Enteral nutrition formulations for acute pancreatitis (Protocol)

Poropat G, Giljaca V, Hauser G, Stimac D
# Table of Contents

- **Header** .............................................. 1  
- **Abstract** ........................................... 1  
- **Background** ......................................... 1  
- **Objectives** ......................................... 3  
- **Methods** ............................................ 3  
- **Acknowledgements** ................................. 6  
- **References** .......................................... 7  
- **Additional Tables** ................................. 9  
- **Appendices** ......................................... 9  
- **Contributions of Authors** ....................... 14  
- **Declarations of Interest** ......................... 15  
- **Sources of Support** ................................ 15
Enteral nutrition formulations for acute pancreatitis

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Editorial group: Cochrane Upper Gastrointestinal and Pancreatic Diseases Group.


ABSTRACT

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

To assess the beneficial and harmful effects of different enteral nutrition formulations in patients with acute pancreatitis.

BACKGROUND

Description of the condition

Acute pancreatitis (AP) is a rather common and potentially life-threatening inflammatory disorder of the pancreatic gland. Its incidence in most Western and Asian countries ranges between 10 to 30 per 100,000 inhabitants, and it accounts for more than 200,000 hospital admissions in the United States annually (DeFrances 2007; Goldacre 2004; Imamura 2004; Lindkvist 2004). Indicative increase in the incidence of acute pancreatitis has been reported, and attributed to the use of more accurate diagnostic tests (i.e. computed tomography (CT), and endoscopic ultrasound), and an increase in the incidence of gallstones and obesity (Frey 2006; Yadav 2006). In about 80 to 85% of cases acute pancreatitis presents as a mild and self-limiting disease, requiring only conservative treatment, while the remaining 15% to 20% are severe forms of the disease characterised by the development of local and systemic complications (Sakorafas 2010; Tonsi 2009). Local complications consist of possible tissue destruction or necrosis; formation of a pseudocyst, an abnormal collection of fluid or necrotic material whose walls are formed by the pancreas and other surrounding organs; and formation of an enclosed collection of liquefied purulent tissue, called abscess. Systemic complications are caused by a systemic inflammatory response possibly leading to organ failure (most commonly, renal failure, respiratory failure and shock). The most common causes of AP are gallstone disease and excessive alcohol consumption, accounting for more than two thirds of cases (Munsell 2010). Less common causes include metabolic disorders, such as hypertriglyceridaemia (abnormal elevation of serum triglycerides, normal constituents of oil and fat), and hypercalcaemia (abnormal elevation of serum calcium), autoimmune pancreatitis, various bacterial or viral infections (i.e. mumps, Coxsackievirus, Mycoplasma pneumoniae), parasitic infestations of the biliary tract (i.e. Ascaris lumbricoides), abdominal abnormalities, trauma, drugs (i.e. steroids, sulphonamides, furosemide, thiazides), etc.

