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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
BACKGROUND	1
OBJECTIVES	3
METHODS	3
ACKNOWLEDGEMENTS	7
REFERENCES	8
APPENDICES	10
CONTRIBUTIONS OF AUTHORS	14
DECLARATIONS OF INTEREST	14
SOURCES OF SUPPORT	14

[Intervention Protocol]

Nutritional supplementation in enteral and parenteral nutrition for people with acute pancreatitis

Marcello Di Martino¹, Angela M Madden², Kurinchi Selvan Gurusamy³

¹Department of HPB & Transplant Surgery, Royal Free Hospital, London, UK. ²Biological & Environmental Sciences, University of Hertfordshire, Hatfield, UK. ³Division of Surgery and Interventional Science, University College London, London, UK

Contact address: Kurinchi Selvan Gurusamy, Division of Surgery and Interventional Science, University College London, 9th Floor, Royal Free Hospital, Rowland Hill Street, London, NW3 2PF, UK. k.gurusamy@ucl.ac.uk.

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the benefits and harms of different types of nutritional supplementation such as glutamine, arginine, essential fatty acids, and nucleotides in enteral and parenteral nutrition for people with acute pancreatitis.

BACKGROUND

Glossary of terms available in [Appendix 1](#).

Description of the condition

The pancreas is an abdominal organ that secretes several digestive enzymes into the pancreatic ductal system that empties into the small bowel. It also lodges the Islets of Langerhans, which secrete several hormones including insulin ([NCBI 2014](#)). Acute pancreatitis is a sudden inflammatory process in the pancreas with variable involvement of nearby organs or other organ systems ([Bradley 1993](#)). The annual incidence of acute pancreatitis ranges from 5 to 30 per 100,000 population ([Roberts 2013; Yadav 2006](#)). There has been an increase in the incidence of acute pancreatitis in the last one to two decades in the UK and USA ([Roberts 2013; Yang 2008](#)). Acute pancreatitis is the commonest gastrointestinal (digestive tract) cause of hospital admission in the USA ([Peery 2012](#)).

Gallstones and alcohol are the two main causes for acute pancreatitis. Approximately, 50% to 70% of acute pancreatitis cases are caused by gallstones ([Roberts 2013; Yadav 2006](#)). This is because of gallstones slipping into the common bile duct and obstructing the ampulla of Vater (a common channel formed by the union of the common bile duct and pancreatic duct) resulting in obstruction to the flow of pancreatic enzymes and leading to activation of trypsinogen (an enzyme that digests protein or a protease) within the pancreas and acute pancreatitis ([Sah 2013](#)). Increasing age, male gender, and lower socioeconomic class are associated with higher incidence of acute pancreatitis ([Roberts 2013](#)). The clinical manifestation of acute pancreatitis is believed to be caused by activation of inflammatory pathways either directly by the pathologic insult or indirectly by activation of trypsinogen, resulting in formation of trypsin, a protease which can break down the pancreas ([Sah 2013](#)). This activation of inflammatory pathways manifests clinically as systemic inflammatory response syndrome (SIRS) ([Banks 2013; Sah 2013; Tenner 2013](#)).

The diagnosis of acute pancreatitis is made when at least two of the following three features are present (Banks 2013).

1. Acute onset of a persistent, severe, epigastric pain often radiating to the back.
2. Serum lipase and amylase activity at least three times greater than the upper limit of normal.
3. Characteristic findings of acute pancreatitis on contrast enhanced computed tomography (CECT) and less commonly magnetic resonance imaging (MRI) or transabdominal ultrasonography.

Depending upon the type of inflammation, acute pancreatitis can be classified into interstitial oedematous pancreatitis (diffuse or occasionally localised enlargement of the pancreas due to inflammatory oedema as seen on CECT) or necrotising pancreatitis (necrosis involving either the pancreas or peripancreatic tissues or both) (Banks 2013). Approximately 90% to 95% of people with acute pancreatitis have interstitial oedematous pancreatitis, while the remainder have necrotising pancreatitis (Banks 2013). Necrotising pancreatitis may be sterile or infected (Banks 2013). Various theories exist as to how pancreatic and peripancreatic tissues get infected. These include spread from blood circulation, lymphatics, bile from the small bowel (duodenum) through the pancreatic duct, and movement through the large bowel wall (translocation) (Schmid 1999).

Local complications of acute pancreatitis include acute peripancreatic fluid collection, pancreatic pseudocyst, acute necrotic collection and walled-off necrosis (Banks 2013). The systemic complications of acute pancreatitis include worsening of pre-existing illnesses such as heart or chronic lung disease (Banks 2013). The mortality rates following an attack of acute pancreatitis are between 6% and 20% (Roberts 2013; Yadav 2006). The mortality rates depend upon the severity of acute pancreatitis.

