN for at least 7 days.

Intention to Treat Mortality

Hospital mortality:
1+ 1/ 11 Group 1 (46% BCAA) died vs.
1+ 2/11 Group 2 patients

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Unclear ☒ No ☐
Consecutive pts enrolled:	Yes ☒ No ☐	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):

9% (2/22) loss to follow-up makes interpretation of the conservative ITT analysis unreliable.[GSD]
On average, parenteral nutrition was initiated 6.6 days (group 1) and 6.7 days (group 2) after injury [FS].
The patients were injured and enrolled in the ICU. APACHE II 12-15. Blunt trauma in 14/22 with 6/22 penetrating trauma. These patients are likely to be critically ill.[AD]

Topic: PN BCAA vs. standard PN

RefID 8

Reference: (Jimenez Jimenez et al. 1991)

Patient Population: Septic ICU patients.

Study entry criteria:

Study intervention/s:

Total number of patients randomised:

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**

Methodological issues:

Method of randomisation reported:	Yes ☒ No ☐	Allocation concealed:	Unclear ☐ No ☒
Consecutive pts enrolled:	Yes ☐ No ☐	Blinding employed:	Yes ☐ No ☐
100% follow-up:	Yes ☐ No ☐	Reporting of losses by study arm	Yes ☐ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):

"Patient selection was carried out in a random fashion, patients being assigned alternately to one or the other group according to the order in which they were admitted to the ICU." This trial is pseudo-randomised. Due to the impact that pseudo-randomisation may have on allocation concealment, this study cannot be considered further.[GSD]

Patients admitted to the ICU with severe sepsis. These patients are likely to be critically ill.[AD]

Topic: PN 45% BCAA vs. PN 19% BCAA

RefID **910**

Reference: (Brown et al. 1990)

Patient Population: Burns patients.

Study entry criteria: Consecutive patients with thermal injuries who would require PN for > 7 days with a TBSA > 10%.

Study intervention/s: Patients were randomised to: 1) PN with 45% BCAA or 2) PN with 19% BCAA.
The PN solutions for both groups were isonitrogenous, isocaloric and isovolaemic.
Intravenous fat emulsion provided approximately 25% of the nonprotein calories for both groups.
Energy requirements were calculated using the Harris Benedict equation (BEE x 1.5-1.7).

Total number of patients randomised: 23 patients were randomised:

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
"Three patients were excluded after entry because two died before completion of 7 days of PN and one patient was transferred to another hospital after 2 days of PN." Groups not specified.	Conservative ITT cannot be calculated. Reported mort: **5/10** Group 1 (45% BCAA) vs. **2/10** Group 2

Methodological issues:

Method of randomisation reported:	Yes ☐ No ☒	Allocation concealed:	Unclear ☒ No ☐
Consecutive pts enrolled:	Yes ☒ No ☐	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☐ No ☒

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):

13% (3/23) loss to follow-up, including two deaths, which are not reported by study arm precludes calculation of a conservative ITT.[GSD]
It is unclear as to when TPN commenced for both groups [FS]
Patients with thermal burns. TBSA around 45 to 49%. These patients are likely to be critically ill.[AD]

Topic: EN antioxidants + EN Composition: arginine

RefID **350**

Reference: (Preiser et al. 2000)

Patient Population: ICU patients

Study entry criteria: Patients over 18 years old admitted to the ICU who required enteral nutrition support.

Study intervention/s: Patients were randomised to: 1) EN with increased amounts of vitamin A (667ug/L of both Vitamin A and B-carotene), vitamin C (133mg/L) and vitamin E (49.4 mg/L) or 2) standard EN.

Group 1 also received free arginine (6.3g/L) which was added to the enriched EN solution.
Both enteral solutions contained 1.25Cal/L, 68.5g protein/L, 136g carbohydrate/L and 49g lipid/L. Solutions were commenced via NGT at a continuous rate of 30ml/hr from study day 0, and increased to a goal rate of 60ml/hr on day 1.

Total number of patients randomised: 51 patients were included

Outcome by study arm:

Outcome Reporting

14 patients 'did not complete the study' due to death (n=8) or recovery to oral diet (n=6) before day 7. Eventual outcomes for the early oral diet patients are not reported. It is not clear to which group these patients were randomised.

Intention to Treat Mortality

A conservative ITT analysis cannot be calculated.
Reported 28 day mortality:
?? + 8/20 Group 1 vs
?? + 6/17 Group 2

Methodological issues:

Method of randomisation reported:	Yes ☒ No ☐	Allocation concealed:	Unclear ☐ No ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☒ No ☐
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☐ No ☒

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomised, or if an ITT analysis cannot be calculated on at least 95% of all randomised patients. Papers with < 10% loss to follow-up were included in sensitivity analysis.

Reviewer comments (and initials):

Due to incomplete reporting and loss to follow-up in 27% (14/51) of randomised patients, this paper cannot be considered further.[GSD]
It is unclear as to the length of time patients were in ICU before EN was commenced. [FS]
Patients were enrolled in the ICU. SAPs II 33-34 with ICU LoS approximately 5 days. These patients are likely to be critically ill.[AD]

RCTs *not* conducted in a critically ill patient population

The RCTs in this section were judged not to have been conducted in critically ill patient populations. They may have additional methodological flaws.
Topic: TPN vs Standard

RefID 1223

Reference: (Yamada et al. 1983)

Patient Population: Gastric carcinoma patients treated by gastrectomy

Study entry criteria: All patients undergoing gastrectomy for stage 3 and stage 4 advanced gastric cancer.

Study intervention/s: Patients were randomised using a factorial design to 1) TPN vs 2) no TPN (low Calorie oral diet) and adjunct chemo with 5FU vs no 5FU-group.

All groups received conventional intravenous therapy for the first 3 days post operatively. On post operative day 4 groups received nutrition support as randomised.
TPN consisted of 2000-2150Cal/day and 10.8-12.7 mg nitrogen/day (solution consisted of 24% glucose and 12% Proteamin) begun immediately after surgery.
Controls received a low Calorie, oral fluid diet consisting of 360Cal/day. Oral intake was not restricted in either group.
Adjuvant oral chemotherapy was begun 1 week after surgery, which continued for as long as possible (5-FU).

Total number of patients randomised: 57 patients: 29 received TPN and 28 served as controls.

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
5 patients in the non-TPN 5 FU group (group 4) were dropped from the trial. Hospital mortality outcomes were reported on these patients.	Hospital Mortality **0/29** Group 1 (TPN) **1/18** Group 2 (low Calorie oral diet)

Methodological issues:

Method of randomization reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):
There are two studies presented in this paper that *may* follow a factorial design (unclear). ICU LoS or interventions that might require ICU stay (mechanical ventilation) are not reported. The in-hospital mortality is low. These patients are not likely to be critically ill.[GSD]

Topic: TPN vs Standard

RefID 1224

Reference: (Askanazi et al. 1986)

Patient Population: Patients undergoing radical bladder cystectomy

Study entry criteria: Patients undergoing radical bladder cystectomy

Study intervention/s: Patients were randomised to receive 1) TPN or 2) standard care (5% dextrose), 24-48 hours post surgery.

Group 1 patients received one of two TPN regimes with non-protein calories given as either glucose alone (glucose system) or a 50% mix of glucose and lipid (lipid system). The caloric intake for group 1 was designed to be 1.3-1.6 times the predicted energy expenditure. Nitrogen intake in the TPN group varied between 280-400mg/kg.
In the 5% dextrose group patients received approximately 400Cal/day in the form of carbohydrate.
In both groups IV therapy continued for at least 6-7 days after which oral intake was gradually introduced.

Total number of patients randomised: 35 patients were randomised, 22 group 1 vs 13 group 2.

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
2 patients are stated to have died from sepsis (group 2)	**0/ 22** Group 1 **2/ 13** Group 2

Methodological issues:

Method of randomization reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):
ICU LoS or interventions that would require ICU treatment (mechanical ventilation) were not reported. These patients are not likely critically ill.[GSD]

Topic: TPN vs. standard

RefID 1207

Reference: (Sax et al. 1987)

Patient Population: Acute pancreatitis

Study entry criteria: Pancreatitis was diagnosed based on: presence of acute abdominal pain; abdominal tenderness in LUQ, nausea or vomiting; history of antecedence alcohol abuse or gallbladder disease; and increased amylase.

Study intervention/s: Patients were randomised to; 1) TPN administered within 24 hours of hospital admission plus conventional care (NPO plus intravenous fluids and nasogastric tube on free drainage) or 2) conventional care, with TPN initiated if no oral intake by day 7.
TPN was composed of 25% dextrose and 4.25% amino acid solution with electrolytes, vitamins and trace elements infused at 40ml/hr. When the lipid profile confirmed the absence of hypertriglyceridemias, a 10% lipid emulsion was infused twice a week. TPN infusion rates were advanced over 2-3 days to address needs calculated with Harris-Benedict equation.

Total number of patients randomised: 54 patients were randomised.

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
	Hospital mortality: **1/28** early PN group **1/26** conventional care

Methodological issues:

Method of randomization reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☐ No ☒

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):
It is unclear as to how many patients were randomized to each group. On the last page of the Discussion, catheter related sepsis rate is mentioned as 3/28 patients. The assumption being that this is the early TPN group. In his published meta-analysis, Daren Heyland reports group size as 29 and 26, however this adds up to more than the 54 patients supposedly randomized into the trial.[GSD]
Patients had on average 1 Ranson criteria. Overall mortality is low. ICU LoS, admission, ventilation and APACHE not recored. These patients are not likely to be critically ill.[AD]

Topic: TPN vs. standard

RefID 1121

Reference: (Mimura et al. 1997)

Patient Population: Major surgery patients

Study entry criteria: Sub-total gastrectomy for gastric cancer.