Although the pathophysiological mechanisms of AP are still controversial, it is believed that a causative factor leads to an uncontrolled enzyme activation within the pancreatic tissue and self-digestion of the gland, causing release of molecules that mediate the inflammatory response, tissue damage and possible necrosis. These local pathological changes can trigger an intense inflammatory cascade leading to the development of systemic inflammatory
response syndrome, a generalised inflammatory response affecting different organs and whole organ systems, which can consequently cause organ failure and death (Frossard 2008; Kilciler 2008). The described events represent the first phase of the clinical course of severe AP, which can be followed in up to 40% of cases by a second phase marked by infection of the necrotic pancreatic tissue (Haney 2007). Infected pancreatic necrosis usually develops after the second week of disease, and is associated with a significant increase in the prevalence of organ failure, with death occurring in about 30% of cases (Büchler 2000; Uhl 2002). According to clinical guidelines (Banks 2006; Forsmark 2007; UK Working Party on Acute Pancreatitis 2005), the diagnosis of AP is established by the presence of two of the following three features: a compatible clinical presentation, including abdominal pain, nausea and vomiting; a three-fold or greater elevation in serum amylase or lipase (digestive enzymes essential in the breakdown of starch and fat, that released to a greater extent from the inflamed pancreas into the blood); or evidence of acute pancreatitis on CT. There is no specific treatment for AP. The majority of cases respond well to conservative management, including fluid volume resuscitation, pain control, oxygen administration, anti-vomiting drugs, and a regulated introduction and administration of food intake. Severe cases require admission to an intensive care unit and continuous monitoring of vital signs. Severe AP precipitates metabolic distress leading to an increased total energy expenditure and enhanced protein consumption. Therefore, nutritional support is an essential part of disease treatment (Gianotti 2009; Meier 2006), and several studies indicate certain advantages of enteral nutrition (EN) versus total parenteral nutrition (TPN) (Al-Omran 2010; Yi 2012). EN involves the application of nutrients in liquid form directly into the stomach or small intestine via specific tubes that can be placed through the oral or nasal cavity, as well as, surgically implanted through the abdominal wall directly into the specified gastrointestinal organ. TPN is the intravenous administration of all nutrient requirements of a patient via a central venous catheter. Use of antibiotics to prevent infection of the necrotic tissue is highly debated. A recent Cochrane review showed no beneficial effects of antibiotic prophylaxis, except for imipenem, an antibiotic from the carbapenem group with a broad spectrum of activity against various bacteria, which showed significant decrease in the incidence of pancreatic infection (Villatoro 2010). Early endoscopic procedures, such as endoscopic retrograde cholangiopancreatography, that help visualise the common bile duct should be considered in the early stages of severe gallstone pancreatitis with co-existing bile ducts obstruction, bile ducts inflammation (cholangitis), or sepsis (Frossard 2008; Te 2012). In these cases, cutting the sphincter of Oddi, a muscle that lies at the junction of the intestine with both the bile and pancreatic ducts, by a procedure called retrograde sphincterotomy could help to remove bile duct stones, or treat other causes of bile obstruction. Surgical removal of necrotic tissue, as well as fluid collection, pseudocyst, or abscess drainage are indicated only when there is presence of infected tissue. Sterile necrosis should be treated conservatively (Isaji 2006; Werner 2005).