Acute pancreatitis can be classified as mild, moderate, or severe, depending upon the presence of local or systemic complications, transient organ failure involving one or more of the lungs, kidneys, and cardiovascular system (heart and blood vessels) lasting up to 48 hours, or persistent organ failure of these organs lasting beyond 48 hours (Banks 2013). In mild pancreatitis, there are no local or systemic complications, or organ failure. In moderately severe acute pancreatitis, there may be local or systemic complications, or transient organ failure. In severe acute pancreatitis, there is persistent organ failure (Banks 2013). Acute severe pancreatitis carries the worst prognosis in terms of mortality, while mild pancreatitis has the best prognosis (Banks 2013).

Initial clinical management of acute pancreatitis consists of the following treatment.

1. Replacement of fluid lost or sequestered into third spaces and restoration of electrolyte balance. Current guidelines provide directions for early and vigorous fluid administration (Tenner 2013).
2. Nutrition, which may be enteral or parenteral nutrition, particularly in people with severe acute pancreatitis (Al-Omran

2010; Chang 2013; Forsmark 2016). Enteral nutrition is any nutrition that is given through the gut and includes oral feeding and tube feeding using nasogastric tubes (NCBI 2018a).

Parenteral nutrition is any nutrition that is given by a route other than the gut (e.g. intravenously, subcutaneously) (NCBI 2018b). Enteral nutrition may be preferable to parenteral nutrition (Al-Omran 2010).

The presence of any inciting factor, like a common bile duct stone should be addressed and treated. People with pancreatitis of suspected or proven biliary origin who have associated cholangitis or persistent biliary obstruction are recommended to undergo biliary sphincterotomy and endoscopic stone extraction within 72 hours of presentation (Williams 2017). Percutaneous or endoscopic drainage based on a step-up approach are indicated in cases of intra-abdominal collections secondary to necrotising infected pancreatitis (van Santvoort 2010). Minimally invasive step-up approach has resulted in fewer adverse events, less organ failure, and lower costs compared to open necrosectomy. Very low-quality evidence suggested that the endoscopic minimally invasive step-up approach resulted in fewer adverse events than the video-assisted minimally invasive step-up approach, but increased the number of procedures required for treatment (Gurusamy 2016).

Description of the intervention

The composition of enteral and parenteral nutrition is variable. Overall, nutrition formulations can be categorised as those containing glucose polymers, individual amino acids, and are low fat derived from long-chain triglycerides (elemental or monomeric formulation); those containing simple sugars, peptides of varying chain length and fat, primarily as medium-chain triglycerides (semi-elemental or oligomeric formulation); and those containing complex carbohydrates, intact proteins and complex lipids (polymeric formulations) (Lodewijkx 2016). Elemental (monomeric formulations) and semi-elemental formulations (oligomeric formulations) are proposed to have improved absorption rates from the intestine, cause less stimulation of the pancreas, and may be associated with improved tolerance (Lodewijkx 2016). However, elemental nutrition is more expensive and has increased osmolality opposed to polymeric nutrition formulas (Lodewijkx 2016).

There are also other formulations that contain specific complexes thought to be beneficial for inflammatory conditions, for example, amino acids such as glutamine, arginine, essential fatty acids such as omega-3 fatty acids, or nucleotides (Asrani 2013; Jafari 2015; Krishnan 2017; Zou 2010). Other specialised formulations can include either fibre-enhanced formulations that can have prebiotic activity, stimulating the growth of normal enteral microorganisms, or probiotics (Poropat 2015),

How the intervention might work

People with acute pancreatitis can quickly develop nutritional deficiencies due to systemic inflammation, organ failure, and an inadequate nutrient intake (Jafari 2015). An adequate early nutrition support and the supplementation of specific supplements can modulate the activity of the host immune system and inflammatory response. Glutamine has demonstrated improvements in lymphocyte functions and important antioxidative functions; hence the reduction in systemic inflammatory responses. It increases the T cell mitogenic response without an altered production of pro-inflammatory cytokines like interleukin-6 or tumour necrosis factor (O’Riordain 1996). Arginine, given in large doses, helps maintain immune homeostasis, particularly with respect to T cell and macrophage functions. Additionally, moderately stressed people in intensive care given an enteral diet containing large amounts of arginine demonstrated preservation or enhancement of T lymphocyte blastogenesis (Barbul 2007). Omega-3 fatty acid can modulate the production of inflammatory eicosanoids and cytokines, improving the immune response and decreasing inflammation (Martin 2010).