Study intervention/s: This publication reports the results from 2 separate studies:
Study 1 compares: 1.1) IV glucose (200mg/day) for two days or
1.2) amino acids (54.4g/day) and glucose (150g/day).
Study 2 compares: 2.1) amino acids (54.4g/day) and glucose (260g/day),
2.2) amino acids (54.4g/day) and glucose (150g/day) plus fat (40g/day) emulsion (Intralipid), and
2.3) amino acids (58.4g/day) and glycerol (60g/day).
All groups received Ringers lactate immediately after surgery until 9am the following morning. All treatments were initiated at 9am the morning following surgery.

Total number of patients randomised: **Study 1** randomized 19 patients (9 to group 1.1, 10 in group 1.2). **Study 2** randomized 26 patients (9 in group 2.1, 10 in group 2.2 and 7 in group 2.3).

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
No patients died within 30 days of surgery.	

Methodological issues:

Method of randomization reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):
Due to the small sample size of each group and lack of mortality, each study becomes 'uninformative' with regards to the primary outcome of mortality.[GSD]
These patients are not likely to be critically ill.[AD]

Topic: TPN vs. standard

RefID 980

Reference: (Bonkovsky et al. 1991)

Patient Population: Moderately severe or severe alcoholic hepatitis.

Study entry criteria: 1) history of prolonged (>1 yr), regular (>5 days/wk) and heavy (>100 g /day) ethanol intake; 2) AST < 500 IU/L, AST/ALT ratio > 1.5, albumin <3.0g/dl, total bilirubin > 5mg/dl and PT < 6s above control and 3) cessation of alcohol intake 5 to 14 days prior to study entry.

Study intervention/s: Patients were randomized to one of three groups: 1) standard therapy, 2) oxandrolone (20mg qid) plus standard therapy, 3) TPN (P-900) plus standard therapy and d) oxandrolone (20mg qid) and TPN (P-900) plus standard therapy. (This is a factorial design)
Randomization took place after 10 days of standard care. All patients were also offered an oral diet (30Cal/kg IBW, 1gm protein/kg IBW). Standard therapy was not defined.

Total number of patients randomised: 39 patients were randomized: 12 into Group 1, 8 into Group 2, 9 into Group 3 and 10 into Group 4.

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**

Methodological issues:

Method of randomization reported:	Yes ☐ No ☐	Allocation concealed:	Yes ☐ No ☐
Consecutive pts enrolled:	Yes ☐ No ☐	Blinding employed:	Yes ☐ No ☐
100% follow-up:	Yes ☐ No ☐	Reporting of losses by study arm	Yes ☐ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):

No mortality events were reported by 21 days. Due to the small sample size of each group and no reported deaths, this study is 'uninformative' with regards to the primary outcome of mortality.[GSD]
Patients with co-morbidity (sepsis, pancreatitis, hemodynamic instability) were excluded. These patients are not likely to be critically ill.[AD]

Topic: TPN vs. standard

RefID 742

Reference: (Achord 1987)

Patient Population: Acute alcoholic hepatitis.

Study entry criteria: Hospitalization for acute alcoholic hepatitis. All patients consumed > 80g alcohol per day for over 5 years.

Study intervention/s: Patients were randomized to: 1) or 2) conventional treatment and supplemental nutrition (2L per 24 h of amino acid / glucose solution [P-900]).

Conventional treatment includes reintroduction of a balanced oral diet with vitamin and mineral supplementation.
P-900 provides 21.25 g protein/L and 430Cal/L.

Total number of patients randomised: 40 patients were randomized: 21 to group 1 (control) and 19 to group 2 (IV supplementation).

Outcome by study arm:

Outcome Reporting

In Group 1, outcomes were not reported in 7 patients: 3 withdrew, 1 developed ATN, 3 protocol violations. 3 deaths were reported of the remaining patients.
In Group 2, outcomes were not reported in 5 patients: 2 withdrew, 1 developed ATN, 1 developed thrombophlebitis and 1 withdrew. 1 death was reported of the remaining patients.

Intention to Treat Mortality

Hospital mortality:
10/21 Group 1 Control (oral diet only) 3 deaths+7 loss to follow-up vs
6/19 Group 2 Supplemented 1 death + 5 loss to follow-up

Methodological issues:

Method of randomization reported:	Yes ☒ No ☐	Allocation concealed:	Yes ☒ No ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):
This study contains greater than 5% loss to follow-up (12/40).[GSD]
Acute alcoholic hepatitis. Six of forty had encephalopathy. No other of severity are reported. These patients are not likely to be critically ill.[AD]

Topic: TPN vs. standard

RefID 730

Reference: (Simon and Galambos 1988)

Patient Population: Moderate to severe alcoholic hepatitis

Study entry criteria: History of chronic ethanol ingestion (> 80 g/day for at least 2 years) and right lobe hepatomegaly

Study intervention/s: Stratified by severity, patients were randomized to: 1) standard therapy or 2) peripheral parenteral nutrition (PPN) plus standard therapy.

Standard therapy included oral intake of 2400 calories/day, 100g of protein/day and a can of Ensure/meal.
PPN consisted of 2L per day of solution containing 35g Aminosyn, 50g dextrose plus electrolytes and 500ml of 10% Intralipid.
Patients were randomized between days 4 and 10 of hospital admission.

Total number of patients randomised: 34 patients were randomized: 18 to Group 1 and 16 to Group 2.

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
Outcomes were reported for all randomized patients.	Hospital mortality: **3/18** Group 1 (oral diet) **4/16** Group 2 (PPN plus oral diet)

Methodological issues:

Method of randomization reported:	Yes ☒ No ☐	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):
Patients with moderate or severe alcoholic hepatitis. Exclusions include most causes of need for ICU admission. These patients are not likely to be critically ill.[AD]

Topic: PN vs. EN

RefID 194

Reference: (Windsor et al. 1998)

Patient Population: Acute Pancreatitis

Study entry criteria: Serum amylase > 1000IU and clinical evidence of acute pancreatitis.

Study intervention/s:

Total number of patients randomised:

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**

Methodological issues:

Method of randomization reported:	Yes ☒ No ☐	Allocation concealed:	Yes ☐ No ☒
Consecutive pts enrolled:	Yes ☐ No ☐	Blinding employed:	Yes ☐ No ☐
100% follow-up:	Yes ☐ No ☐	Reporting of losses by study arm	Yes ☐ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):

Patients were 'randomized' based on odd or even hospital number. Since this paper used pseudo-randomization and could not maintain allocation concealment, it cannot be considered further.[GSD]

Patients with moderately severe pancreatitis. Only 5 pts were admitted to ICU. None of the enterally fed patients were admitted to ICU. Patients are not likely to be critically ill.[AD]

Topic: PN vs. EN

RefID 215

Reference: (Sand et al. 1997)

Patient Population: Curative total gastrectomy performed for gastric carcinoma.

Study entry criteria: Curative total gastrectomy performed for gastric carcinoma.

Study intervention/s: Patient was randomized to: 1) post-op TPN or 2) post-op EN (via N-J tube, 50-60cm distal to the oesophagojejunal anastomosis).
Both groups received 3L of 5% glucose IV on Day 1 post-op.
EN patients also received 1L 10% glucose via N-J tube. On day 2 EN patients received 1500mls of Pre-Nutrison. From day 3 onwards the EN group received 2L of Nutrison standard.
From day 2 the TPN group received 2,600ml Infumix Medium was delivered on day 2 post-op.

Total number of patients randomised: 29 patients were randomized: 16 to Group 1 and 13 to Group 2

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
Outcome information was reported on all patients.	Hospital discharge mortality: **1/16** Group 1 (TPN) vs **0/13** Group 2 (EN)

Methodological issues:

Method of randomization reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):
It is not clear whether any patients required post-op ICU care.[GSD]
These patients are not likely to be critically ill.[AD]

Topic: PN vs. EN

RefID 120

Reference: (Braga et al. 2001)

Patient Population: Patients requiring surgery for cancer of the stomach, pancreas and esophagus.

Study entry criteria: Diagnosis of cancer of the upper GI tract suitable for curative surgery.

Study intervention/s: Patients were randomized to: 1) TPN or 2) early enteral nutrition via catheter feeding jejunostomy or nasojejunal tube. Formulas were balanced for nitrogen, energy, electrolyte and trace element content.
TPN was begun on post-op day 1 by meeting 50% of nutritional goals in the first 24hrs and reaching goal rate by day 2.
EN was begun 6 hours after surgery at 10ml/hr and increased to reach goal requirements by day 4.
Nutritional goal was 25Cal/kg/day. Feeding continued until patients were consuming 800Cal/day orally.
Total number of patients randomised: 257 patients were randomized: 131 to Group 1 and 126 to Group 2

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
	Hospital discharge mortality: **4/131** Group 1 (TPN) vs. **3/126** Group 2 (EEN)

Methodological issues:

Method of randomization reported:	Yes ☒ No ☐	Allocation concealed:	Yes ☒ No ☐
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):
Less than 4% of all patients randomized required ICU care.[GSD]
These patients are not likely to be critically ill.[AD]

Topic: PN vs. EN

RefID 100

Reference: (Bozzetti et al. 2001)

Patient Population: Malnourished major elective surgery patients.

Study entry criteria: Weight loss > 10% over the previous 6 months, histologically proven cancer and major planned elective surgery.

Study intervention/s: Patients were randomized to 1) post-op TPN or 2) post-op EN.
EN patients were fed via a jejunostomy feeding catheter or nasojejunal feeding tube placed during surgery. Feeding regimes for both groups were designed to be isonitrogenous and isocaloric and provide 1.4g amino acids and 27Cal/kg/day. Feeding for both groups started at 8am the morning after surgery, continuing until an oral intake of ~800Cal/day was able to be consumed.