### Description of the intervention

Over decades one of the main principles in treating patients with acute pancreatitis has been ‘nil-by-mouth’, with or without the use of TPN, in order to achieve suppression of pancreatic enzyme secretion and bowel rest. However, experimental and clinical studies have demonstrated that this approach can lead to an increased risk of infectious complications due to bacterial overgrowth and translocation in the gut, resulting in higher morbidity and mortality in patients with severe forms of disease. Furthermore, severe AP is marked by an increased amount of energy required to obtain vital functions at complete rest, also called basal metabolism, with a potential negative effect on nutritional status and disease progression (Meier 2006). Therefore, an adequate nutritional support is essential, preferably applied by enteral route. The administration should start as soon as possible, especially if there is pre-existing malnutrition, and usually prior to 48 hours of admission (McClave 2009). Nutritional support is preferably administered via a tube inserted through the nasal cavity and the upper gastroduodenal tract (oesophagus and stomach), into the middle part of the small intestine called the jejunum. This nasojejunal tube should be placed distal to the duodenojejunal junction (the point where the proximal part of the small intestine, the duodenum, ends and the jejunum begins) either blindly, endoscopically, or by using radiologic procedures. It has been discussed that tube positioning has several advantages: it avoids the problem of decreased stomach motility or gastroparesis, and possible duodenal obstruction due to inflammation or pseudocyst formation; provides increased energy delivery to the small bowel; and ensures better pancreatic rest than tubes placed proximally (Thomson 2008). However, there are studies showing no significantly different effects between the use of nasojejunal and nasogastric route of administration, where nutrients are being delivered into the stomach (Eatock 2005; Kumar 2006). A wide range of different enteral nutrition formulations are available for clinical usage and different indications. They can be divided into three groups: polymeric, oligomeric, and specialised formulations. Polymeric formulations contain intact proteins; carbohydrates are represented in the form of maltodextrins or water-soluble molecules containing three or more glucose molecules, and oligosaccharides, which are molecules containing two to six simple basic sugar molecules known as monosaccharides; finally, lipids are present in the form of long-chain fatty-acids. Oligomeric, also known as elemental or semi-elemental, comprise of maltodextrins and monosaccharides, medium-chain fatty acids and free fatty acids, while protein components consist of smaller molecules, such as free amino acids, dipeptides and tripeptides (two or three interconnected amino acids). Oligomeric formulations are preferred to polymeric formulations in the treatment of AP, mostly because of better tolerance...
and absorption in the gut, and better achievement of pancreatic rest (Makola 2006; Tiengou 2006). However, they are several times more expensive than polymeric formulations. Specialised formulations represent a larger group of specifically designed formulas enriched with different supplements. These include immunoenhanced formulations, which are enhanced by substances potentially able to modify the immune response. Mostly, they contain specific amino acids like glutamine and arginine, omega-3 fatty acids, and nucleotides (chemical compounds composed of a base, a sugar molecule, and a phosphate group, which are the main structural element of nucleic acids, i.e. deoxyribonucleic acid (DNA)). Other specialised formulations are fibre-enhanced formulations, formulations supplemented with probiotics (substances containing live bacteria or yeast that supplements normal gastrointestinal flora), and disease-specific formulations (Petrov 2009). The cost of the latter preparations is even higher, and without reliable evidence of their efficiency. In addition, formulations enriched with certain strains of probiotics have even been associated with increased mortality (Besselink 2008; Gianotti 2006).

How the intervention might work

Intestinal barrier dysfunction has a pivotal role in the course of AP. It is known that microorganisms responsible for pancreatic infection and septic complications, are generally common enteric bacteria, normally present in the gut (Beger 1986; MacFie 1999). Disruption and overgrowth of these bacterial population forms the normal intestinal flora in a metabolically deprived and inert bowel could lead to bacterial and endotoxin translocation, meaning that bacteria and their toxic products could move through the intestinal membrane to emerge in the lymphatic or internal organs circulation. This mechanism is further supported by an increased permeability of the intestinal membrane and local ischaemia (insufficient blood supply) of the gut due to dynamic changes of blood flow regulation in AP. The intense inflammatory state and above mentioned processes cause impairment of the patient’s immunological system (Xu 2006). Direct delivery of nutrients to the gut, and the stimulation of metabolic activity helps maintaining the structural and functional integrity of intestinal mucosa, and therefore, could reduce septic complications and morbidity (Buchman 1995). Data suggest that enteral nutrition reduces the acute phase response by preserving protein metabolism of internal organs and down-regulating the cytokine response (proteins that act as intercellular mediators, as in the generation of an immune response) (Windsor 1998). The use of immuno-enhanced formulas is supposed to intensify this effect. Glutamine released from muscle tissues acts as a gene promoter for cellular protection and immune responsiveness by activating the peroxisome proliferator-activated receptor gamma, an intracellular receptor that regulates glucose metabolism and fatty-acids storage. In addition, glutamine is a potent antioxidant through its metabolite glutathione, which is a tripeptide important for the protection of various cellular structures and the detoxification of harmful compounds. Furthermore, glutamine stimulates arginine production, which is another supplement that has demonstrated potential effects by influencing the synthesis of nitric oxide (a naturally occurring gas in the body that stimulates vessel dilation and improves blood flow). Nucleotides act as prebiotics, substances that stimulate the growth of beneficial enteric bacteria. Fish oils containing omega-3 fatty acids have a suppressive effect on endothelial cells and pro-inflammatory mediators. Their effects are supposedly acquired by inhibition of nuclear factor kappa B (a protein controlling gene expression), displacement of arachidonic acid from cellular membranes, and stimulation of leukotriene B4 and prostaglandin E2 production (Santora 2010). Arachidonic acid is an essential fatty acid and the precursor to leukotrienes and prostaglandins, which are classes of molecules produced by cells to mediate allergic and inflammatory reactions.