Why it is important to do this review

None of the nutritional supplements mentioned above are routinely recommended in clinical practice despite some studies showing that glutamine and omega-3 fatty acids have shown to be beneficial in reducing mortality and morbidity (Lei 2015; Yong 2016). Meta-analyses increase the precision of the treatment effects (i.e. they provide a narrower range of the average treatment effect) (Higgins 2011), and so decrease the risk of a type II error (concluding that there is no difference between treatments when there is actually a difference). Many of these interventions have been compared with placebo or with no treatment. It is therefore not possible to obtain accurate information on how one treatment compares with another treatment. Multiple treatment comparisons or a network meta-analysis allow comparison of several treatments simultaneously and provide information on the relative effect of one treatment versus another, even when no direct comparison has been made. There is no Cochrane Review or network meta-analysis on this topic. This systematic review and network meta-analysis will identify the relative effects of different treatments and identify any research gaps.

OBJECTIVES

To assess the benefits and harms of different types of nutritional supplementation such as glutamine, arginine, essential fatty acids, and nucleotides in enteral and parenteral nutrition for people with acute pancreatitis.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) including cluster-RCTs and cross-over RCTs. We will include studies reported as full text, those published as abstract only, and unpublished data.

Types of participants

We will include adults with acute pancreatitis irrespective of the severity (mild, moderately severe, or severe acute pancreatitis), the route of administration of nutritional formulation (oral, tube feeding, parenteral), and the timing of initiation of feeding. However, if there is any evidence of inconsistency (see [Data synthesis](#)), we will perform a meta-analysis for interventions for mild pancreatitis separately from moderately severe or severe pancreatitis.

Types of interventions

We will include studies comparing any of the following nutritional supplementation (regardless of route or dosage) in parenteral or enteral nutrition provided that the only difference between the randomised groups is the nutritional supplementation or supplementation being assessed.

1. Aminoacids such as glutamine, arginine
2. Fatty acids such as omega-3 fatty acids
3. Carbohydrates
4. Nucleotides
5. Placebo or no intervention.

If sufficient information is available we will consider each aminoacid as a separate intervention, each fatty acid as a separate intervention, and so on. We will exclude nutritional supplementation such as probiotics since these contain live or attenuated bacteria, do not constitute different polymeric and oligomeric composition of the nutritional intervention, and have been covered in a different Cochrane Review (Moggia 2017).

Types of outcome measures

Primary outcomes

1. Short-term mortality (in-hospital mortality or mortality within six months).
2. Serious adverse events (within six months). We will accept any of the following definitions of serious adverse events (and

perform meta-analysis regardless of which of the following definitions used by authors:

- i) International Conference on Harmonisation - Good Clinical Practice guideline ([ICH-GCP 1997](#)): serious adverse events are defined as any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity;
- ii) other variations of ICH-GCP classifications such as Food and Drug Administration (FDA) classification ([FDA 2006](#)), Medicines and Healthcare products Regulatory Agency (MHRA) classification ([MHRA 2013](#)).
3. Health-related quality of life (using any validated scale) at medium term (three months to one year).

Secondary outcomes

1. Long-term mortality (at maximum follow-up).
2. Organ failure (however reported by authors).
3. Infected pancreatic necrosis (cytology or culture proven).
4. Health-related quality of life (using any validated scale):
 - i) short term (four weeks to three months);
 - ii) long term (more than one year).
5. Adverse events (within six months). We will accept all adverse events reported by the study authors, irrespective of the severity of the adverse event.
6. Measures of decreased complications and earlier recovery (within six months):
 - i) length of hospital stay (including the index admission for acute pancreatitis and any disease-related or intervention related readmissions including those for recurrent episodes);
 - ii) length of intensive therapy unit (ITU) stay (including the index admission for acute pancreatitis and any disease- or intervention-related readmissions);
 - iii) requirement for additional invasive intervention such as necrosectomy for pancreatic necrosis, endoscopic or radiological drainage of collections;
 - iv) time to return to normal activity (return to pre-acute pancreatitis episode mobility without any additional carer support);
 - v) time to return to work (in those who were employed previously).
7. Costs (within six months).

The choice of the above clinical outcomes is based on the necessity to assess whether the polymeric and oligomeric formulations are effective in decreasing complications, thereby decreasing the length of ITU and hospital stay, decreasing any additional interventions, and resulting in earlier return to normal activity and work, and improvement in quality of life. The costs provide an indication of resource requirement.

Reporting of the outcomes listed here will not be an inclusion criterion for the review.

Search methods for identification of studies

Electronic searches

We will conduct a literature search to identify all published and unpublished randomised controlled trials in all languages. We will translate non-English language papers and fully assess them for potential inclusion in the review as necessary.

We will search the following electronic databases:

1. Cochrane Central Register of Controlled Trials (CENTRAL; [Appendix 2](#));
2. MEDLINE (1966 to present; [Appendix 3](#));
3. Embase (1988 to present; [Appendix 4](#)); and
4. Science Citation Index (1982 to present) ([Appendix 5](#)).