Total number of patients randomised: 317 patients were enrolled and randomized: 158 to Group 1 and 159 to Group 2

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
	Hospital discharge mortality: **5/158** Group 1 (TPN) vs. **2/159** Group 2 (EN)

Methodological issues:

Method of randomization reported:	Yes ☒ No ☐	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):
Only 6% of all randomized patients required ICU care.[GSD]
These patients are not likely to be critically ill.[AD]

Topic: PN vs. EN

RefID 754

Reference: (McClave et al. 1997)

Patient Population: Mild acute pancreatitis

Study entry criteria: Admitted to hospital with acute pancreatitis or acute flare of chronic pancreatitis, characterised by abdominal pain with elevated amylase and lipase.

Study intervention/s: Patients were randomized to: 1) TPN or 2) EN (Peptamen) via N-J tube.
TPN and EN feedings were designed to be isocaloric and isonitrogenous and meet goal requirements of 25Cal/kg and 1.2g protein/kg/d.
Both TPN and EN were begun within 48 hours of admission.

Total number of patients randomised: 38 patients initially evaluated met study criteria but 30 were ultimately included in the study. 2 of the 30 patients were admitted to hospital twice and randomized to each group. Thus the study reports 16 patients in Group 1 and 16 patients in Group 2.

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
8 patients were excluded after 'enrollment for: 2 for failing to start TPN or EN within 48 hours; 2 for removal of N-J tube; 2 for inability to place N-J tube; 1 due to 'complicated post-op anatomy' and 1 for noncompliance with dietary restrictions.	

Methodological issues:

Method of randomization reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☐	Blinding employed:	Yes ☐ No ☐
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☐ No ☒

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):

Although some patients were admitted to the ICU, no mortality events were reported throughout the duration of the study. Due to differential loss to follow-up, the randomization of 2 patients twice and zero mortality events, this study becomes 'uninformative' at best and cannot be considered further.[GSD]
Low initial Parons criteria, ICU stay < 3 days. Patients are not likely to be critically ill.[AD]

Topic: PN vs. EN

RefID 68

Reference: (Pacelli et al. 2001)

Patient Population: Major abdominal surgery.

Study entry criteria: Patients undergoing major elective abdominal surgery with a Nutritional Risk Index less than 90%.

Study intervention/s: Patients were randomized to: 1) TPN or 2) EN.
Feeding was initiated at 9am on the first postoperative day in both groups. Goal feeding rate was 25Cal/kg/d.
TPN consisted of 0.2 g nitrogen/kg/d, 25 non-protein calories/kg/d (including 30% lipids) and vitamins and minerals as appropriate.
The EN group (group 2) was fed via an intraoperatively placed nasojejunal tube (34%) or jejunostomy tube (68%). Nutrison (1 Cal/ml, 40g protein/L, 38.9g lipid/L, and 123g carbohydrate/L) was commenced at 30ml/hr full strength and increased gradually over 3 days. For the first 3 days after surgery the EN group also received TPN supplementation (same composition as TPN group) in order to match the total intake received in the TPN group. The above regimes continued until oral intake of at least 1000mls was taken or until day 10 of the study was reached.

Total number of patients randomised: 241 patients were randomized: 122 to Group 1 (TPN) and 119 to Group 2 (EN).

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
Outcomes were reported in all randomized patients.	30 day post-op mortality **3/122** Group 1 (TPN) patients died vs. **7/119** Group 2 (EN) patients

Methodological issues:

Method of randomization reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):
Need for ICU admission or length of ICU stay is not reported for this patient population.[GSD]
The majority of these patients would not normally be admitted routinely to the ICU. These patients are non likely critically ill.[AD]

Topic: PN vs. EN

RefID 968

Reference: (Abou-Assi et al. 2002)

Patient Population: Acute pancreatitis.

Study entry criteria: Patients admitted with acute abdominal pain and a 3-fold elevation of serum pancreatic enzymes, amylase and lipase, with a primary diagnosis of pancreatitis. Only patients not tolerating oral diet after 48 hours were randomized.

Study intervention/s: Patients were randomized to: 1) TPN or 2) EN (jejunal elemental diet).
Goal feeding was 25-30Cal/kg/d and 1.5g protein/kg/d. Individual enteral and parenteral formulas used were not explicitly reported.
Total number of patients randomised: 53 patients were randomized: 27 to Group 1 (TPN) and 26 to Group 2 (EN)

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
Outcomes are reported on all randomized patients.	Hospital discharge mortality: **6/27** Group 1 (TPN) patients died vs. **8/26** Group 2 (EN) patients

Methodological issues:

Method of randomization reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☐ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):

ICU stay is not explicitly reported.[GSD]
Average time to feeding commencement was not stated for either group [FS]
Majority have mild disease, 3.2% have severe disease. 15% require ICU management. Overall patients are not likely to be critically ill.[AD]

Topic: PN vs. EN

RefID 250

Reference: (Baigrie et al. 1996)

Patient Population: Major upper GI tract surgery.

Study entry criteria: Patients undergoing esophagectomy or gastrectomy.

Study intervention/s: Patients were randomized to 1) post-op TPN or 2) post-op EN via jejunostomy tube.
TPN was started post-op Day 1. TPN composition was not stated.
EN was begun post-op Day 3 with an infusion of 5% dextrose (total quantity not specified). Osmolite HN was commenced on post-op Day 4 and increased over 48hrs to a goal rate of 100mls/hr (continuous feeding over 24hrs).
Feeding was continued in both groups until patients were able to tolerate an oral diet of 2000Cal/day.

Total number of patients randomised: 97 patients were randomized: 47 to Group 1 and 50 to Group 2.

Outcome by study arm:

Outcome Reporting
Outcomes were reported on all patients.

Intention to Treat Mortality
30 day post-op mortality:
6/47 Group 1 (TPN) patients died vs.
4/50 Group 2 (EN) patients.

Methodological issues:

Method of randomization reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):

ICU admission rate or ICU LoS are not reported.[GSD]
Patients had oesophagectomy or gastrectomy. No report of numbers of each. Patients are not likely to be critically ill.[AD]

Topic: PN vs. EN

RefID 92

Reference: (Olah et al. 2002)

Patient Population: Acute pancreatitis

Study entry criteria: Patients admitted to the surgical ward with clinical symptoms and laboratory signs (amylase > 200U/L) of acute pancreatitis and brief histories of the disease (24 to 72 hours since onset).

Study intervention/s: Patients were randomized to: 1) PN vs 2) EN

Total number of patients randomised: 89 patients.

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**

Methodological issues:

Method of randomization reported:	Yes ☒ No ☐	Allocation concealed:	Yes ☐ No ☒
Consecutive pts enrolled:	Yes ☐ No ☐	Blinding employed:	Yes ☐ No ☐
100% follow-up:	Yes ☐ No ☐	Reporting of losses by study arm	Yes ☐ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):

Patients were ‘randomized’ based on their birth dates. Due to the use of pseudo-randomization, allocation concealment could not be maintained and this study could not be considered further.[GSD]
Only 17/89 had severe disease. Overall, patients not likely to be critically ill.[AD]

Topic: Timing of EN (early vs late feeding) + EN vs. standard

RefID 776

Reference: (Carr et al. 1996)

Patient Population: GI resection

Study entry criteria: All patients undergoing intestinal resection were eligible.

Study intervention/s: Patients were randomized to receive: 1) Immediate EN upon return from surgery using a N-J tube or 2) conventional care (NPO).

N-J tube was placed at time of surgery.
Conventional care patients received IV fluids and NPO until passage of flatus.

Total number of patients randomised: 30 patients were randomized after informed consent, but prior to surgery.

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
2 patients were randomized but did not receive surgery. It is not reported to which group these two patients were randomized to. This is a 6.66% differential loss to follow-up.	Hospital mortality: **0/14** Group 1 (EN) vs **1/14** Group 2 (NPO)

Methodological issues:

Method of randomization reported:	Yes ☒ No ☐	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☐ No ☒

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):

There was a differential loss to follow-up in 6.66% of all randomized patients (2/30). It is not clear how many patients were admitted to ICU post-op.[GSD]
Patients undergoing gastrointestinal resection. Record of ventilation or renal replacement was made but not reported. These patients were not likely to be critically ill.[AD]

Topic: Timing of EN (early vs late feeding) + EN vs. standard

RefID 751

Reference: (Beier-Holgersen and Boesby 1996)

Patient Population: Major abdominal surgery

Study entry criteria: All patients who suffered from gastro-intestinal diseases and who were treated by bowel resection with an anastomosis, and enterostomy, a gastric or oesophageal resection.

Study intervention/s: Patients were randomized to receive 1) Early EN feeding (Nutridrink, 1.5Cal/ml and 50g protein/L) or 2) Early enteral Placebo.

All patients received a nasoduodenal feeding tube at time of surgery. Enteral feeding for both groups was begun on return from surgery (600mls of either Nutridrink or placebo, given over 10hrs). Enteral feeding (Nutridrink or placebo as randomised) continued to be upgraded to the following daily goals - 1000mls (day 1), 1400mls (day 2) and 1800mls (days 3 and 4).
Placebo fluid was administered in an identical container to the Nutridrink. All patients were permitted to eat a normal oral diet from day 5 post surgery if tolerated.

Total number of patients randomised: 60 patients were randomized: 30 to Group 1 and 30 to Group 2.

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
Outcomes were reported on all patients.	Hospital discharge mortality: **2/30** Group 1 (EN) vs. **4/30** Group 2 (Placebo)

Methodological issues:

Method of randomization reported:	Yes ☐ No ☐	Allocation concealed:	Yes ☐ No ☐
Consecutive pts enrolled:	Yes ☐ No ☐	Blinding employed:	Yes ☐ No ☐
100% follow-up:	Yes ☐ No ☐	Reporting of losses by study arm	Yes ☐ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):
Only 8 of 60 patients (13%) required ICU care (2 in Group 1 and 6 in Group 2). [GSD]
Patients having gastrointestinal resections (52/60 colonic, 5/60 gastrectomy). These patients are not likely to be critically ill.[AD]

Topic: Timing of EN (early vs late feeding) + EN vs. standard

RefID 195

Reference: (Singh et al. 1998)

Patient Population: Nontraumatic intestinal perforation and peritonitis.