Why it is important to do this review

Acute pancreatitis represents a global burden of morbidity and mortality with an increasing incidence. Due to the differences in the studies conducted to date, and a variety of accessible preparations for enteral feeding, it is important to do a systematic review of specific formulations and try to point out the most efficient and cost-effective method of enteral nutrition in these patients.

OBJECTIVES

To assess the beneficial and harmful effects of different enteral nutrition formulations in patients with acute pancreatitis.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised clinical trials assessing enteral nutrition in patients with acute pancreatitis. We will include randomised clinical trials irrespective of publication status, language, or blinding. Non-randomised studies and other observational studies identified with the search for randomised clinical trials will be excluded for the report of benefit but will be included for the report of harm.
Types of participants
We will include patients diagnosed with acute pancreatitis by any method according to, or compatible with, at least two of the three following criteria:
1. abdominal pain consistent with acute pancreatitis;
2. a three-fold or greater elevation in serum amylase or lipase;
3. morphological changes consistent with acute pancreatitis detected on CT.

Exclusion criteria
- Undefined EN formulations
- Use of EN and TPN combinations
- Acute pancreatitis after surgery
- Malignancy
- Patients under 18 years of age

Types of interventions
Any kind of enteral nutrition regimen with clearly specified type of nutritional formulation irrespective of the route, start, rate, or duration of administration versus another different type of enteral nutrition formulation, placebo, or no intervention used for the treatment of acute pancreatitis. Any concomitant interventions will be allowed if received equally by all treatment groups in a trial.

Types of outcome measures

Primary outcomes
1. All-cause mortality
2. Systemic inflammatory response syndrome, defined by two or more of the following criteria: pulse rate > 90 beats per minute; respiratory rate > 20 per minute or an arterial partial pressure of carbon dioxide (PaCO₂) < 32 mmHg; body temperature > 38°C or < 36°C; white cells count > 12,000 or < 4000 cells per mm³ (Buter 2002)
3. Multiple organ dysfunction syndrome, as defined by the Modified Marshall Scoring System, by which organ failure is defined as a score ≥ 2 for at least one of the three organ systems (Table 1) (Banks 2012)
4. Adverse events

Secondary outcomes
1. Local septic complications (infected necrosis, abscess)
2. Other local complications (sterile necrosis, fluid collections, pseudocyst, fistula)
3. Other infection (pneumonia, urinary tract infection, septicemia)
4. Length of hospital stay
5. Quality of life

Search methods for identification of studies

Electronic searches
We will identify relevant randomised clinical trials by electronic searches of the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group Specialist register of clinical trials, the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, MEDLINE, EMBASE, and Science Citation Index Expanded (Royle 2003). We have given the preliminary search strategies with the expected time span of the searches in Appendix 1 and Appendix 2. We will improve the search strategies if possible as the review progresses, and if changes to the search strategies are introduced, we will use the improved search strategy to perform a new search of the literature which will replace the previous one for identification of studies.

Searching other resources
We will identify further trials by reading the reference lists of the identified studies. Review articles will be checked in order to find randomised trials not identified by the electronic searches. We will write to the principal authors of the identified randomised trials and to the researchers active in the field to enquire about additional randomised clinical trials they might know of. In order to obtain unpublished trials, we will contact pharmaceutical companies who are involved in the production and assessment of enteral nutrition formulations. We will search for ongoing trials in ClinicalTrials.gov (http://clinicaltrials.gov/) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal (http://apps.who.int/trialsearch/).