We will also search the ClinicalTrials.gov ([Appendix 6](#)) and World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) ([Appendix 7](#)) study registers.

Searching other resources

We will check reference lists of all primary studies and review articles for additional references. We will contact authors of identified studies and ask them to identify other published and unpublished studies.

We will search for errata or retractions from eligible studies on PubMed (www.ncbi.nlm.nih.gov/pubmed) and report the date this was done in the review.

Data collection and analysis

Selection of studies

Two review authors (KG and MDM) will independently screen titles and abstracts of all the potential studies we identify as a result of the search, and code them as 'retrieve' (eligible, potentially eligible, or unclear) or 'do not retrieve'. We will retrieve the full text of study reports or publications and two review authors (KG and MDM) will independently screen the full text, and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion. We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and characteristics of excluded studies table.

Data extraction and management

We will use an Excel-based data collection form for study characteristics and outcome data, which will be piloted on at least three

studies in the review. Two review authors (KG and MDM) will independently extract study characteristics and outcome data from included studies. We will extract the following study characteristics.

1. Methods: study design, total duration study and run in, number of study centres and location, study setting, withdrawals, date of study.
2. Participants: N, mean age, age range, gender, severity of condition, diagnostic criteria, inclusion criteria, exclusion criteria.
3. Interventions: intervention, comparison, and any cointerventions.
4. Outcomes: primary and secondary outcomes specified and collected, time points reported.
5. Notes: funding for study, notable conflicts of interest of study authors.

We will note in the characteristics of included studies table if outcome data were reported in an unusable way. We will resolve disagreements by consensus. One review author (MDM) enter the data from the data collection form into the Review Manager file. We will double check that the data are entered correctly by comparing the study reports with how the data are presented in the systematic review. A second review author (KG) will spot-check study characteristics for accuracy against the study report.

Assessment of risk of bias in included studies

Two review authors (KG and MDM) will independently assess the risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreement will be resolved by discussion. We will assess the risk of bias according to the following domains.

1. Random sequence generation
2. Allocation concealment
3. Blinding of participants and personnel
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective outcome reporting
7. Other bias

We will grade each potential source of bias as high, low, or unclear, and provide a quote from the study report and justification for our judgment in the 'Risk of bias' table. We will summarise the 'Risk of bias' judgements across studies for each of the domains listed. We will consider blinding separately for different key outcomes where necessary, e.g. unblinded outcome assessment and risk of bias for all-cause mortality may be very different than for a participant reported pain scale. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome, as part of the GRADE methodology.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data (short-term mortality, proportion of participants with adverse events, requirement for additional interventions) as odds ratio and continuous data as mean difference when similar scales are used (length of hospital stay, ITU stay, time to return to normal activity, time to return to work, and costs), or standardised mean difference (health-related quality of life) when different scales are used. We will ensure that higher scores for continuous outcomes have the same meaning for the particular outcome, explain the direction to the reader and report where the directions were reversed if this is necessary. For count outcomes such as number of adverse events, we will calculate the rate ratio; for time-to-event outcomes such as mortality at maximal follow-up, we will calculate the hazard ratio.

We will undertake meta-analyses only where this is meaningful, i.e. if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense.

A common way that trialists indicate they have skewed data is by reporting medians and interquartile ranges. When we encounter this, we will note that the data are skewed and consider the implication of this. If the data are skewed, we will not perform a meta-analysis, but will provide a narrative summary instead.

Where multiple study arms are reported in a single study, we will include only the relevant arms.

Unit of analysis issues

The unit of analysis will be individual participants with acute pancreatitis. If we find any cluster-randomised trials unexpectedly, we will include the data in the analysis if results are adjusted for intra-cluster correlation. If we find any cross-over randomised trials, we will include the data prior to the cross-over.

In multi-arm studies, the models will account for the correlation between study-specific treatment effects from the same study.

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data as indicated (e.g. when a study is identified as abstract only). If we are unable to obtain the information from the investigators or study sponsors, we will impute the mean from the median (i.e. consider median as the mean) and the standard deviation from the standard error (SE), interquartile range, or P values, according to the *Cochrane Handbook for Systematic Reviews of Interventions* (

[Higgins 2011](#)). We will assess the impact of including such studies by performing a sensitivity analysis. If we are unable to calculate the standard deviation from standard error, interquartile range, or P values, we will impute standard deviation as the highest standard deviation in the remaining studies included in the outcome, fully aware that this method of imputation will decrease the weight of the studies in the meta-analysis of mean difference, and shift the effect towards no effect for standardised mean difference.

