Effect of timing of pharmaconutrition (immunonutrition) administration on outcomes of elective surgery for gastrointestinal malignancies: A systematic review and meta-analysis

Emma Osland, BHSc, MPhil[1] (Emma_Osland@health.qld.gov.au)
Md Belal Hossain, PhD[2] (bjoardar2003@yahoo.com)
Shahjahan Khan, PhD[2] (Shahjahan.khan@usq.edu.au)
Muhammed Ashraf Memon, MBBS, MA Clin Ed, DCH, FRACS, FRCSI, FRCSEd, FRCSEng[3,4,5,6] (mmemon@yahoo.com)

[1]Department of Nutrition, Royal Brisbane and Womens Hospital, Brisbane, Queensland, Australia
[2]Department of Mathematics and Computing, Australian Centre for Sustainable Catchments, University of Southern Queensland, Toowoomba, Queensland, Australia
[3]Sunnybank Obesity Centre, Suite 9, McCullough Centre, 259 McCullough Street, Sunnybank, Queensland, Australia
[4]Mayne Medical School, School of Medicine, University of Queensland, Brisbane, Queensland, Australia
[5]Faculty of Health Sciences and Medicine, Bond University, Gold Coast, Queensland, Australia
[6]Faculty of Health and Social Science, Bolton University, Bolton, Lancashire, UK

REPRINTS/CORRESPONDENCE
Professor M. A. Memon, FRCS, FRACS, Sunnybank Obesity Centre, Suite 9, McCullough Centre, 259 McCullough Street, Sunnybank, QLD 4109, Australia
Tel: +61 7 3345 6667 Fax: +61 7 3344 1752 Mobile: +61 448614170
Email: mmemon@yahoo.com

RUNNING TITLE
Pharmaconutrition and gastrointestinal surgery

CLINICAL RELEVANCY STATEMENT

In an elective surgical population, the provision of pharmaconutrition containing supraphysiological doses of arginine, with or without glutamine, omega-3 fatty acids, and nucleotides has been theorized to modulate the immune and metabolic responses. Therefore pharmaconutrition may improve clinical outcomes such as posteroperative infective complications and length of hospital stay (LOS) without adversely affecting mortality. However the results of a number of randomized controlled trials (RCTs) have been conflicting. This meta-analysis appears to confirm the commonly accepted benefits of arginine-dominant pharmaconutrition in relation to reductions in postoperative infective complications and LOS. Nonetheless these benefits were only seen in peri- and postoperative pharmaconutrition administration in the current work. It is therefore evident that the timing of pharmaconutrition provision is of utmost importance and this information is necessary to guide clinical practice and institutional policy. The current work differs from previous meta-analyses through the emphasis on timing of pharmaconutrition provision, use of stricter inclusion criteria to reduce heterogeneity in the results obtained, and by including the latest available publications.

STRUCTURED ABSTRACT

Background: Pharmaconutrition has previously been reported in elective surgery to reduce postoperative infective complications and duration of hospital length of stay.

Objective: To update previously published meta-analyses and elucidate potential benefits of providing arginine-dominant pharmaconutrition in surgical patients specifically with regard to the timing of administration of pharmaconutrition.

Design: RCTs comparing the use of pharmaconutrition with standard nutrition in elective adult surgical patients between 1980 and 2011 were identified. The meta-analysis was prepared in accordance with PRISMA recommendations.

Results: Twenty studies yielding twenty-one sets of data met inclusion criteria. A total of 2005 patients were represented (pharmaconutrition n = 1010; control n = 995), in whom pharmaconutrition was provided preoperatively (k = 5), perioperatively (k = 2) or postoperatively (k =14). No differences were seen in postoperative mortality with the provision of pharmaconutrition irrespective of timing of administration. Statistically significant reductions in infectious complications and LOS were found with perioperative and postoperative administration. Perioperative administration was also associated with a statistically significant reduction in anastomotic dehiscence while a reduction in non-infective complications was demonstrated with postoperative administration. Preoperative pharmaconutrition demonstrated no notable advantage over standard nutritional provision in any of the clinical outcomes assessed.

Conclusions: This meta-analysis highlights the importance of timing as a clinical consideration in the provision of pharmaconutrition in elective gastrointestinal surgical patients and identifies areas of where further research is required.