Data collection and analysis

Selection of studies
Two authors (GP, VG) will retrieve the identified relevant trials for assessment. They will independently evaluate whether the trials meet the inclusion criteria. Excluded trials will be listed with the reasons for exclusion. Disagreements regarding trial selection will be solved by a third author (GH).
Data extraction and management

Two authors (GP, VG) will extract and validate data independently using data extraction forms that will be designed for the purpose. If there are non-English language publications, we will request the help of the Cochrane Upper Gastrointestinal and Pancreatic Disease Group in extracting information from these. If more than one publication of a trial exists, we will list the publications under the publication with the most complete data and will mark it as primary. We will search for additional information and missing data by correspondence with the principal investigators or co-investigators of trials in cases where the relevant data were not published. We will add any information obtained through correspondence with these authors to the data extraction form. We will provide the date when the information is requested and eventually received in the ‘Notes’ section of the respective trial (‘Characteristics of included studies’ section). We will try to resolve potential disparities in the extracted data from the retrieved publications with the trial authors. Disagreements will be resolved by discussion among the review authors. If discussion does not resolve disagreements, a third author (GH) will arbitrate the decision.

We will extract the following information from each trial: primary author, country of origin, trial design, number of patients randomised, inclusion and exclusion criteria, patients characteristics, etiology of acute pancreatitis, intervention regimens, the period of follow-up, patients lost to follow-up, primary and secondary outcomes of the trials at the latest available follow-up, sample-size estimation, intention-to-treat analysis. For detailed description, a data extraction sheet will be provided upon request by the primary author (GP).

Assessment of risk of bias in included studies

The confidence that the design and report of the randomised clinical trial would restrict bias in the comparison of the intervention defines methodological quality, and hence risk of bias (Gluud 2006; Kjaergard 2001; Moher 1998; Schulz 1995; Wood 2008). We have assessed risk of bias using the following domains.

Allocation concealment

- Low risk of bias: if the allocation of patients involved a central independent unit, on-site locked computer, identically appearing numbered drug bottles or containers prepared by an independent pharmacist or investigator, or sealed envelopes.
- Uncertain risk of bias: if the trial was described as randomised, but the method of allocation concealment was not described.
- High risk of bias: if the allocation sequence was known to the investigators who assigned participants or if the study was quasi-randomised. Quasi-randomised studies will be excluded for the assessment of benefits, but not for harms.

Blinding

- Low risk of bias: the trial was described as blind, the parties that were blinded, and the method of blinding was described, so the knowledge of allocation was adequately prevented during the trial.
- Uncertain risk of bias: the trial was described as blind, but the method of blinding was not described, so that the knowledge of allocation was possible during the trial.
- High risk of bias: the trial was not blinded, so that the allocation was known during the trial.

Incomplete outcome data

- Low risk of bias: if the numbers and reasons for withdrawals and dropouts in all intervention groups were described or if it was specified that there were no withdrawals or dropouts.
- Uncertain risk of bias: if the report gave the impression that there had been no withdrawals or dropouts, but it was not specifically stated.
- High risk of bias: if the number or reasons for withdrawals or dropouts were not stated.

Selective outcome reporting

- Low risk of bias: if pre-defined, or clinically relevant and reasonably expected outcomes (e.g. mortality, systemic inflammatory response syndrome, multiple organ dysfunction syndrome, adverse events) are reported on.
- Uncertain risk of bias: if not all pre-defined, or clinically relevant and reasonably expected outcomes are reported on, or are not reported fully, or it is unclear whether data on these outcomes were recorded or not.
- High risk of bias: if one or more clinically relevant and reasonably expected outcomes were not reported on; data on these outcomes were likely to have been recorded.

Allocation sequence generation

- Low risk of bias: if the allocation sequence was generated by a computer or random number table. Drawing lots, tossing a coin, shuffling cards, or throwing dice were considered as adequate.
- Uncertain risk of bias: if the trial was described as randomised, but the method used for the allocation sequence generation was not described.
- High risk of bias: if a method involving dates, names, or admittance numbers was used for the allocation of patients. These trials will be excluded for the assessment of benefits, but not for harms.
Other biases

- Low risk of bias: if the trial appears to be free of other sources of bias, e.g., conflict of interest bias.
- Uncertain risk of bias: if there is insufficient information to assess whether other sources of bias are present.
- High risk of bias: if it is likely that potential sources of bias related to specific design used, early termination due to some data-dependent process, lack of sample size or power calculation, or other bias risks are present.