Assessment of heterogeneity

We will assess clinical and methodological heterogeneity by carefully examining the characteristics and design of included studies. We will assess the presence of clinical heterogeneity by comparing effect estimates in mild and moderate or severe acute severe pancreatitis. Different study designs and risk of bias can contribute to methodological heterogeneity.

We will assess the statistical heterogeneity by comparing the results of the fixed-effect model meta-analysis and the random-effects model meta-analysis, between-study standard deviation by calculating τ^2 and comparing this with values reported in study of the distribution of between-study heterogeneity ([Turner 2012](#)), and by calculating an I^2 (using [Stata/SE 14.2](#)). If we identify substantial heterogeneity that is clinical, methodological, or statistical, we will explore and address the heterogeneity in a subgroup analysis (see [Subgroup analysis and investigation of heterogeneity](#) section).

Assessment of transitivity across treatment comparisons

We will assess the assumption of transitivity by comparing the distribution of the potential effect modifiers (clinical: mild versus moderate or severe acute pancreatitis; methodological: risk of bias, year of randomisation, and duration of follow-up) across the different pairwise comparisons.

Assessment of reporting biases

For the network meta-analysis, we will judge the reporting bias by the completeness of the search (i.e. searching various databases and including conference abstracts) and the comparison-adjusted funnel plot ([Chaimani 2012](#)).

Data synthesis

Methods for indirect and mixed comparisons

We will conduct network meta-analyses to compare multiple interventions simultaneously for each of the primary and secondary outcomes. Network meta-analyses combine direct evidence within studies and indirect evidence across studies ([Mills 2012](#)). We will

obtain a network plot to ensure that the studies are connected by interventions using [Stata/SE 14.2](#) ([Chaimani 2013](#)). We will exclude any studies that are not connected to the network. We will conduct a Bayesian network meta-analysis using the Markov chain Monte Carlo method in [OpenBUGS 3.2.3](#) as per guidance from the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) documents ([Dias 2016](#)). We will model the treatment contrast (i.e. log odds ratio for binary outcomes, mean difference or standardised mean difference for continuous outcomes, log rate ratio for count outcomes, and log hazard ratio for time-to-event outcomes) for any two interventions ('functional parameters') as a function of comparisons between each individual intervention and an arbitrarily selected reference group ('basic parameters') using appropriate likelihood functions and links ([Lu 2006b](#)). We will use binomial likelihood and logit link for binary outcomes, Poisson likelihood and log link for count outcomes, binomial likelihood and complementary log-log link for time-to-event outcomes, and normal likelihood and identity link for continuous outcomes. We will use 'placebo' or 'no treatment' as the reference group. We will use the random-effects model as default but will perform a sensitivity analysis using the fixed-effect model for the network meta-analysis. We will report the random-effects model for comparison with the reference group in a forest plot if the two models report similar results; otherwise, we will report the more conservative model. For each pairwise comparison in a table, we will report the random-effects model if the two models report similar results; otherwise, we will report the more conservative model.

We will use a hierarchical Bayesian model using three different initial values, employing codes provided by NICE DSU ([Dias 2016](#)). We will use a normal distribution with large variance (10,000) for treatment effect priors (vague or flat priors). For the random-effects model, we will use a prior distributed uniformly (limits: 0 to 5) for between-study standard deviation but will assume similar between-study standard deviation across treatment comparisons ([Dias 2016](#)). We will use a 'burn-in' of 5000 simulations, check for convergence visually, and will run the models for another 10,000 simulations to obtain effect estimates. If we do not obtain convergence, we will increase the number of simulations for 'burn-in'. If we still do not obtain convergence, we will use alternate initial values and priors employing methods suggested by [van Valkenhoef 2012](#). We will also estimate the probability that each intervention ranks at one of the possible positions using the NICE DSU codes ([Dias 2016](#)).

Assessment of inconsistency

We will assess inconsistency (statistical evidence of the violation of transitivity assumption) by fitting both an inconsistency model and a consistency model. We will use the inconsistency models employed in the NICE DSU manual, as we will use common between-study standard deviation ([Dias 2014](#)). In addition, we

will use design-by-treatment full interaction model and IF (inconsistency factor) plots to assess inconsistency (Chaimani 2013; Higgins 2012). In the presence of inconsistency, we will assess whether the inconsistency was due to clinical or methodological heterogeneity by performing separate analyses for each of the different subgroups mentioned in the [Subgroup analysis and investigation of heterogeneity](#) section.

If there is evidence of inconsistency, we will identify areas in the network where substantial inconsistency might be present in terms of clinical and methodological diversities between studies and, when appropriate, limit network meta-analysis to a more compatible subset of studies.