INTRODUCTION

Nutrition provision is recognized to be an important aspect in the perioperative management of elective gastrointestinal surgery patients, and the timely provision of nutrition has been associated with improved postoperative outcomes[1, 2]. The benefits of nutritional provision in surgical patients are traditionally thought to arise from the provision of macronutrients such as calories for energy and protein for wound healing, and to reduce the impact of catabolism in the postoperative period. However, it has been theorized that due to the complex inflammatory, immune and oxidative stress that is experienced postoperatively, providing specific nutrients in supraphysiological doses may provide vital substrates that serve to modulate these immune and metabolic responses and thus improve clinical outcomes[3]. In view of this, during the early 1990s new nutrition support formulas emerged containing higher quantities of arginine, with or without glutamine, omega-3 fatty acids, and nucleotides[3]. These products have been commonly referred to as 'immunonutrition', 'immune-enhancing diets', and more recently as 'pharmaconutrition' in recognition of their intended pharmaceutical-like action rather than purely as nutrient provision[3].

In an elective surgical population, the use of pharmaconutrition has been reported to reduce postoperative infective complications and LOS, without adversely affecting mortality described in medical and trauma subgroups of a critically ill population[4-10]. The results of individual studies have been conflicting[11-15], however the use of these products gain increasing acceptance following their incorporation into practice guidelines[16, 17]. Seven meta-analyses on this topic have been conducted on surgical patients[18-21] or with surgical patients as a subgroup analysis of a critical care population[22-24], however there are limitations to applying the outcomes of these meta-analyses to practice due to the inclusion of studies utilizing non-equivalent control groups, inclusion of diverse surgical populations, and the failure to account for practical differences between the studies (i.e. administration protocols of pharmaconutrition).

The objective of the current work is to further explore the literature describing the postoperative outcomes from RCTs comparing the timing of provision of arginine-dominant pharmaconutrition formulations with standard products in an elective gastrointestinal surgery population. The timing of pharmaconutrition provision is considered of the utmost importance as this information is necessary to guide clinical practice and institutional policy. The current work differs from previous meta-analyses through the emphasis on timing of pharmaconutrition provision, use of stricter inclusion criteria to reduce heterogeneity in the results obtained, and by including the latest available publications.

MATERIALS AND METHODS

Inclusion and Exclusion Criteria

Studies comparing the provision of arginine-dominant (>9g Arg/L) pharmaconutritional formulations with or without other immune-modulating nutrients to those of standard nutritional composition were reviewed. Only RCTs with primary comparisons between the different nutritional formulations were considered for inclusion. For inclusion, studies must also have been conducted in adult (>18 years) elective gastrointestinal surgical patients, and have reported on clinically relevant outcomes pertaining to the postoperative period. Outcomes assessed were those considered to exert influence over practical aspects of surgical practice and institutional policy decisions. All studies reporting on outcomes of this

nature were considered and final analyses were run on outcome variables where numbers were sufficient to allow statistical analysis.

Additional exclusion criteria included studies that investigated the effect of parenteral provision supplemented with pharmaconutrients, and duplicate publications.

Search Strategies and Data Collection

Electronic databases (Medline, Pubmed, EMBASE, CINAHL, Cochrane Register of Systematic Reviews, Science Citation Index) were cross-searched for RCTs published between 1980 and 2011, using search terms customized to each search engine in an attempt to detect published papers meeting the inclusion criteria. Limits were set to RCTs and adult patients to reflect the inclusion criteria. Search strategies utilized included (IMMUNONUTRITON and SURGERY), (IMMUN* and NUTRITION), (PHARMACONUTRITION), (ARGININE or OMEGA-3 or RNA or NUCLEOTIDE and SURGERY). Reference lists of reviews and existing meta-analyses were hand searched for further appropriate citations. Companies that produce pharmaconutrition products and experts in the field were contacted for information about unpublished studies. Where necessary, authors were contacted by e-mail (and follow-up letter by post where a response to a second e-mail was not received) for clarification or additional information.

The data were prepared in accordance with the Preferred Reporting of Systematic Reviews and Meta-Analyses (PRISMA) statement[25]. Data extraction and critical appraisal of identified studies were carried out by two authors (EO and MAM) for compliance with inclusion criteria. The authors were not blinded to the source of the document or authorship for the purpose of data extraction. The data were compared and discrepancies were addressed with discussion until consensus was achieved.

Evaluation of methodological quality of identified studies was conducted using the Jadad scoring system which provides a numerical quality score based on the reporting of randomization, blinding and reporting of withdrawals[26].

Statistical Analysis

Meta-analyses were performed using odds ratios (ORs) for binary outcomes and weighted mean differences (WMDs) for continuous outcome measures. A slightly amended estimator of OR was used to avoid the computation of reciprocal of zeros among observed values in the calculation of the original OR[27]. Random effects models, developed by using the inverse variance weighted method approach[28], were used to combine the data. Heterogeneity among the study measures was assessed using the Q statistic[28-30] and I^2 index[31, 32].