Study entry criteria: Patients admitted to a single surgical unit over a 1 year period with nontraumatic intestinal perforation and peritonitis. Patients were randomized before abdominal closure.

Study intervention/s: Patients were randomized to: 1) post-op EN or 2) control.

Group 1 patients received a 12F feeding jejunostomy tube. EN was begun within 12 to 24 hours post-op initially using IV fluids (normal saline and 5% dextrose) and electrolytes. Feeding in group 1 began at 24-48hrs post operatively using a low residue milk (skim milk powder, sugar, vegetable oil, water) based diet.1L of half-strength milk solution was commenced at 50ml/hr, 2L at 48-72 hrs postoperatively and from 72 hrs onward 2L of full strength feed was provided.
Group 2 (control) patients received IV fluids and electrolytes as needed.
Oral feeding was resumed once bowel activity returned.

Total number of patients randomised: 43 patients were randomized: 21 to Group 1 and 22 to Group 2.

Outcome by study arm:

Outcome Reporting
Outcomes are reported on all patients.

Intention to Treat Mortality
Hospital mortality:
4/21 Group 1 (EN) vs.
4/22 Group 2 (Control)

Methodological issues:

Method of randomization reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):

ICU admission rate and ICU LoS are not reported.[GSD]
Enteral feed used was non-commercial [FS]
Nontraumatic intestinal perforation and peritonitis. Sepsis score was low. Low rate of respiratory failure (3/43). These patients are not likely critically ill.[AD]

Topic: EN vs. Standard

RefID 1210

Reference: (Hartsell et al. 1997)

Patient Population: Elective colorectal surgery patients

Study entry criteria: Patients undergoing elective colorectal surgery.

Study intervention/s: Patients were randomized to 1) early enteral feeding vs. 2) traditional (later) enteral feeding.

All patients received orogastric tubes placed intraoperatively.
Early enteral feeding (Group 1) was begun on post-op Day 1 an oral diet was commenced when group 1 patients consumed 1000mls enterally in 24hrs.
Traditional enteral feeding (Group 2) was begun upon return of normal bowel function with passage of flatus or stool. Description of enteral formula was not provided.

Total number of patients randomised: 58 patients (29 to group 1 and 29 to group 2)

Outcome by study arm:

Outcome Reporting
Outcomes were reported on all patients.

Intention to Treat Mortality
Hospital mortality:
0/29 Group 1 (Early EN) vs.
1/29 Group 2 (Traditional EN)

Methodological issues:

Method of randomization reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):

ICU admission rate or ICU LoS was not reported.[GSD]
Elective colorectal surgery. ICU admission is not reported. Patients were relatively young. Co-morbidity is not reported. Low rates of complications. These patients are NOT likely to be critically ill.[AD]

Topic: EN vs. Standard

RefID 1212

Reference: (Stewart et al. 1998)

Patient Population: Patients with elective colorectal resections.

Study entry criteria: Patients undergoing elective colorectal resection with anastomosis and without stoma formation.

Study intervention/s: Patients were randomized to receive 1) Free fluids from 4h post-op or 2) NPO until passage of flatus or bowel motion.

All nasogastric tubes were removed in the Recovery room.

Total number of patients randomised: 88 patients were randomized.

Outcome by study arm:

Outcome Reporting

After randomization, 3 patients having extensive division of adhesions of > 2h duration and 5 patients having rectal anastomoses with covering stomas were excluded.

Intention to Treat Mortality

Cannot be calculated due to incomplete reporting of follow-up.

Methodological issues:

Method of randomization reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☐ No ☒

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):

8 of 88 randomized patients (9.1%) are lost to follow-up and cannot be attributed to their original groups. Since feeds were delivered orally (without a gastric tube), it is unlikely this study represents critically ill patients.[GSD]
The patients were having elevctive colorectal resections. Mortality is low, ICU admission is not reported. These patients are NOT likely to be critically ill.[AD]

Topic: EN vs. Standard

RefID 484

Reference: (Heslin et al. 1997)

Patient Population: Surgery of upper GI cancer.

Study entry criteria: All patients undergoing laparotomy for resection of neoplasms of the esophagus, stomach, pancreas and distal bile duct.

Study intervention/s: Patients were randomized to 1) early enteral feeding (using Impact, an immunoenhanced formula) via a jejunostomy tube or 2) control (IV crystalloid).

Patients were randomized after resection. Group 1 patients received a jejunostomy tube and feeding using Impact formula (1 Cal/ml, 59g protein/L, 28g lipid/L, and 132g carbohydrate/L) began within 24 hours of operation. Goal rate of feeding was 25Cal/kg/day.
Control patients received only IV crystalloid fluids. Both groups continued on the above regimens until either the resumption of an adequate oral intake (1000mls fluid/day), until study day 10, or until there was a complication that indicated prolonged restriction of oral intake. In the latter two cases participants could be given enteral or parenteral nutrition at the discretion of the surgeon.

Total number of patients randomised: 195 patients were randomized: 97 to Group 1 and 98 to Group 2.

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
Outcomes are reported on all randomized patients.	Hospital mortality: **2/97** Group 1 (Early Impact) vs **3/98** Group 2 (Control)

Methodological issues:

Method of randomization reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):
ICU admission rate and ICU LoS are not reported.[GSD]
5/97 (5%) of group 1 and 7/98 (7%)_of group 2 also received TPN. 5/98 (5%) of group 2 was also given enteral feeding. [FS]
Patients were having laparotomy for upper GI malignancy. The overall mortality is low. Some of the patients may be admitted to an ICU for overnight monitoring but the rate of major complications that would need ICU input is low (eg ARF 2/195, anastomotic leak 7/195). These patients are NOT likely to be critically ill.[AD]

Topic: EN vs. Standard

RefID 977

Reference: (Hartgrink et al. 1998)

Patient Population: Hip fracture

Study entry criteria: Patients with a hip fracture and a pressure-sore risk score of 8 or more.

Study intervention/s: Patients were randomized to receive: 1) EN via a N-G tube plus standard hospital diet or 2) standard hospital diet only.
Group 1 had a nasogastric tube placed either in surgery or 12hrs post-op. Feeding started within 24hrs. 1L of Nutrison Energy Plus (1.5 Cal/l, 60g protein/L) was given overnight (21.00-05.00) for two weeks with oral intake as tolerated during the day.

Total number of patients randomised: 140 patients were randomized.

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
Re-evaluation at admission, but after randomization, resulted in 11 patients lost to follow-up due to: presence of grade 2 pressure sores (4 pts), pressure sore risk score < 8 (7 pts).	

Methodological issues:

Method of randomization reported:	Yes ☐ No ☐	Allocation concealed:	Yes ☐ No ☐
Consecutive pts enrolled:	Yes ☐ No ☐	Blinding employed:	Yes ☐ No ☐
100% follow-up:	Yes ☐ No ☐	Reporting of losses by study arm	Yes ☐ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):

Incomplete reporting and loss to follow-up on 11 of 140 randomized patients (7.8%).[GSD]
These patients with hip fractures are not likely to be critically ill.[AD]

Topic: EN vs. Standard

RefID 1209

Reference: (Sagar et al. 1979)

Patient Population: Major GI surgery.

Study entry criteria: Patients undergoing major GI surgery.

Study intervention/s: Patients were randomized to receive: 1) EN via N-G tube or 2) control.

Group 1 patients received an elemental diet beginning on post-op day 1.
Group 1 (control) patients received electrolytes and 5% dextrose IV until post-op day 3, when fluids were begun per os. On post-op day 6 or 7, a light oral diet was begun.

Total number of patients randomised: 30 patients were randomized: 15 to Group 1 and 15 to Group 2

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**

Methodological issues:

Method of randomization reported:	Yes ☐ No ☐	Allocation concealed:	Yes ☐ No ☐
Consecutive pts enrolled:	Yes ☐ No ☐	Blinding employed:	Yes ☐ No ☐
100% follow-up:	Yes ☐ No ☐	Reporting of losses by study arm	Yes ☐ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):
Clinically meaningful outcomes (mortality) not explicitly reported. This study cannot be considered further.[GSD]

Topic: EN vs. Standard

RefID 954

Reference: (Sullivan et al. 1998)

Patient Population: Elderly hip fracture patients

Study entry criteria: Age > 64 and acute femoral neck or intertrochanteric fracture requiring surgery.

Study intervention/s: Patients were randomized to receive: 1) nightly post-op EN or 2) control.
Group 1 had their feeding tubes placed in either surgery or recovery. EN was then provided over an 11-hr period starting at 7pm using Promote formula (85.8 g protein/L, 1.031 Cal/L) via nasogastric or nasojejunal tubes. During the day both groups consumed standard postoperative diets.
EN continued in group 1 until patients were able to meet > 90% of their needs orally for at least 3 days

Total number of patients randomised: 18 patients were randomized: 8 to Group 1 and 10 to Group 2.

Outcome by study arm:

Outcome Reporting
Outcomes are reported on all patients.

Intention to Treat Mortality
Hospital mortality:
0/8 Group 1 (EN) vs.
3/10 Group 2 (control)
Six-month mortality:
0/8 Group 1 vs.
5/10 Group 2 (control)
p=0.036

Methodological issues:

Method of randomization reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):

Although mortality is high, ICU admit rate or ICU LoS are not reported.[GSD]
Time to commencement of EN was not specifically stated [FS]
MMSE score was low (< 24 out of a possible 30). These patients are unlikely to come to ICU. These patients are NOT likely to be critically ill.[AD]

Topic: EN vs. Standard

RefID 232

Reference: (Bastow et al. 1983)

Patient Population: Fractured neck of femur.

Study entry criteria: Patients with fractured neck of femur judged to be 'thin' or 'very thin' based on arm circumference and triceps skinfold thickness tests were eligible.