Direct comparison (head-to-head comparison or pairwise meta-analysis)

We will perform the direct comparisons alongside network meta-analysis using the same codes and the same technical details (i.e. use Bayesian methods for meta-analysis). We will use random-effects model by default. For testing the robustness of our findings, regardless of which method was chosen, we will conduct a sensitivity analyses for primary outcomes using a fixed-effect model. In case of divergence between the two models, we will present the more conservative results; otherwise, we will present only results from the random-effects model.

Presentation of results

We will present the effect estimates with 95% credible intervals for each pairwise comparison calculated from the direct comparisons and network meta-analysis. We will also present the cumulative probability of the treatment ranks (i.e. the probability that the intervention is within the top two, the probability that the intervention is within the top three, etc.) in graphs (SUCRA) (Salanti 2011). We will also plot the probability that each intervention was best, second best, third best, etc. for each of the different outcomes (rankograms), which are generally considered more informative (Dias 2012b; Salanti 2011).

We will present 'Summary of findings' tables for the primary outcomes. In the 'Summary of findings' table, we will follow the approach suggested by Puhan and colleagues (Puhan 2014). First, we will calculate the direct and indirect effect estimates and 95% credible intervals using the node-splitting approach (Dias 2010), i.e. calculate the direct estimate for each comparison by including only studies in which there was direct comparison of interventions and the indirect estimate for each comparison by excluding the studies in which there was direct comparison of interventions. Next, we will rate the quality of direct and indirect effect estimates using GRADE methodology, which takes into account the risk of

bias, inconsistency, directness of evidence, imprecision, and publication bias (Guyatt 2011). We will then present the estimates of the network meta-analysis and rate the quality of network meta-analysis effect estimates as the best quality of evidence between the direct and indirect estimates (Puhan 2014). In addition, we will present information on the number of studies and participants as per the standard 'Summary of findings' table.

Subgroup analysis and investigation of heterogeneity

We will assess the differences in the effect estimates between the following subgroups using meta-regression for the primary outcomes with the help of the codes provided in NICE DSU guidance if we included a sufficient number of studies (Dias 2012a). We will use the following study-level covariates for meta-regression.

1. Studies at low risk of bias compared to studies at high risk of bias

2. Mild versus moderate or severe acute pancreatitis

We will calculate a single common interaction term when applicable (Dias 2012a). If the 95% credible intervals of the interaction term did not overlap zero, we will consider this statistically significant.

Sensitivity analysis

If a study reported only per-protocol analysis results, we will re-analyse the results using the best-worst case scenario and worst-best case scenario analyses as sensitivity analyses whenever possible. We will also perform a sensitivity analysis using the fixed-effect model for analysis.

Reaching conclusions

We will only base our conclusions on findings from the quantitative or narrative synthesis of studies included in this review. We will avoid making recommendations for practice; our implications for research will give the reader a clear sense of the needed focus of future research and remaining uncertainties in the field.

A C K N O W L E D G E M E N T S

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The methods section of this protocol is based on a standard template used by Cochrane Gastrointestinal and Pancreatic Diseases Review Group modified for network meta-analysis used by the author group.

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* Indicates the major publication for the study

APPENDICES

Appendix I. Glossary of terms

Acute: sudden.

Autodigestion: breakdown of the same organ that secretes the substance.

Cholangiopancreatography: fully known as endoscopic retrograde cholangiopancreatography (ERCP); a procedure carried out on the pancreatic and bile ducts using an endoscope and x-rays.

Cholangitis: bile infection

Elemental formula: made of simple amino acids or fatty acids (i.e. single molecules).

Endoscopic sphincterotomy: endoscopic operation to cut the muscle surrounding the common bile duct and the pancreatic duct.

Endoscopic: with the help of an endoscope, a tube inserted into body (in this context, through the mouth and into the stomach and upper part of the small intestine).

Enteral nutrition: nutrition through the gut

Enzyme: substance that enables and speeds up chemical reactions that are necessary for the normal functioning of the body.

Epigastric: upper central abdomen.

Epigastric pain: upper central abdominal pain.

Heterogeneity: variability.

Inflammatory process: response by the body to injury or infection.

Insulin: substance which helps regulate blood sugar.

Interstitial: space in between.

Mitogenic: encourages a cell to commence cell division

Morbidity: illness (in this context, it means complications).

Mortality: death.

Necrosectomy: removal of dead tissue.

Necrosis: death and decomposition of living tissue usually caused by lack of blood supply but can be caused by other pathological insult.

Necrotising: causing necrosis.

Oedema: excessive accumulation of serous fluid in the intercellular spaces of tissues.

Oedematous: with oedema.

Oligomer: a polymer (please see below) whose molecules consist of relatively few repeating units

Pancreatic pseudocysts: fluid collections in the pancreas or the tissues surrounding the pancreas, surrounded by a well-defined wall and contain only fluid with little or no solid material.

Pancreatitis: inflammation of the pancreas.