Sensitivity analyses were conducted by removing studies that utilized experimental formulations with considerable differences in their product formulation to assess their influence on the results obtained.

Funnel plots were synthesized in order to determine the presence of publication bias in the meta-analysis. Standard error was plotted against the treatment effects (Log OR for the dichotomous and WMD for continuous variables respectively)[28, 33, 34] to allow 95% confidence interval limits to be displayed. All estimates were obtained using computer programs written in R[35]. All plots were obtained using the 'rmeta' package[36].

A significance level of 5% (α =0.05) was applied to tests of hypotheses.

RESULTS

Included studies

Cross searching of electronic databases yielded a total of 211 abstracts and hand searches of reference lists provided a further 16 citations. After exclusion of 136 duplicate citations, 91 unique citations of potential relevance were retrieved for review. The process by which these were excluded from inclusion is described in Figure 1. Two potentially relevant studies[37, 38] were unable to be assessed due to lack of access to the non-English language journals in which they were published. While a further potentially relevant unpublished study ('Sydney') was identified through a citation search of a previous published meta-analysis[18], attempts to contact authors and the company manufacturing the product did not yield any additional information; therefore the study could not be assessed for inclusion. Correspondence with the companies producing commercially available pharmaconutrition products did not yield additional unpublished studies, however the plans for an upcoming RCT were obtained through correspondence with an author of the Waitzberg et al[18] meta-analysis.

The twenty studies that met the inclusion criteria are described in Tables 1 to 4, however due to multiple arms of single studies independently meeting the inclusion criteria in one study[12] there were twenty-one individual sets of data analyzed. For eligible studies that incorporated multiple intervention arms in their study design, only those that utilized the enteral route were included in the analysis. Pooled results yielded 2005 patients (n=1010 pharmaconutrition; n=995 control) from studies published between 1988 and 2011. Studies were categorized according to the timing of pharmaconutrition provision: four studies, yielding five sets of data, provided preoperative interventions (pharmaconutrition provided five to seven days preoperatively as oral supplement), fourteen studies described postoperative interventions (pharmaconutrition product commenced via jejunal feeding tube on Postoperative Day (POD) 1 or 2, used to meet a defined nutritional goal until POD7 or when oral intake was established); and two studies provided perioperative interventions (providing both pre- and postoperative provision of pharmaconutrition as described above).

The included studies collectively demonstrate moderate methodological quality according to the Jadad score with an average score of 3.1 (out of five), with a range of one to five. Fourteen studies reported on withdrawals[4, 5, 9, 11-15, 39-44], thirteen described an appropriate method of randomization[4-7, 9, 13, 14, 39-42, 45, 46], and eight studies reported utilizing blinding[5, 9, 12, 42, 44, 47]. One study was not included in the eight that reported using a blinded method, as although it states it was a double-blind methodology in the title, this was not referred to throughout the article[40]. Jadad scores are reported in Tables 2 to 4.

All but seventeen patients (fourteen from Jiang et al[43], two from Sodergren[45] and one from Daly et al[47] representing <1% of the total patients analyzed) received elective surgery for the curative management of gastrointestinal malignancies (see Table 4). Twelve studies reported on the rates of malnutrition within their study population[4-7, 9, 12-15, 40, 41, 47]: Rates varied greatly, ranging from 9% to 100% with an average of about 40%. Malnutrition was defined as ≥10% body weight loss in most studies.

The nutritional composition products utilized in the included studies are summarized in Tables 5 and 6. All but three studies used commercially available pharmaconutrition products of similar composition (that is, Arginine 9-12g/L, with omega-3 fatty acids and nucleotides): Impact® or Oral Impact® account for 65% of the studied products. The experimental products used by McCarter et al[12] and Daly et al[47] were of significantly different composition (higher arginine (26g/L) content, with or without glutamine or omega-3 fatty acids). The Sodergren et al[45] study product was reported to be a prototype of Intestamin® that contains arginine, glutamine, omega-3 fatty acids, and micronutrients, however the exact composition of the product could not be ascertained due to it being subject to 'commercial in confidence' conditions (personal communication). The authors' [EO and MAM] interpretation of the nature of the feeding regimen for the prototype product suggests a composition more similar to the existing pharmaconutrition products used in a surgical population than to the commercially available Intestamin® product[48], it was therefore included in the meta-analysis but omitted for sensitivity analyses.