Study intervention/s: Patients were randomly allocated receive: 1) nightly EN via N-G tube feeding or 2) control.

All patients were allowed oral intake during the day. Group 1 received additional feeding overnight, started within 5 days post-op. Overnight EN consisted of 1 L of Clinifeed Iso (1 Cal/ml, 28g protein/L) given over 8hrs.

Total number of patients randomised: 122 patients were randomized: 64 to Group 1 and 58 to Group 2

Outcome by study arm:

Outcome Reporting
Outcomes were reported in all patients.

Intention to Treat Mortality
Hospital mortality:
7/64 Group 1 (nightly EN) vs
9/58 Group 2 (control)

Methodological issues:

Method of randomization reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):

Although mortality is reasonably high, ICU admit rate and ICU LoS are not reported.[GSD]
By day 5 post injury all patients had been transferred to the orthopaedic rehabilitation ward [FS]
These patients had fractured neck of femur. They are not likely to be critically ill.[AD]

Topic: EN Glutamine vs. EN and vs NPO

RefID 126

Reference: (Hsu et al. 2000)

Patient Population: Colorectal cancer surgery patients

Study entry criteria: Patients undergoing colon resection for colorectal cancer.

Study intervention/s: Patients were randomized to receive: 1) glutamine containing EN via N-G tube (AlitraQ); 2) low-residual EN via N-G (Osmolite HN); 3) high-fat EN via N-G (Pulmocare); or 4) NPO for 7 days.
Two of the formulas were manipulated to make them 1Cal/ml (Pulmocare was diluted from 1.5Cal/ml to 1.0Cal/ml and Polycose was added to AlitraQ to make it up to 1Cal/ml). All formulas contained 42g protein/L. All EN feeding was begun on the second post-op day.

Total number of patients randomised: 80 patients were randomized: 20 to each group.

Outcome by study arm:
Outcome Reporting **Intention to Treat Mortality**
Outcomes were reported on all patients.

Methodological issues:

Method of randomization reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):
There was no peri-operative mortality reported in any group, thus due to the relatively small sample size and zero events, this study becomes ‘uninformative’.[GSD]
Patients were having colonic resection for colon cancer. Zero mortality. These patients are NOT critically ill.[AD]

Topic: EN Arginine vs. standard EN

RefID 1216

Reference: (Daly et al. 1995)

Patient Population: Patients with gastrointestinal malignancies.

Study entry criteria: Patients undergoing major abdominal surgery for upper GI cancer with: no history of intestinal disease; no previous abdominal or pelvic radiotherapy; no preoperative infection (defined as temp > 37.6C, WBC > 10,000 cells/mL or bacteremia) and no administration of steroids or other immunosuppressive agents.

Study intervention/s: Patients were randomized to: 1) jejunostomy feeding with Impact or 2) standard EN (Traumacal).
Group 1 formula (Impact) consisted of 1.0Cal/ml, 134 g carbohydrate/L, 55.8 g protein/L (of which 12.5 g/L was L-arginine), 27.8 g fat/L. Standard EN (group 2) consisted of 107 g carbohydrate/L, 62 g protein/L (nil added arginine), 49g fat/L.
EN feeding was begun on post-op day 1 at 25ml/hr full strength feeding and increased to a goal rate of 75-100ml/hr by the third postoperative day. Feeding goals were to provide 25Cal/kg/day in both groups.

Total number of patients randomised: 60 patients were randomized: 30 to Group 1 and 30 to Group 2.

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
	In-hospital mortality: **1/30** Group 1 (Impact) vs. **2/30** Group 2 (Traumacal)

Methodological issues:

Method of randomization reported:	Yes ☒ No ☐	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):
Patients were upper GIT malignancy, undergoing abdominal surgery. ICU admission and ICU LoS is not reported. Excluded renal and liver impairment, pre-operative infection or previous surgery or radiotherapy. These patients are NOT likely to be critically ill.[AD]

Topic: EN Arginine vs. standard EN

RefID 885

Reference: (Daly et al. 1992)

Patient Population: Patients with upper GI malignancies.

Study entry criteria: Patients undergoing major abdominal surgery for upper GI cancer with: no history of intestinal disease; no previous abdominal or pelvic radiotherapy; no preoperative infection (defined as temp > 37.6C, WBC > 10,000 cells/mL or bacteremia) and no administration of steroids or other immunosuppressive agents.

Study intervention/s: Patients were randomized to: 1) arginine enhanced EN (Impact) or 2) standard EN (Osmolite HN).
Group 1 formula (Impact) consisted of 1.0Cal/ml, 132 g carbohydrate/L, 58.8 g protein/L (of which 12.5 g/L was L-arginine), 28 g fat/L. Standard EN (Osmolite HN) consisted of 1.06 Cal/ml, 141 g carbohydrate/L, 44.4 g protein/L (no added arginine), 36.8 g fat/L.
Feeding began on the first postoperative day at 25ml/hr (full strength), aiming to provide a goal of 25Cal/kg/day by the forth-postoperative day.

Total number of patients randomised: 85 patients were randomized: 41 to Group 1 and 44 to Group 2.

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
	Hospital mortality: 2/41 Group 1 (Impact) vs 0/44 Group 2 (standard)

Methodological issues:

Method of randomization reported:	Yes ☒ No ☐	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):
Patients undergoing major abdominal operation for upper GIT malignancy. Excluded patients with renal and hepatic insufficiency, previous surgery or radiotherapy or pre-op infection. ICU admission or ICU LoS are not reported. Hospital LoS averaged 15 to 20 days. Excluded patients with hemodynamic abnormality. These patients are NOT likely to be critically ill.[AD]

Topic: EN Composition: Carbohydrate/Fats Fish Oils

RefID 729

Reference: (Swails et al. 1997)

Patient Population: Upper GI cancer patients

Study entry criteria: Scheduled for abdominal surgery for upper GI cancer.

Study intervention/s: Patients were randomized to receive: 1) fish-oil based EN or 2) standard EN (Osmolite HN).

The two formulas were identical in terms of percentage of total calories from carbohydrate (53.3%), fat (30%) and protein (16.7%). They only differed in their individual lipid compositions. Both solutions were 1Cal/ml. Group 1 (fish-oil EN) received 70% of their total fat content as fish oils and MCT oil (and the remainder consisted of 20% canola oil, 6.8% soybean oil and 3.2% soy lecithin). Group 2 received 48.4% of their total fat as MCT oil (and the remainder consisted of 38.7% corn oil, 9.7% soybean oil and 3.2% soy lecithin).
All patients had a nasojejunal or jejunostomy tube placed at the time of abdominal surgery and feeding began within 48 hours of surgery. EN was commenced at 10ml/hr (full strength) and increased by 10mls q12hrs, to reach goal rate 3-4 days postoperatively. Both groups aimed for 25-30Cal/kg body weight/day and 1.2-1.5g protein/kg/day.
Oral diets were advanced as per the surgeon and the enteral feeding rate was gradually reduced. Dietary fat was restricted and measured.

Total number of patients randomised: 20 patients were randomized: 9 to Group 1 and 11 to Group 2.

Outcome by study arm:

Outcome Reporting

Outcomes were not explicitly reported in patients who did not receive >40ml/h of EN (one in each group).

Intention to Treat Mortality

A conservative ITT cannot be calculated.
Reported mortality:
0/8 Group 1 (added fish oil) vs.
0/10 Group 2

Methodological issues:

Method of randomization reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☒ No ☐
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☐ No ☒

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):
Lack of complete follow-up in 10% of patients makes this study susceptible to bias. A conservative ITT cannot be calculated. Zero mortality events in the remaining patients makes this study 'uninformative'.[GSD]
The fish oil fortified formula was made especially for this trial. [FS]
Patients having surgery for upper GI cancer. APACHE II score 8-9. ICU LoS, ventilation, inotrope use or renal failure not reported. These patients are not likely to be critically ill.[AD]

Topic: PN Glutamine vs. PN

RefID 98

Reference: (Mertes et al. 2000)

Patient Population: Major abdominal surgery.

Study entry criteria: Patients admitted for elective major abdominal or abdomino-thoracic surgery.

Study intervention/s: Patients were randomized to receive: 1) PN supplemented with glutamine (0.5 g/kg body weight/day) or 2) isonitrogenous, isocaloric PN.

Total number of patients randomised: 50 patients were randomized:

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
8 patients did not complete the study protocol: 4 because of acute surgical re-intervention; 3 with dislocated central venous lines and 1 due to allergic reaction to one of the therapeutic components. 5 patients received less than 85% of the prescribed parenteral feeding, hence could not be included in the final evaluation. Outcomes or Group allocation are not explicitly reported for these 13 patients.	

Methodological issues:

Method of randomization reported:	Yes ☐ No ☐	Allocation concealed:	Yes ☐ No ☐
Consecutive pts enrolled:	Yes ☐ No ☐	Blinding employed:	Yes ☐ No ☐
100% follow-up:	Yes ☐ No ☐	Reporting of losses by study arm	Yes ☐ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):

With 26% loss to follow-up, this paper cannot be considered further.[GSD]
The patients were undergoing elective abdominal or thoracoabdominal surgery. ICU days < 1 in both groups. These patients are NOT likely to be critically ill.[AD]

Topic: PN Glutamine vs. PN

RefID 9

Reference: (Ockenga et al. 2002)

Patient Population: Acute pancreatitis.

Study entry criteria: Patients with moderate to severe acute pancreatitis.

Study intervention/s: Patients were randomized to receive: 1) PN supplemented with glutamine (0.3g/kg L-alanine-L-glutamine) or 2) isonitrogenous, isocaloric PN (no glutamine).
Goal protein intake was 1.5 g/kg/day for both groups. Both groups received approximately 60% their non-protein energy as glucose and 40% as lipid (Lipofundin 20%).
Requirements were calculated via the Harris Benedict equation using a factor of 1.2-1.5 depending on the presence of systemic inflammation and activity level.