We will assess all included trials for risk of bias. If the risk of bias in a trial is judged as 'low' in all of the above specified domains, the trial will fall in the 'low risk of bias' group of trials. If the risk of bias is judged 'unclear' or 'high', then the trial will fall in the group with 'high risk of bias'.

Measures of treatment effect

We plan to perform all the statistical analyses using the Cochrane Collaboration's statistical software, (Review Manager 2013). For dichotomous outcomes, we plan to express results as risk ratios (RRs) with 95% confidence intervals (CIs). When continuous scales of measurement were used to assess the effects of treatment, we plan to use the mean difference (MD) with 95% CIs. If there is only one trial that reports data on a certain outcome, we will not be able to perform meta-analysis and will use Fisher's exact test for dichotomous variables or t-test for continuous variables in the analysis between two groups of patients.

Dealing with missing data

For any missing data we will try to contact the original investigators to obtain the missing data. We plan to perform all analyses according to the intention-to-treat method including all participants irrespective of compliance or follow-up. We will include patients with incomplete or missing data in the sensitivity analyses by imputing them according to the below two scenarios (Hollis 1999).

1. 'Best-worst' case scenario analyses: participants with missing outcome are considered successes in the experimental group and failures in the control group. The denominator will include all the participants in the trial.

2. 'Worst-best' case scenario analyses: participants with missing outcome data are considered failures in the experimental group and successes in the control group. The denominator will include all the participants in the trial.

If continuous data are missing, we will use the 'last observation carried forward' method to deal with missing data.

Assessment of heterogeneity

We will assess the presence of statistical heterogeneity by Chi² test with significance set at P < 0.10 and measure the quantities of heterogeneity by I² statistic (Higgins 2003).

Assessment of reporting biases

We plan to use a funnel plot to explore bias. We will use asymmetry in funnel plot of trial size to assess this bias in case we find a minimum of 10 trials (Egger 1997).

Data synthesis

We will perform this review according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We will perform meta-analysis of data with both a random-effects model (and a fixed-effect model to ensure robustness of the results (Demets 1987; DerSimonian 1986). In case of significant differences of the results that the two models may produce, we will present the result with both methods. If there would be no difference between the results of the two models, we will report only the results of the fixed-effect model analysis.

Subgroup analysis and investigation of heterogeneity

We plan to perform subgroup analysis on:

- trials comparing two or more types of different EN formulations;
- trials comparing EN to placebo;
- trials comparing EN to no intervention;
- patients with severe acute pancreatitis;
- nasojejunal compared to nasogastric route of administration;
- early (< 48 hours) compared to late (> 48 hours) start of administration;
- oral refeeding started ≤ seven days after admission compared to oral refeeding started > seven days after admission;
- trials with low risk of bias compared to trials with high risk of bias.

Acknowledgements

We wish to express our thanks to Karin Dearness and Racquel Simpson, both from the Cochrane Upper Gastrointestinal and Pancreatic Disease Review Group, for excellent collaboration and their contribution to this review.
Additional references