Thirteen of the twenty studies included stated they received support from the companies that produce the products being studied[4-7, 9, 11, 12, 39, 41, 42, 44, 45, 47]. Support was most commonly received through the provision of pharmaconutrition products, and occasionally though direct financial support. Other studies are unclear about the nature of company involvement[14, 15, 43, 46, 49], and only two studies deny any conflict of interest or financial support[13, 40].

Clinical Outcomes

Sufficient data were available for the analysis for six clinically relevant outcomes: in-hospital mortality; infective complications; anastomotic dehiscence; non-infectious complications; LOS; and gastrointestinal tolerance.

Statistically significant reductions in infectious complications and LOS were found with perioperative and postoperative administration of pharmaconutrition (OR 0.44, 95% CI 0.24, 0.81, p=0.001; WMD -2.57, 95% CI -3.70, -1.44, p=0.001 and OR 0.61, 95% CI 0.47, 0.79, p<0.01; WMD -2.30, 95% CI -3.71, -0.89, p=0.001 respectively). Perioperative administration was also associated with a statistically significant reduction in anastomotic dehiscence (OR 0.39, 95% CI 0.17, 0.93, p=0.03), while a reduction in non-infective complications was demonstrated with postoperative administration of pharmaconutrition (OR 0.70, 95% CI 0.52, 0.94, p=0.02). No significant difference in mortality was demonstrated irrespective of timing of pharmaconutrition. Preoperative pharmaconutrition demonstrated no notable advantage over standard nutritional provision in any of the clinical outcomes assessed. Results are summarized in Tables 7 to 9 and selected forest plots are presented in Figures 2 to 5.

Omission of studies[45, 47] using non-commercially available products did not alter the outcomes obtained in the sensitivity analyses (data not presented).

Heterogeneity

In general there was a high degree of accord between the outcomes in the included studies, with significant heterogeneity only detected in LOS. The latter was consistent across all timings of pharmaconutrition administration for this outcome.

Publication Bias

Funnel plots demonstrate symmetry and thus suggest the absence of publication bias for all outcomes except LOS. (Figure 6).

DISCUSSION

This meta-analysis both confirms previous findings regarding arginine-dominant pharmaconutrition and provides further insight into the effects of its use. Firstly it continues to show no adverse effect on postoperative mortality in elective gastrointestinal surgical populations. It also supports the commonly accepted benefits of arginine-dominant pharmaconutrition with relation to reductions in postoperative infective complications, however these benefits were only seen in peri- and postoperative pharmaconutrition administration in the current work. Similarly, reductions in LOS were noted in peri- and postoperative administration, however heterogeneity evidenced by a high I^2 index and publication bias present in this data makes it difficult to draw concrete conclusions on this parameter.

Distinct differences in the attributed benefits of pharmaconutrition and the timing of its administration is an important finding of this meta-analysis. Previous meta-analyses performing *a priori* analyses on timing of pharmaconutrition report benefit irrespective of when in the clinical course it is provided[19, 20]. One notable exception is that preoperative pharmaconutrition was not shown to reduce LOS by Cerantola et al[20]. The current work demonstrates no benefit from the provision of preoperative pharmaconutrition across any of the outcomes assessed. A possible explanation for this is the stricter inclusion criteria applied to minimise heterogeneity. Thus the results reported may be a truer indication of the effect of preoperative pharmaconutrition in this surgical population. The pharmacokinetics of pharmaconutrients may assist in understanding this finding. Serum arginine levels have been shown to significantly increase following seven days of preoperative[12, 50] and postoperative administration[41, 51]. Sustained elevated serum levels have been demonstrated at POD8 with perioperative administration[50]. However no study appears to have investigated the postoperative serum levels of patients receiving preoperative pharmaconutrients as a standalone intervention. It is therefore conceivable that the cessation of pharmaconutrition on the day of surgery may result in sub-therapeutic or declining levels of circulating pharmaconutrients within the postoperative period when their action may be most valuable. Beta-error (false negative) may also play a part in the findings reported in this and/or previous meta-analyses given the small number of studies investigating preoperative pharmaconutrition interventions.