Total number of patients randomised: 28 patients were randomized: 14 to Group 1 and 14 to Group 2.

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
Outcomes are reported on all patients.	Hospital discharge mortality: **0/14** Group 1 (glutamine) vs. **1/14** Group 2

Methodological issues:

Method of randomization reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☒ No ☐
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):
TPN was commenced 45hrs (group 1) versus 40.3 hrs after admission (group 2) [FS]
Patients with acute pancreatitis. APACHE II 5.1 to 5.7 (severe are > 8). Average CRP at end of 1 week is low at 30 to 34 (severe is > 120). These patients are NOT likely to be critically ill.[AD]

Topic: PN Glutamine vs. PN

RefID 1155

Reference: (Neri et al. 2001)

Patient Population: Major abdominal surgery.

Study entry criteria: Patients undergoing major abdominal surgery for cancer with curative intent.

Study intervention/s: Patients were randomized to receive: 1) PN supplemented with glutamine or 2) isonitrogenous, isocaloric PN.

All groups received isocaloric (30 Cal/kg body weight/day), isonitrogenous (0.2 g nitrogen/kg body weight/day) TPN.
Group 2 (control) received 1.5 g amino acids/kg/day, and group 1 received 1.2 g amino acids/kg/day supplemented with 0.3 g/kg body weight/day of alanyl-glutamine.
TPN began the day after surgery.

Total number of patients randomised: 33 patients were randomized: 16 to Group 1 and 17 to Group 2.

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
Outcomes were reported on all patients.	Hospital mortality: **0/16** Group 1 (glutamine) vs. **0/17** Group 2

Methodological issues:

Method of randomization reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☒ No ☐	Blinding employed:	Yes ☒ No ☐
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):

These patients were undergoing major abdominal surgery. The surgery was for colerectal cancer (19/33), gastric cancer (9/33) and pancreatic cancer (5/33). No patients died. No ICU LoS, ventilation or inotrope use reported. These patients are NOT likely to be critically ill.[AD]

Topic: PN Glutamine vs. PN

RefID 969

Reference: (Lin et al. 2002)

Patient Population: Major abdominal surgery

Study entry criteria: Patients with APACHE II 2-10 and TISS > 10.

Study intervention/s: Patients were randomized to: 1) PN supplemented with glutamine or 2) isonitrogenous, isocaloric PN

Both groups received 0.228g/kg nitrogen/day and 30Cal/kg/day postoperatively. Group 1 received 0.28g glutamine/kg/day as part of their protein intake. 70% of the nonprotein calories were given as glucose and 30% as fat (Lipovenos 20%).

Total number of patients randomised: 48 patients were randomized: 25 to Group 1 and 23 to Group 2.

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
Outcomes were reported in all patients.	30 day mortality: **0/25** Group 1 (glutamine) vs. **0/23** Group 2

Methodological issues:

Method of randomization reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☒ No ☐
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):

Due to the lack of mortality, this study becomes ‘uninformative’.[GSD]
Patients were undergoing major elective abdominal surgery. 32/48 had surgery for gastric cancer. All APACHE II < 10. These patients are NOT likely to be critically ill.[AD]

Topic: EN Composition: ornithine α-ketoglutarate (OKG)

RefID 4

Reference: (Wiren et al. 2002)

Patient Population: Elective abdominal surgery patients.

Study entry criteria: Patients admitted for elective major abdominal surgery expected to need at least 5 days of post operative rehydration.

Study intervention/s: Patients were randomized to receive: 1) post-op EN supplemented with 7.9g/L of OKG or 2) standard post-op EN.

Formulas were designed to be isonitrogenous and isocaloric. Group 1 formula (OKG supplemented) consisted of 51 g/L protein, 45g/L fat, 146g/L carbohydrate, and 7.9 g/L OKG. Group 2 formula consisted of 49 g/L protein, 43g/L fat, 158g/L carbohydrate, and no OKG. EN began on postoperative day 1 in both groups using a needle catheter jejunostomy or a gastrojejunostomy placed in surgery. Feeding commenced at 50ml/hr (full strength) and gradually increased to 150-200mls/hr via feeding pump. Feeding goals at day 4 were 25Cal/kg body weight/day, 0.17g nitrogen/kg body weight/day and 30mls/kg body weight/day. Patients in both groups were allowed non-caloric fluids, which were usually started at day 3.

Total number of patients randomised: 22 patients were randomized: 11 to each group

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
2 patients were withdrawn from the control group due to dislocation of feeding tube and unwillingness to continue on-study.	No mortality events were experienced during 30 days post surgery.

Methodological issues:

Method of randomization reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☐ No ☒

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):

Due to 9% loss to follow-up, conservative ITT cannot be calculated. Due to lack of mortality events, this study becomes 'uninformative'.[GSD]

Patients undergoing major elective abdominal surgery. ICU LoS, need for ventilation or inotropes not reported. No mortality at 30d. These patients are NOT likely to be critically ill.[AD]

Topic: PN Lipids (2.5% lipid calories vs. 30% lipid calories)

RefID 598

Reference: (Craig et al. 1994)

Patient Population: Patients requiring TPN.

Study entry criteria: All patients felt to require TPN for at least 2 weeks.

Study intervention/s: Patients were randomized to receive: 1) TPN with 2.5% of calories supplied by lipids or 2) isocaloric TPN with 30% of calories supplied by lipids.

Both TPN solutions were designed to be equicaloric, differing in the percentage of non-protein calories coming from lipid (2.5% in group 1 and 30% in group 2). Amino acids were provided in order to provide a protein : calorie ratio of 1:150-200 for both groups. The remainder of the calories came from glucose. Each patient received 100-150% of basal energy requirements as determined by the Harris Benedict equation. Patients were randomised within 48 hours of commencing TPN.

Total number of patients randomised: 26 patients were randomized: 12 to Group 1 and 14 to Group 2.

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
Outcomes are reported in all patients.	Hospital mortality: **0/12** Group 1 (2.5% lipid) **0/14** Group 2 (30% lipid)

Methodological issues:

Method of randomization reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):

Due to the small sample size and lack of mortality events, this study becomes 'uninformative'.[GSD]
Time to TPN commencement for either groups was not stated [FS]
Patients requiring TPN for at least 2 weeks. Underlying diagnosis, ICU LoS or intervention not reported. Zero mortality. These patients are not likely to be critically ill.[AD]

Topic: PN Composition: kcal:N ratio + PN Dose

RefID 870

Reference: (De Oca et al. 1992)

Patient Population: Patients with GI cancer

Study entry criteria: Patients who received oesophagogastric or colorectal resections for GI tumours.

Study intervention/s: Patients were randomized to receive: 1) TPN at 23Cal/kg/day with a 100:1 kcal:g N_2 ratio or 2) isonitrogenous TPN at 35 Cal/kg/day with a 150:1 kcal:g N_2 ratio.

The only difference between the two TPN regimes was stated to be the amount of total Calories received. Regimes were designed to be isonitrogenous. Both groups received 10% L-amino acid (Aminofusin 10) which provided a total nitrogen intake of 0.23g/kg/day.
Group 1 received a 23Cal/kg/day in a 65/35 glucose/lipid TPN mix. Group 2 received 35Cal/kg/day. The amount of electrolytes, vitamins and trace elements were the same for both groups and TPN was given by a central venous catheter.
TPN was commenced 24 hours post surgery in both groups. Exclusive PN continued until oral intake was allowed on day 6.

Total number of patients randomised: 44 patients were randomized: 22 to each Group

Outcome by study arm:

Outcome Reporting

It is reported that at least 1 of the 44 patients died, however the authors do not report which group this patient was randomized to.

Intention to Treat Mortality

No other mortality reported.

Methodological issues:

Method of randomization reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☐ No ☒	Reporting of losses by study arm	Yes ☐ No ☒

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):

Due to incomplete reporting, the mortality reported in this paper cannot be attributed to the appropriate group. This paper cannot be considered further.[GSD]
Patients had 'curative' surgery for GIT neoplasm. Severity of illness is not reported. ICU LoS is not reported. Patients with renal and liver disease were excluded. These patients are NOT likely to be critically ill.[AD]

Topic: Tube Placement

RefID 228

Reference: (Stiegmann et al. 1988)

Patient Population: All patients referred for gastrostomy.

Study entry criteria: Patients over 18 years of age referred to the surgical or gastroenterologic service for placement of feeding gastrostomy because of inability to maintain adequate nutritional intake orally.

Study intervention/s: Patients were randomized to receive: 1) percutaneous endoscopic gastrostomy or 2) surgical gastrostomy.

Both gastrostomy procedures were scheduled to be performed within 5 days of randomisation. A gastroenterology fellow performed endoscopic procedures and junior surgical residents under supervision from a faculty surgeon performed operative gastrostomies.
Once feeding tubes were inserted management was similar between groups. The tube was left to drain via gravity for 12-24 hours and then feeding was begun. Clear liquids or dilute EN were commenced the morning after the procedure, with feeding increased at 8-12 hourly intervals to goal rate. Detailed feeding protocols were not provided for either group.

Total number of patients randomised: 51 patients were randomized: 25 Group 1 vs. 26 Group 2

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
Three patients died after randomization but prior to receiving a gastrostomy. (2 in Group 1 and 1 in Group 2)	30 day mortality: **2 / 25** Group 1 (percutaneous) **3 / 26** Group 2 (operative) 90 day mortality: **2 / 25** Group 1 (percutaneous) **4 / 26** Group 2 (operative)

Methodological issues:

Method of randomization reported:	Yes ☒ No ☐	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):
No details are provided as to the amount of EN given pre-insertion of the gastrostomies. Detailed feeding protocols were not provided for either group post insertion [FS]
Patients were referred for gastrostomy. Underlying diagnosis was not detailed. Severity of illness was not described. ICU LoS or interventions are not detailed. These patients are NOT likely to be critically ill.[AD]

Topic: Tube Placement

RefID 859

Reference: (Gorman et al. 1993)

Patient Population: Patients who required long-term enteral feedings.