Al-Omran 2010

Banks 2006

Banks 2012

Beger 1986

Besselink 2008

Buchman 1995

Buter 2002

Büchler 2000

DeFrances 2007

Demets 1987

DerSimonian 1986

Eatock 2005

Egger 1997

Forssmark 2007

Frey 2006

Frossard 2008

Gianotti 2006

Gianotti 2009

Gluud 2006

Goldacre 2004

Haney 2007

Higgins 2003

Higgins 2011

Hollis 1999

References
Isaji 2006

Kilciler 2008

Kjaergard 2001

Kumar 2006

Lindkvist 2004

MacFie 1999

Makola 2006

McCleve 2009

Meier 2006

Moher 1998

Munsell 2010

Petrov 2009

Review Manager 2013

Royle 2003

Sakorafas 2010

Santora 2010

Schulz 1995

Thomson 2008

Tiengou 2006

Tonsi 2009

Tse 2012
ADDITIONAL TABLES

Table 1. Modified Marshall Scoring System

<table>
<thead>
<tr>
<th>Organ system</th>
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<th>Score = 2</th>
<th>Score = 3</th>
<th>Score = 4</th>
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<td>Respiratory (PaO₂/FiO₂) b</td>
<td>&gt; 400</td>
<td>301 to 400</td>
<td>201 to 300</td>
<td>101 to 200</td>
<td>&lt; 101</td>
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<td>Renal (serum creatinine, µmol/L)</td>
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<td>134 to 169</td>
<td>170 to 310</td>
<td>311 to 439</td>
<td>&gt; 439</td>
</tr>
<tr>
<td>Cardiovascular (systolic blood pressure, mm Hg)</td>
<td>&gt; 90</td>
<td>&lt; 90 fluid responsive</td>
<td>&lt; 90 not fluid responsive</td>
<td>&lt; 90 pH &lt; 7.3</td>
<td>&lt; 90 pH &lt; 7.2</td>
</tr>
</tbody>
</table>

*a* Organ failure that resolves within 48 hours is defined as transient, while organ failure lasting for more than 48 hours is defined as persistent.

*b* Ratio of partial pressure of arterial oxygen to fraction of inspired oxygen.
Appendix 1. CENTRAL search strategy

1. Pancreatitis, Acute Necrotizing/
2. Pancreatitis/et [Etiology]
3. (acute adj2 pancrea*).tw.
4. (necro* adj2 pancrea*).tw.
5. (inflam* adj3 pancrea*).tw.
6. ((interstitial or edema*) adj2 pancrea*).tw.
7. or/1-6
8. Food, Formulated/
9. (elemental adj2 diet*).tw.
10. (formulat* adj2 (food* or nutrition* or feed*)).tw.
11. Enteral Nutrition/
12. ((enteral or enteric) adj2 (feed* or nutrition*)).tw.
13. (nasojejunal adj2 (feed* or nutrition*)).tw.
14. (tube adj feed*).tw.
15. (polymeric adj3 mixture*).tw.
16. polymeric feed*.tw.
17. oligomeric feed*.tw.
18. (oligomeric adj3 mixture*).tw.
19. Nutritional Support/
20. Glutamine/
21. Arginine/
22. Fatty Acids, Omega-3/
23. Probiotics/
24. prebiotic.tw.
25. Dietary Fiber/
26. ((fibre or fiber) adj enrich* adj diet*).tw.
27. semi-elemental.tw.
28. or/8-27
29. 7 and 28

Appendix 2. MEDLINE search strategy

1. Pancreatitis, Acute Necrotizing/
2. Pancreatitis/et [Etiology]
3. (acute adj2 pancrea*).tw.
4. (necro* adj2 pancrea*).tw.
5. (inflam* adj3 pancrea*).tw.
6. ((interstitial or edema*) adj2 pancrea*).tw.
7. or/1-6
8. Food, Formulated/
9. (elemental adj2 diet*).tw.
10. (formulat* adj2 (food* or nutrition* or feed*)).tw.
11. Enteral Nutrition/
12. ((enteral or enteric) adj2 (feed* or nutrition*)).tw.
13. (nasojejunal adj2 (feed* or nutrition*)).tw.
14. (tube adj feed*).tw.
15. (polymeric adj3 mixture*).tw.
16. polymeric feed*.tw.
Appendix 3. EMBASE search strategy