The current work further suggests that pharmaconutrition may provide additional benefits in terms of reduction of anastomotic dehiscence and non-infective complications in perioperative and postoperative administration respectively – these phenomena have not previously been reported in association with arginine-dominant pharmaconutrition. Reduced non-infectious complications in postoperative pharmaconutrition provision may potentially be explained by the higher caloric and/or nitrogen content of many of the pharmaconutrition formulations when compared to the control formulations. Six of the fourteen studies (42%) included in the postoperative meta-analysis use intervention products that contain between 20 and 46% more protein[11, 14, 40, 43, 47, 49] and/or up to 600kcal (20%) more energy[14] than the control formulations. In a gastrointestinal surgical population with a high prevalence of

malnutrition, the higher overall nutritional provision may be enough to account for this unexpected finding given that malnourished patients experience more profound improvements in clinical outcomes attributable to nutritional provision than their well-nourished counterparts[52]. This explanation, however, does not adequately explain the reduced anastomotic dehiscence reported with the perioperative administration of pharmaconutrition as these used comparable products for both arms of their studies. As leukocytosis is recognised as a risk factor for anastomotic dehiscence[53] it seems plausible that the reduction in infective complications associated with pharmaconutrition may provide additional protection in the surgical anastomosis through this mechanism. However given the small number of perioperative studies analysed (*k*=2), beta-error may also be a plausible explanation for this finding.

Although seven meta-analyses on this topic already exist, there are limitations contained within these that justify a further meta-analysis. Heyland et al[23], Beale et al[24] and Heys et al[22] all include elective surgical patients as a subgroup analysis of meta-analyses on the critically ill. While all utilise inclusion criteria comparable to the current work, there have been many RCTs eligible for inclusion since their publication. Waitzberg et al[18] conducted a meta-analysis on studies published before 2003 that utilised the commercially available product, Impact® [Novartis Consumer Health, Switzerland]. This meta-analysis included cardiac surgery with an otherwise largely gastrointestinal surgery population, and included studies that utilised non-equivalent control groups such as intravenous fluids or crystalloids, or nil-by-mouth. The heterogeneity introduced through these inclusions, the exclusion of studies conducted using other similarly composed commercial products, and the suggestion that this meta-analysis has been funded by Novartis result in the need to interpret the outcomes of this analysis with caution.

Zheng et al[21] restricts inclusion criteria to gastrointestinal surgery but makes no attempt to control for the differences within the administration of pharmaconutrition between studies. Furthermore, an additional ten studies have been identified as being published since 2006 that were not available to be included in this study.

Marik and Zaloga[19] compared the effect of arginine and/or omega-3 containing pharmaconutrition products with standard formulations, and included *a priori* analyses on differing compositions and timing of pharmaconutrition. Their results are difficult to apply to practice, however, due to the heterogeneous surgical populations included (head and neck, cardiac, gastrointestinal) and the significant methodological flaw of performing meta-analysis statistics in instances where only one study met the inclusion criteria[54].

The most recent meta-analysis was published by Cerantola et al[20] in 2011. This paper incorporated recently published studies on an exclusively gastrointestinal surgical population, addressed the timing of pharmaconutrition provision through performing subgroup analyses, and is the first meta-analysis on this topic to comply with PRISMA reporting guidelines. However, it also includes studies that use non-equivalent control groups[7, 8, 10, 55]: This may produce outcomes that appear to favour pharmaconutrition independent of the role of immune-enhancing components.

For these reasons the current work has attempted to contribute to the literature on this topic through producing a meta-analysis that utilises stricter inclusion criteria with regards to the

control group (as far as the literature allows), and to exclusively analyse studies according to the timing of pharmaconutrition delivery. We believe this issue is of vital importance to guide the translation of research to clinical practice.

This meta-analysis is not without its limitations. Firstly, there are variations in the composition of included pharmaconutrition products that may confound the results obtained. The decision to allow inclusion of studies using products containing arginine +/- other pharmaconutrients was based on consideration that arginine has been the most consistently utilized pharmaconutrient in elective gastrointestinal surgical populations, and remains the consistent ingredient that links commercial and experimental formulas in this genre of products. Other pharmaconutrients included in the commercially available formulas have limited clinical evidence of individual benefit when provided enterally in this patient group in the absence of arginine. On this basis we argue that there is clinical relevance to classifying the intervention products as ‘arginine-dominant’.

Secondly, while all studies described the nutritional goals for their patients throughout the study period, few quantified the amount of nutrition actually received. We have therefore been forced to assume that nutrition goals were consistently met unless otherwise stated. This has obvious implications for the conclusions drawn, as reduced nutritional provision for reasons such as feed intolerance, non-compliance with oral supplements, tube-related complications or protocol deviations may have reduced the provision of nutrients and therefore may confound the results obtained. This aspect of reporting trials on pharmaconutrition need to be addressed in future studies on this topic.