Parenteral nutrition: nutrition through a route other than the gut (usually through the veins).

Pathologic insult: substance or mechanism that causes the condition.

Percutaneous: through the skin.

Peripancreatic tissues: tissues surrounding the pancreas.

Polymer: a very large, chain-like molecule made up of repeating units of small molecules.

Probiotics: micro-organisms that are believed to provide health benefits when consumed.

Pseudocyst: a fluid-filled cavity that resembles a cyst but lacks a wall or lining.

Radiology guided percutaneous treatments: treatments carried out by insertion of needle from the external surface of the body which are guided by a scan (usually an ultrasound or CT (computed tomography) scan).

Randomisation: using chance methods to assign people to treatments.

Retrograde: moving backwards.

Semi-elemental formulation: Same as oligomers.

Sepsis: life-threatening illness due to blood infection with bacteria, fungus, or virus.

Serum: clear fluid that separates out when blood clots.

Transabdominal: through the abdomen.

Transient: temporary.

Tumour necrosis factor-alpha antibody: antibody to tumour necrosis factor-alpha, an intermediary substance in the inflammatory pathway.

Appendix 2. CENTRAL search strategy (via OvidSP)

1. exp Pancreatitis/
2. pancreatitis.mp.
3. or/1-2
4. exp *Dietary Supplements/
5. enteral nutrition/ or parenteral nutrition/ or nutrition therapy/
6. ((dietary or nutrient* or nutrition* or micronutrient*) adj3 (supplement* or intake* or intervention* or therap* or treatment*)).tw.
7. (enteral nutrition* or parenteral nutrition*).tw,kw.
8. exp Amino Acids/
9. (amino acid* or aminoacid* or glutamine* or arginine).tw,kw.
10. (Aminobutyrate* or Aminolevulinic Acid or Canavanine or creatine or Glycine or Homoserine or Kynurenine or Oxamic Acid or Phosphoamino Acid* or Quisqualic Acid).tw,kw.
11. exp fatty acids/
12. (fatty acid* or Fish Oil* or omega 3 or omega 6 or n3 oil or n 3 oil or n3 pufa or n 3 pufa).tw.
13. (glyceride* or caprylate* or decanoic acid* or eicosanoic acid* or endocannabinoids or heptanoic acid* or lauric acid* or mupirocin or mycolic acid* or mycophenolic acid* or myristic acid* or palmitic acid* or prostanoic acid* or sodium morrhuate or stearic acid* or thioctic acid*).tw.
14. exp Carbohydrates/
15. (carbohydrate* or dietary Fiber or dietary sugar* or Starch or Monosaccharides or Polysaccharides).tw.
16. exp Nucleotides/
17. (nucleotide* or Nucleoside Diphosphate Sugars).tw,kw.
18. or/4-17

19. 3 and 18

Appendix 3. MEDLINE search strategy (via OvidSP)

1. exp Pancreatitis/
2. pancreatitis.mp.
3. or/1-2
4. exp *Dietary Supplements/
5. enteral nutrition/ or parenteral nutrition/ or nutrition therapy/
6. ((dietary or nutrient* or nutrition* or micronutrient*) adj3 (supplement* or intake* or intervention* or therap* or treatment*)).tw.
7. (enteral nutrition* or parenteral nutrition*).tw,kw.
8. exp Amino Acids/
9. (amino acid* or aminoacid* or glutamine* or arginine).tw,kw.
10. (Aminobutyrate* or Aminolevulinic Acid or Canavanine or creatine or Glycine or Homoserine or Kynurenone or Oxamic Acid or Phosphoamino Acid* or Quisqualic Acid).tw,kw.
11. exp fatty acids/
12. (fatty acid* or Fish Oil* or omega 3 or omega 6 or n3 oil or n 3 oil or n3 pufa or n 3 pufa).tw.
13. (glyceride* or caprylate* or decanoic acid* or eicosanoic acid* or endocannabinoids or heptanoic acid* or lauric acid* or mupirocin or mycolic acid* or mycophenolic acid* or myristic acid* or palmitic acid* or prostanoic acid* or sodium morrhuate or stearic acid* or thioctic acid*).tw.
14. exp Carbohydrates/
15. (carbohydrate* or dietary Fiber or dietary sugar* or Starch or Monosaccharides or Polysaccharides).tw.
16. exp Nucleotides/
17. (nucleotide* or Nucleoside Diphosphate Sugars).tw,kw.
18. or/4-17
19. 3 and 18
20. randomized controlled trial.pt.
21. controlled clinical trial.pt.
22. random*.mp.
23. placebo.ab.
24. drug therapy.fs.
25. trial.ab.
26. groups.ab.
27. or/20-26
28. exp animals/ not humans.sh.
29. 27 not 28
30. 19 and 29

Appendix 4. Embase search strategy (via OvidSP)

1. exp pancreatitis/
2. pancreatitis.mp.
3. or/1-2
4. exp *diet therapy/
5. enteric feeding/ or parenteral nutrition/
6. ((dietary or nutrient* or nutrition* or micronutrient*) adj3 (supplement* or intake* or intervention* or therap* or treatment*)).tw.
7. (enteral nutrition* or parenteral nutrition*).tw,kw.
8. exp amino acid/
9. (amino acid* or aminoacid* or glutamine* or arginine).tw.