1. acute pancreatitis/
2. acute hemorrhagic pancreatitis/
3. pancreatitis/et [Etiology]
4. (acute adj2 pancrea*).tw.
5. (necro* adj2 pancrea*).tw.
6. (inflam* adj3 pancrea*).tw.
7. ((interstitial or edema*) adj2 pancrea*).tw.
8. or/1-7
9. elemental diet/
10. (elemental adj2 diet*).tw.
11. (formulat* adj2 (food* or nutrition* or feed*)).tw.
12. enteric feeding/
13. ((enteral or enteric) adj2 (feed* or nutrition*)).tw.
14. nose feeding/
15. (nasojejunal adj2 (feed* or nutrition*)).tw.
16. (tube adj feed*).tw.
17. (polymeric adj3 mixture*).tw.
18. polymeric feed*.tw.
19. oligomeric feed*.tw.
21. *nutritional support/
22. glutamine/
23. arginine/
24. omega 3 fatty acid/
25. Dietary Fiber/
26. ((fibre or fiber) adj enrich* adj diet*).tw.
27. semi-elemental.tw.
28. or/8-27
29. 7 and 28
30. randomized controlled trial.pt.
31. controlled clinical trial.pt.
32. randomized.ab.
33. placebo.ab.
34. drug therapy.fs.
35. randomly.ab.
36. trial.ab.
37. groups.ab.
38. or/30-37
39. exp animals/ not humans.sh.
40. 38 not 39
41. 29 and 40

17. oligomeric feed*.tw.
18. (oligomeric adj3 mixture*).tw.
19. Nutritional Support/
20. Glutamine/
21. Arginine/
22. Fatty Acids, Omega-3/
23. Probiotics/
24. prebiotic.tw.
25. Dietary Fiber/
26. ((fibre or fiber) adj enrich* adj diet*).tw.
27. semi-elemental.tw.
28. or/8-27
29. 7 and 28
30. randomized controlled trial.pt.
31. controlled clinical trial.pt.
32. randomized.ab.
33. placebo.ab.
34. drug therapy.fs.
35. randomly.ab.
36. trial.ab.
37. groups.ab.
38. or/30-37
39. exp animals/ not humans.sh.
40. 38 not 39
41. 29 and 40

Enteral nutrition formulations for acute pancreatitis (Protocol)
25. probiotic agent/
26. prebiotic agent/
27. dietary fiber/
28. ((fibre or fiber) adj enrich* adj diet*).tw.
29. semi-elemental.tw.
30. or/9-29
31. 8 and 30
32. random:.tw. or placebo:.mp. or double-blind:.tw.
33. 31 and 32

**Appendix 4. Science Citation Index Expanded search strategy**

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<table>
<thead>
<tr>
<th># 31</th>
<th>#30 OR #29</th>
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<th># 30</th>
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<tr>
<th># 29</th>
<th>Topic=((singl* OR doubl* OR trebl* OR tripl*)) AND Topic=((blind* OR mask*))</th>
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<tr>
<th># 25</th>
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<td>16</td>
<td>Polymeric feed*</td>
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<td>15</td>
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<td>14</td>
<td>Tube feed*</td>
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<tr>
<td>13</td>
<td>Nasojejunal nutrition*</td>
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<td>12</td>
<td>Nasojejunal feed*</td>
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<td>#</td>
<td>Topic</td>
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<tr>
<td>11</td>
<td>(((enteral or enteric) NEAR (feed* or nutrition*)))</td>
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<tr>
<td>9</td>
<td>(((formulation* NEAR (food* or nutrition* or feed*))))</td>
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<td>(Formulated Food)</td>
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<td>#5 OR #4 OR #3 OR #2 OR #1</td>
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<td>5</td>
<td>(((interstitial or edema*) NEAR pancrea*))</td>
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<td>(acute hemorrhagic pancreatitis)</td>
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CONTRIBUTIONS OF AUTHORS

GP drafted the protocol and is the guarantor of the review. The remaining authors revised the protocol. All authors agreed on the final version of the protocol.

DECLARATIONS OF INTEREST

None known.

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Internal sources

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External sources

- No sources of support supplied