Thirdly, the majority of the pharmaconutrition studies have been funded at least in part by the companies that manufacture the products being investigated. This is of concern as funding bias is recognised for its potential to influence the results in favour of the product being investigated in pharmaceutical studies[56, 57]. As meta-analysis is known to amplify biases included in the individual studies, the concern that funding bias may be present and has the potential to exaggerate the beneficial effects of pharmaconutrition should not be overlooked: This is true of both the current work and the existing meta-analyses on this topic. This is of particular concern given the increasing acceptance that pharmaconutrition has found in clinical practice through its incorporation into clinical guidelines[16, 17]. Interestingly, discussion of this aspect of pharmaconutrition is notably absent from the literature at the present time.

Closely tied to concerns regarding funding bias is the frequent use of non-comparable control groups: this is a commonly observed trend in pharmaceutically funded studies that are subsequently shown to favour the intervention product[57]. Significantly different protein contents between some of the intervention and control products were noted in several of the included studies. One such example is the Klek et al[14] study that uses Peptisorb® [Nutricia Ltd, Poland] (40g protein/L; 1kcal/mL) as the control product against Stresson® [Nutricia Ltd, Poland] (75g protein/L; 1.25kcal/mL). While the lack of reporting of received nutrition make the significance of these differences on the current work impossible to evaluate, even in studies that utilise individualized nutritional goals based on caloric targets, such marked differences in formulations may ultimately undermine the controlled nature of individual studies due to the lack of appropriate control group.

We made multiple attempts to contact authors for additional information or clarification of data within their publications but with disappointing response rates. In the absence of response from the group from Milan, Italy who published many of the papers on this topic in the mid-1990s and early 2000s, we excluded any of their studies we strongly suspected of representing multiple reports on the same patients[58-60]. It is clear from the published reports, however, that in so doing we have excluded approximately 80 otherwise eligible patients with gastric cancer that we could not include without a high likelihood of duplicating analyses on patients with pancreatic cancer included in other studies[6].

Furthermore, several potentially relevant sources were identified ('Sydney' study in Waitzberg et al[18], Jiang et al[38] [in Chinese] and an abstract for Yao et al[37] [in Chinese]), however adequate data to assess them for inclusion were unavailable despite our best efforts to obtain these. This unfortunate situation suggests the presence of location bias within the present work.

Finally, this meta-analysis retains the unavoidable heterogeneity introduced by the failure of the included studies to report the results of individual surgical procedures. This is significant as the complications likely to occur after procedures performed at various locations along the gastrointestinal tract vary greatly, and as such the indiscriminate grouping of these may confound the complications reported, and thus the effect attributed to the pharmaconutrition interventions provided.

This meta-analysis has highlighted areas for future research. As described above, the nutritional aspects of studies on this topic including the reporting of nutritional consumption in both groups throughout the study period, and the need for careful selection of control formulas are potential confounders in many of the existing published studies. Dietitians are largely absent from the authorship of the studies to date, and it seems likely that a more multidisciplinary approach to the research in this area is necessary, and is likely to alleviate these oversights in future studies. Secondly, convincing data supporting significant economic benefit related to the use of pharmaconutrition over standard nutrition products remains scarce in the literature. A strong body of evidence supporting the cost-benefit of pharmaconutrition is going to be increasingly vital to justify its continued use in healthcare environments that are increasing subjected to financial scrutiny in these difficult economic times.

CONCLUSIONS:

While this meta-analysis lends support to the acknowledged beneficial effects of pharmaconutrition in the management of elective gastrointestinal surgical patients, it highlights the importance of timing of administration as a clinical consideration. Contrary to previous findings, preoperative pharmaconutrition failed to deliver any benefit over standard formulations when used as a standalone intervention, and the accepted benefits of pharmaconutrition (reduction in infectious complications and LOS) were only reported in peri- and postoperative administration, and limitations in the LOS data obscure the conclusions we can draw on this outcome. It also suggests previously unreported benefits of pharmaconutrition with respect to reduced non-infective complications and anastomotic dehiscence in postoperative and perioperative administration respectively. Better quality, multi-disciplinary intervention and cost-benefit studies are required to further clarify the remaining questions on this topic.

ACKNOWLEDGEMENTS

Many thanks to Drs Jianmin Xu, Glyn Jamieson and Stanislaw Klek for their responses to queries regarding their publications.