Study entry criteria: All patients evaluated by the nutrition support service who required long-term enteral feedings and were at risk of aspiration (obtundation, diminished gag reflex, history of prior aspiration, gastroesophageal reflex, gastric outlet obstruction) or who were not candidates for a percutaneous endoscopic gastrostomy (obstructing oropharyngeal or esophageal lesion, esophagitis, esophageal varices, prior gastrectomy).

Study intervention/s: Patients were randomized to receive: 1) a button jejunostomy or 2) a 14 French red rubber catheter jejunostomy.

All feeding jejunostomies were inserted 20cm distal to the ligament of Treitz via a serosal tunnel (catheter) or double pursestring (button) technique.
The red rubber catheter was allowed to drain via gravity for 24 hours. The jejunostomy button was capped for 24 hours and then an infusion of D5 W was commenced for 24 hours (50ml/hr).
EN was commenced in both groups at 24 hours post insertion using non elemental tube feedings as recommended by the nutrition support service. Nutritional goals were determined using indirect calorimetry and feedings advanced to goal as tolerated. All patients were followed up for 30 days.

Total number of patients randomised: 42 patients were randomized: 21 to each group

Outcome by study arm:

Outcome Reporting	**Intention to Treat Mortality**
Outcomes are reported for all patients.	30d mortality: **6/21** Group 1 (Button j-tube) **5/21** Group 2

Methodological issues:

Method of randomization reported:	Yes ☐ No ☒	Allocation concealed:	Yes ☐ Unclear ☒
Consecutive pts enrolled:	Yes ☐ No ☒	Blinding employed:	Yes ☐ No ☒
100% follow-up:	Yes ☒ No ☐	Reporting of losses by study arm	Yes ☒ No ☐

Note – papers are excluded if mortality is NOT reported, patients were NOT truly randomized, or if an ITT analysis cannot be calculated on at least 95% of all randomized patients.

Reviewer comments (and initials):
No details are provided as to the amount of EN given pre insertion of the jejunostomies [FS]
Patients requiring long term enteral feeding. No severity of illness is reported. These patients are NOT likely to be critically ill.[AD]

Papers that did not qualify for detailed appraisal

The following papers were retrieved and reviewed (GSD and FS) and found not to qualify for detailed appraisal for the following reasons:

15 cross-over studies
7 non-English language studies
28 not primary feeding study
5 not intensive care patients
8 observational studies (not RCT)
107 Phase II studies
1 post-operative intervention (oral intake for 10weeks post Sx)
12 pre-operative interventions
1 pseudo randomized
1 part 1 of a 2 part publication

Total: 185 papers

RefID	Paper and reason
RefID 1	(Jauch et al. 1995) - non-English language study
RefID 7	(Rayes et al. 2002) - non-English language study
RefID 12	(Vignali et al. 1995) - non-English language study
RefID 15	(Senkal et al. 1995) - Phase II study, no clinically meaningful outcomes
RefID 28	(Gianotti et al. 2002) - pre-operative intervention
RefID 30	(Kohlhardt et al. 1994) - Phase II study, no clinically meaningful outcomes
RefID 31	(Shaker et al. 2002) - Phase II study, no clinically meaningful outcomes
RefID 32	(Duerksen et al. 2002) - cross-over study
RefID 33	(Chlebowski et al. 1993) - not intensive care patients (home-based HIV patients)
RefID 42	(Braga et al. 2002b) - pre-operative intervention
RefID 56	(Ford et al. 1992) - Phase II study, no clinically meaningful outcomes
RefID 58	(Hajek et al. 2001) - non-English language study
RefID 66	(DeMeo et al. 1998) - Phase II study, no clinically meaningful outcomes
RefID 69	(Shindo et al. 1989) - not RCT (observational study)
RefID 74	(Neumann and DeLegge 2002) - Phase II study, no clinically meaningful outcomes
RefID 91	(Braga et al. 2002a) - not RCT (observational study)
RefID 96	(Aiko et al. 2001) - Phase II study, no clinically meaningful outcomes
RefID 101	(Gervasio et al. 2000) - not feeding study (oxandralone)
RefID 108	(Wu et al. 2001) - Phase II study, no clinically meaningful outcomes
RefID 116	(Aoki et al. 2000) - non-English language study
RefID 122	(Peng et al. 2001) - Phase II study, no clinically meaningful outcomes
RefID 124	(Beattie et al. 2000) - post-op intervention (oral nutritional supplement for 10wks post-elective surgery)
RefID 130	(Sustic et al. 2000) - Phase II study, no clinically meaningful outcomes
RefID 141	(Kocan and Hickisch 1986) - Phase II study, no clinically meaningful outcomes
RefID 148	(Gianotti et al. 1999) - pre-operative intervention
RefID 156	(Jin et al. 1999) - Pre-operative intervention
RefID 163	(Nataloni et al. 1999) - Phase II study, no clinically meaningful outcomes
RefID 171	(Beier-Holgersen and Brandstrup 1999) - not intensive care patients (post-op oral intake)
RefID 175	(Taylor 1999) - not RCT (observational study)
RefID 176	(Braga et al. 1998) - pre-operative intervention

RefID 180 (Brooks et al. 1999) - Phase II study, no clinically meaningful outcomes
RefID 186 (McCarter et al. 1998) - pre-operative intervention
RefID 187 (Bettany et al. 1998) - not RCT (before-after rhGH)
RefID 192 (Gianotti et al. 1998) - non-English language study
RefID 198 (Poyhonen et al. 1993) - Phase II study, no clinically meaningful outcomes
RefID 203 (Watters et al. 1997) - Phase II study, no clinically meaningful outcomes
RefID 208 (Almond et al. 1989) - Phase II study, no clinically meaningful outcomes
RefID 221 (Smith and Hartemink 1988) - pre-operative intervention
RefID 222 (Campillo et al. 1988) - Phase II study, no clinically meaningful outcomes
RefID 224 (Lerebours et al. 1988) - cross-over study
RefID 229 (Engel et al. 1997) - non-English language study
RefID 233 (Fish et al. 1997) - Phase II study, no clinically meaningful outcomes
RefID 236 (Shirabe et al. 1997) - Phase II study, no clinically meaningful outcomes
RefID 256 (Heyland et al. 1996a) - not RCT (observational study)
RefID 266 (Long et al. 1995) - Phase II study, no clinically meaningful outcomes
RefID 271 (Heller et al. 2002) - Phase II study, no clinically meaningful outcomes
RefID 298 (Saadeh et al. 2001) - not feeding study (rhGH)
RefID 305 (Barquist et al. 2001) - not feeding study (swallowing evaluation post-extubation)
RefID 320 (Kearns and Donna 2001) - Phase II study, no clinically meaningful outcomes
RefID 323 (Day et al. 2001) - Phase II study, no clinically meaningful outcomes
RefID 329 (Baudet et al. 2002) - not feeding study (octreotide in pancreatitis)
RefID 354 (Berard et al. 2000) - Phase II study, no clinically meaningful outcomes
RefID 357 (Schultz et al. 2000) - Phase II study, no clinically meaningful outcomes
RefID 358 (Bauer et al. 2000) - Phase II study, no clinically meaningful outcomes
RefID 360 (Kulling et al. 2000) - Phase II study, no clinically meaningful outcomes
RefID 366 (Dive et al. 2000) - cross-over study
RefID 376 (Abribat et al. 2000) - Phase II study, no clinically meaningful outcomes
RefID 395 (Jeevanandam et al. 2000) - not feeding study (rhGH)
RefID 396 (Linseisen et al. 2000) - Phase II study, no clinically meaningful outcomes
RefID 398 (Bourdel-Marchasson et al. 2000) - not intensive care patients (healthy volunteers)
RefID 401 (Ortolani et al. 2000) - not feeding study (glutathione and n-acetylcysteine in sepsis)
RefID 432 (Planas et al. 1999) - Phase II study, no clinically meaningful outcomes
RefID 436 (Kalfarentzos et al. 1998) - Phase II study, no clinically meaningful outcomes
RefID 460 (Van den et al. 1998) - cross-over study
RefID 491 (Malmberg 1997) - not feeding study (insulin infusion)
RefID 500 (Heimburger et al. 1997) - Phase II study, no clinically meaningful outcomes
RefID 501 (Braunschweig et al. 1997) - Phase II study, no clinically meaningful outcomes
RefID 504 (Hatton et al. 1997) - not feeding study (insulin-like growth factor)
RefID 509 (Emery et al. 1997) - Phase II study, no clinically meaningful outcomes
RefID 513 (Goldhill et al. 1997) - Phase II study, no clinically meaningful outcomes
RefID 517 (Hasse et al. 1995) - Phase II study, no clinically meaningful outcomes
RefID 520 (Nishizaki et al. 1996) - Phase II study, no clinically meaningful outcomes
RefID 524 (Kohn-Keeth et al. 1996) - Phase II study, no clinically meaningful outcomes
RefID 525 (Heyland et al. 1996b) - Phase II study, no clinically meaningful outcomes
RefID 529 (Kalliafas et al. 1996) - Phase II study, no clinically meaningful outcomes
RefID 533 (Pelfrene et al. 1996) - not feeding study (cimetidine vs. ranitidine)
RefID 534 (Hernandez-Socorro et al. 1996) - not RCT (observational study)
RefID 548 (Palmer et al. 1996) - Phase II study, no clinically meaningful outcomes
RefID 551 (Paz et al. 1996) - Phase II study, no clinically meaningful outcomes
RefID 554 (Pichard et al. 1996) - not feeding study (rhGH)
RefID 555 (Widhalm et al. 1996) - Phase II study, no clinically meaningful outcomes