10. (Aminobutyrate* or Aminolevulinic Acid or Canavanine or creatine or Glycine or Homoserine or Kynurenone or Oxamic Acid or Phosphoamino Acid* or Quisqualic Acid).tw.
11. exp fatty acid/
12. (fatty acid* or Fish Oil* or omega 3 or omega 6 or n3 oil or n 3 oil or n3 pufa or n 3 pufa).tw.
13. (glyceride* or caprylate* or decanoic acid* or eicosanoic acid* or endocannabinoids or heptanoic acid* or lauric acid* or mupirocin or mycolic acid* or mycophenolic acid* or myristic acid* or palmitic acid* or prostanoic acid* or sodium morrhuate or stearic acid* or thioctic acid*).tw.
14. exp carbohydrate/
15. (carbohydrate* or dietary Fiber or dietary sugar* or Starch or Monosaccharides or Polysaccharides).tw.
16. exp nucleotide/
17. (nucleotide* or Nucleoside Diphosphate Sugars).tw,kw.
18. or/4-17
19. 3 and 18
20. Randomized controlled trial/
21. Random\$.ti,ab.
22. randomization/
23. intermethod comparison/
24. placebo.ti,ab.
25. (compare or compared or comparison).ti.
26. ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.
27. (open adj label).ti,ab.
28. ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.
29. double blind procedure/
30. parallel group\$1.ti,ab.
31. (crossover or cross over).ti,ab.
32. ((assign\$ or match or matched or allocation) adj5 (alternate or group\$1 or intervention\$1 or patient\$1 or subject\$1 or participant\$1)).ti,ab.
33. (assigned or allocated).ti,ab.
34. (controlled adj7 (study or design or trial)).ti,ab.
35. (volunteer or volunteers).ti,ab.
36. trial.ti.
37. or/20-36
38. (random\$ adj sampl\$ adj7 ("cross section\$" or questionnaire\$1 or survey\$ or database\$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)
39. Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group\$1.ti,ab.)
40. (((case adj control\$) and random\$) not randomi?ed controlled).ti,ab.
41. (nonrandom\$ not random\$).ti,ab.
42. "Random field\$".ti,ab.
43. (random cluster adj3 sampl\$).ti,ab.
44. (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset\$1).ti. and animal experiment/
45. Animal experiment/ not (human experiment/ or human/)
46. or/38-45
47. 37 not 46
48. 19 and 47

Appendix 5. Science Citation Index search strategy

#1 TS=((dietary OR nutrient* OR nutrition* OR micronutrient*) near/3 (supplement* OR intake* OR intervention* OR therap* OR treatment*))
#2 TS= (enteral nutrition* OR parenteral nutrition* OR amino acid* OR aminoacid* OR glutamine* OR arginine OR fatty acid* OR Fish Oil* OR omega 3 OR omega 6 OR glyceride* OR carbohydrate* OR dietary Fiber OR dietary sugar* OR Starch OR Monosaccharides OR Polysaccharides OR nucleotide*)
#3 #1 OR #2
4 TS=(pancreatitis)
5 TS=(random* OR rct OR RCTs OR masked OR blind* OR placebo* OR meta-analysis OR systematic review* OR meta-analys*)
#6 #3 AND #4 AND #5

Appendix 6. ClinicalTrials.gov search strategy

“Interventional” [STUDY-TYPES] AND acute pancreatitis [DISEASE] AND (“Phase 2” OR “Phase 3” OR “Phase 4”) [PHASE]

Appendix 7. WHO ICTRP search strategy

Acute pancreatitis (condition)

C O N T R I B U T I O N S O F A U T H O R S

Conceiving the protocol: KG, MDM

Designing the protocol: KG, MDM

Coordinating the protocol: KG

Designing search strategies: KG

Writing the protocol: MDM, KG

Providing general advice on the protocol: AM

Securing funding for the protocol: Not applicable

Performing previous work that was the foundation of the current study: Not applicable

D E C L A R A T I O N S O F I N T E R E S T

None known.

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Internal sources

- University College London, UK.
K Gurusamy is an employee of University College London (UCL) and uses equipment and library resources provided by UCL.

External sources

- None, Other.