STATEMENT OF AUTHORS' CONTRIBUTIONS TO MANUSCRIPT

E.O. and M.A.M. designed research; E.O. and M.A.M. conducted research; E.O., M.A.M., M.B.H. and S.K. analyzed data; E.O., M.A.M., M.B.H. and S.K. wrote the paper. M.A.M. had primary responsibility for the final content. All authors read and approved the final manuscript.

REFERENCES

1. Andersen HK, Lewis SJ, Thomas S. Early enteral nutrition within 24h of colorectal surgery versus later commencement of feeding for postoperative complications. *Cochrane Database Syst Rev* 2006:CD004080.
2. Osland E, Yunus RM, Khan S, Memon MA. Early versus traditional postoperative feeding in patients undergoing resectional gastrointestinal surgery: a meta-analysis. *JPEN J Parenter Enteral Nutr* 2011;35:473-87.
3. Jones NE, Heyland DK. Pharmaconutrition: a new emerging paradigm. *Curr Opin Gastroenterol* 2008;24:215-22.
4. Daly JM, Weintraub FN, Shou J, Rosato EF, Lucia M. Enteral nutrition during multimodality therapy in upper gastrointestinal cancer patients. *Ann Surg* 1995;221:327-38.
5. Braga M, Gianotti L, Radaelli G, et al. Perioperative immunonutrition in patients undergoing cancer surgery: results of a randomized double-blind phase 3 trial. *Arch Surg* 1999;134:428-33.
6. Gianotti L, Braga M, Gentilini O, Balzano G, Zerbi A, Di Carlo V. Artificial nutrition after pancreaticoduodenectomy. *Pancreas* 2000;21:344-51.
7. Braga M, Gianotti L, Vignali A, Carlo VD. Preoperative oral arginine and n-3 fatty acid supplementation improves the immunometabolic host response and outcome after colorectal resection for cancer. *Surgery* 2002;132:805-14.
8. Braga M, Gianotti L, Nespoli L, Radaelli G, Di Carlo V. Nutritional approach in malnourished surgical patients: a prospective randomized study. *Arch Surg* 2002;137:174-80.
9. Farreras N, Artigas V, Cardona D, Rius X, Trias M, Gonzalez JA. Effect of early postoperative enteral immunonutrition on wound healing in patients undergoing surgery for gastric cancer. *Clin Nutr* 2005;24:55-65.

10. Xu J, Zhong Y, Jing D, Wu Z. Preoperative enteral immunonutrition improves postoperative outcome in patients with gastrointestinal cancer. *World J Surg* 2006;30:1284-9.

11. Schilling J, Vranjes N, Fierz W, et al. Clinical outcome and immunology of postoperative arginine, omega-3 fatty acids, and nucleotide-enriched enteral feeding: a randomized prospective comparison with standard enteral and low calorie/low fat i.v. solutions. *Nutrition* 1996;12:423-9.

12. McCarter MD, Gentilini OD, Gomez ME, Daly JM. Preoperative oral supplement with immunonutrients in cancer patients. *JPEN J Parenter Enteral Nutr* 1998;22:206-11.

13. Klek S, Kulig J, Sierzega M, et al. Standard and immunomodulating enteral nutrition in patients after extended gastrointestinal surgery--a prospective, randomized, controlled clinical trial. *Clin Nutr* 2008;27:504-12.

14. Klek S, Kulig J, Sierzega M, et al. The impact of immunostimulating nutrition on infectious complications after upper gastrointestinal surgery: a prospective, randomized, clinical trial. *Ann Surg* 2008;248:212-20.

15. Gunerhan Y, Koksal N, Sahin UY, Uzun MA, Eksioglu-Demiralp E. Effect of preoperative immunonutrition and other nutrition models on cellular immune parameters. *World J Gastroenterol* 2009;15:467-72.

16. Weimann A, Braga M, Harsanyi L, et al. ESPEN Guidelines on Enteral Nutrition: Surgery including organ transplantation. *Clin Nutr* 2006;25:224-44.

17. Carey S, He L, Ferrie S. Nutritional management of patients undergoing major upper gastrointestinal surgery: A survey of current practice in Australia. *Nutrition and Dietetics* 2010;67:219-223.

18. Waitzberg DL, Saito H, Plank LD, et al. Postsurgical infections are reduced with specialized nutrition support. *World J Surg* 2006;30:1592-604.

19. Marik PE, Zaloga GP. Immunonutrition in high-risk surgical patients: a systematic review and analysis of the literature. *JPEN J Parenter Enteral Nutr* 2010;34:378-86.

20. Cerantola Y, Hubner M, Grass F, Demartines N, Schafer M. Immunonutrition in gastrointestinal surgery. *Br J Surg* 2011;98:37-48.