RefID 557 (Weingartmann et al. 1996) - Phase II study, no clinically meaningful outcomes
RefID 575 (Petersen et al. 1995) - not feeding study (rhGH)
RefID 576 (Heimburger et al. 1995) - Phase II study, no clinically meaningful outcomes
RefID 580 (Jeevanandam et al. 1995b) - Phase II study, no clinically meaningful outcomes
RefID 581 (O'Riordain et al. 1994) - Phase II study, no clinically meaningful outcomes
RefID 596 (Beylot et al. 1994) - Phase II study, no clinically meaningful outcomes
RefID 605 (Wagner et al. 1994) - Phase II study, no clinically meaningful outcomes
RefID 612 (Jones et al. 1989) - Phase II study, no clinically meaningful outcomes
RefID 621 (Tacke et al. 1994) - not feeding study (rhGH)
RefID 627 (Kudsk 1994) - Phase II study, no clinically meaningful outcomes
RefID 635 (Sandstrom et al. 1993) - Phase II study, no clinically meaningful outcomes
RefID 639 (Diboune et al. 1993) - Phase II study, no clinically meaningful outcomes
RefID 641 (Mathus-Vliegen et al. 1993) - Phase II study, no clinically meaningful outcomes
RefID 644 (Voerman et al. 1992) - not feeding study (growth hormone)
RefID 646 (Lord et al. 1993) - Phase II study, no clinically meaningful outcomes
RefID 658 (Levinson and Bryce 1993) - Phase II study, no clinically meaningful outcomes.
RefID 663 (Heyland et al. 1992) - Phase II study, no clinically meaningful outcomes
RefID 666 (D'Angio et al. 1992) - Pseudo-randomized. Treatment allocation was based on the last digit of social security number.
RefID 672 (Madan et al. 1991) - Phase II study, no clinically meaningful outcomes
RefID 677 (de Chalain et al. 1992) - cross-over study
RefID 678 (Wojtysiak et al. 1992) - Phase II study, no clinically meaningful outcomes
RefID 684 (Ruiz-Santana et al. 1991) - not feeding study (ranitidine vs sucralfate vs placebo in TPN)
RefID 692 (Layon et al. 1991) - Phase II study, no clinically meaningful outcomes
RefID 698 (Vente et al. 1990) - Phase II study, no clinically meaningful outcomes
RefID 702 (Ziegler et al. 1990) - cross-over study
RefID 703 (Larsson et al. 1990) - Phase II study, no clinically meaningful outcomes
RefID 711 (Dobb and Towler 1990) - Phase II study, no clinically meaningful outcomes
RefID 719 (Ball and White 1989) - cross-over study
RefID 723 (Hart and Dobb 1988) - Phase II study, no clinically meaningful outcomes
RefID 726 (Pichard et al. 1988) - Phase II study, no clinically meaningful outcomes
RefID 727 (Hochwald et al. 1997) - Phase II study, no clinically meaningful outcomes
RefID 732 (Harrison et al. 1997) - Phase II study, no clinically meaningful outcomes
RefID 735 (Petersen et al. 1997) - not feeding study (rhGH)
RefID 739 (Lopez-Hellin et al. 1997) - Phase II study, no clinically meaningful outcomes
RefID 743 (Clarke et al. 1987) - Phase II study, no clinically meaningful outcomes
RefID 744 (Waitzberg et al. 1997) - cross-over study
RefID 756 (Jeevanandam et al. 1996) - not feeding study (rhGH)
RefID 767 (Skiest et al. 1996) - Phase II study, no clinically meaningful outcomes
RefID 768 (Himmelseher et al. 1996) - pre-operative intervention
RefID 772 (Arias-Diaz et al. 1996) - Phase II study, no clinically meaningful outcomes
RefID 784 (Norton et al. 1996) - not intensive care patients (Stroke patients 14 days post stroke.)
RefID 790 (Wachtler et al. 1995) - pre-operative intervention
RefID 798 (Landry et al. 1995) - cross-over study (health volunteers)
RefID 804 (McArthur et al. 1995) - not feeding study (sedation M&M vs. propofol)
RefID 807 (Jeevanandam et al. 1995a) - not feeding study (rhGH)
RefID 813 (McKinlay et al. 1995) - Phase II study, no clinically meaningful outcomes
RefID 818 (Wong et al. 1995) - not feeding study (rhGH)
RefID 820 (Behrman et al. 1995) - not feeding study (rhGH)

RefID 822 (Homann et al. 1994) - Phase II study, no clinically meaningful outcomes
RefID 826 (Stern and Wolf 1994) - Phase II study, no clinically meaningful outcomes
RefID 834 (Van den et al. 1994) - Phase II study, no clinically meaningful outcomes
RefID 840 (Paauw and Davis 1994) - Phase II study, no clinically meaningful outcomes
RefID 847 (Petersen et al. 1994) - not feeding study (rhGH)
RefID 851 (Botoman et al. 1994) - Phase II study, no clinically meaningful outcomes
RefID 854 (Kudsk et al. 1994) - not feeding study (rh insulin-like growth factor)
RefID 856 (Kruif Th and Vos 1993) - Phase II study, no clinically meaningful outcomes
RefID 858 (Iovinelli et al. 1993) - Phase II study, no clinically meaningful outcomes
RefID 861 (Couse et al. 1993) - Phase II study, no clinically meaningful outcomes
RefID 865 (Van der Hulst et al. 1993) - Phase II study, no clinically meaningful outcomes
RefID 875 (Ciocon et al. 1992) - Phase II study, no clinically meaningful outcomes
RefID 877 (Sternlieb et al. 1992) - not feeding study (octreotied in pancreatitis)
RefID 883 (Clark-Christoff et al. 1992) - not feeding study (triple lumen catheters)
RefID 884 (Von Meyenfeldt et al. 1992) - pre-operative intervention
RefID 888 (Heather et al. 1991) - Phase II study, no clinically meaningful outcomes
RefID 889 (Rees et al. 1992) - cross-over study
RefID 896 (Strong et al. 1992) - Phase II study, no clinically meaningful outcomes
RefID 903 (Schroeder et al. 1991) - Phase II study, no clinically meaningful outcomes
RefID 919 (Pigon et al. 1985) - Phase II study, no clinically meaningful outcomes
RefID 921 (Whatley et al. 1984) - Phase II study, no clinically meaningful outcomes
RefID 925 (Baker et al. 1984) - cross-over study
RefID 943 (Iapichino et al. 1982) - Phase II study, no clinically meaningful outcomes
RefID 947 (Iapichino et al. 1981) - Phase II study, no clinically meaningful outcomes
RefID 948 (Magnusson et al. 1989) - Phase II study, no clinically meaningful outcomes
RefID 950 (Bleichner et al. 1997) - Phase II study, no clinically meaningful outcomes
RefID 951 (Tappy et al. 1998) - Phase II study, no clinically meaningful outcomes
RefID 952 (Levy et al. 1998) - Phase II study, no clinically meaningful outcomes
RefID 956 (Berman et al. 1999) - not feeding study (rhGH and insulin)
RefID 960 (Bokhorst-De van der Schueren et al. 2001) - pre-operative intervention
RefID 961 (Heyland et al. 2001) - Phase II study, no clinically meaningful outcomes
RefID 963 (Lien et al. 2001) - cross-over study
RefID 967 (Boelens et al. 2002) - Phase II study, no clinically meaningful outcomes
RefID 970 (Erdem et al. 2002) - pre-operative intervention
RefID 971 (Berg et al. 2002) - not feeding study
RefID 972 (Brown et al. 1994) - Phase II study, no clinically meaningful outcomes
RefID 975 (Saluja et al. 2002) - not intensive care patients (oral ward diet vs. oral ward diet plus sip drink)
RefID 978 (Jeevanandam and Petersen 1994) - not feeding study (rhGH)
RefID 979 (Bonkovsky et al. 1991) - Publication number 2 of a single trial. Clinical outcomes are reported in Part I (ref 980)
RefID 994 (Babineau et al. 1998) - not RCT (observational study)
RefID 995 (Morlion et al. 1998) - Phase II study, no clinically meaningful outcomes
RefID 1025 (Vander et al. 1986) - cross-over study
RefID 1067 (Kakkos et al. 1996) - Phase II study, no clinically meaningful outcomes
RefID 1082 (Suchner et al. 2002) - cross-over study
RefID 1125 (Eckart et al. 1980) - cross-over study
RefID 1127 (Moller-Loswick et al. 1991) - not RCT (observational study)
RefID 1130 (Kruimel et al. 2001) - Phase II study, no clinically meaningful outcomes
RefID 1158 (Umpleby et al. 2002) - Phase II study, no clinically meaningful outcomes
RefID 1165 (Fiaccadori et al. 1997) - Phase II study, no clinically meaningful outcomes

RefID 1192 (Belknap et al. 1997) - Phase II study, no clinically meaningful outcomes
RefID 1193 (Dietscher et al. 1998) - Phase II study, no clinically meaningful outcomes
RefID 1211 (Ortiz et al. 1996) - not feeding study (laproscopic laparotomy vs. standard laparotomy)
RefID 1225 (Roulet et al. 1997) - Phase II study, no clinically meaningful outcomes
RefID 1226 (Steevens et al. 2002) - Phase II study, no clinically meaningful outcomes
RefID 1243 (Long et al. 1996) - Phase II study, no clinically meaningful outcomes.
RefID 1246 (Bower et al. 1986) - Phase II study, no clinically meaningful outcomes.

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All references are sorted in alphabetical order by author. Each paper's **RefID** is reported immediately after the full citation found in the Reference List.

Papers can be searched in this document using the author name or using the **RefID**. For example, the paper by (Chuntrasakul et al. 1996) has **RefID 511**. To find the occurrences of this paper, search for Chuntrasakul or search for **RefID 511**. To conduct a search within Adobe Acrobat, click on the 'binoculars' icon or select Edit | Search from the toolbar menu.

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