21. Zheng Y, Li F, Qi B, et al. Application of perioperative immunonutrition for gastrointestinal surgery: a meta-analysis of randomized controlled trials. *Asia Pac J Clin Nutr* 2007;16 Suppl 1:253-7.

22. Heys SD, Walker LG, Smith I, Eremin O. Enteral nutritional supplementation with key nutrients in patients with critical illness and cancer: a meta-analysis of randomized controlled clinical trials. *Ann Surg* 1999;229:467-77.

23. Heyland DK, Novak F, Drover JW, Jain M, Su X, Suchner U. Should immunonutrition become routine in critically ill patients? A systematic review of the evidence. *JAMA* 2001;286:944-53.

24. Beale RJ, Bryg DJ, Bihari DJ. Immunonutrition in the critically ill: a systematic review of clinical outcome. *Crit Care Med* 1999;27:2799-805.

25. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.

26. Jadad AR, Moore A, Carroll D, et al. Assessing the Quality of Reports of Randomized Clinical Trials: Is Blinding Necessary? *Controlled Clinical Trials* 1996;17:1-12.

27. Agresti A. An introduction to Categorical Data Analysis: Wiley & Sons, 1996.

28. Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F. Methods for Meta-analysis in Medical Research: John Wiley, 2000.

29. Cochran WG. The combination of estimates from different experiments. *Biometrics* 1954;10:101-129.

30. Hedges LV, Olkin I. Statistical methods for meta analysis. Orlando: Academic Press, 1985.

31. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* 2002;21:1539-1558.

32. Huedo-Medina TB, Sanchez-Meca J, Marin-Martinez F, Botella J. Assessing heterogeneity in meta analysis: statistic or index? *The American Psychological Association* 2006;11:193 - 206.

33. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Br Med J* 1997;315:629-634.

34. Tang JL, Liu JL. Misleading funnel plot for detection of bias in meta-analysis. *J Clin Epidemiol* 2000;53:477-84.

35. Hornik K. R: A language and environment for statistical computing. 2.8.0 ed. Vienna: Foundation for Statistical computing, 2008.

36. *The rmeta Package* [computer program] Version 2.14. Washington: Lumley, T; 2008.

37. Yao G, Xue X, Liu X, Wang J, Qian J. Effects of postoperative enteral immune-enhancing diet on plasma endotoxin level, plasma endotoxin inactivation capacity and clinical outcome. *J Huazhong Univ Sci Technolog Med Sci* 2005;25:431-4.

38. Jiang ZM, Gu ZY, Chen FL, et al. [The role of immune enhanced enteral nutrition on plasma amino acid, gut permeability and clinical outcome (a randomized, double blind, controlled, multi-center clinical trail with 120 cases)]. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao* 2001;23:515-8.

39. Lobo DN, Williams RN, Welch NT, et al. Early postoperative jejunostomy feeding with an immune modulating diet in patients undergoing resectional surgery for upper gastrointestinal cancer: a prospective, randomized, controlled, double-blind study. *Clin Nutr* 2006;25:716-26.

40. Klek S, Sierzega M, Szybinski P, et al. The immunomodulating enteral nutrition in malnourished surgical patients - a prospective, randomized, double-blind clinical trial. *Clin Nutr* 2011;30:282-8.

41. Daly JM, Lieberman MD, Goldfine J, et al. Enteral nutrition with supplemental arginine, RNA, and omega-3 fatty acids in patients after operation: immunologic, metabolic, and clinical outcome. *Surgery* 1992;112:56-67.

42. Senkal M, Mumme A, Eickhoff U, et al. Early postoperative enteral immunonutrition: clinical outcome and cost-comparison analysis in surgical patients. *Crit Care Med* 1997;25:1489-96.

43. Jiang XH, Li N, Zhu WM, Wu GH, Quan ZW, Li JS. Effects of postoperative immune-enhancing enteral nutrition on the immune system, inflammatory responses, and clinical outcome. *Chin Med J (Engl)* 2004;117:835-9.

44. Senkal M, Zumtobel V, Bauer KH, et al. Outcome and cost-effectiveness of perioperative enteral immunonutrition in patients undergoing elective upper gastrointestinal tract surgery: a prospective randomized study. *Arch Surg* 1999;134:1309-16.

45. Sodergren MH, Jethwa P, Kumar S, Duncan HD, Johns T, Pearce CB. Immunonutrition in patients undergoing major upper gastrointestinal surgery: a prospective double-blind randomised controlled study. *Scand J Surg* 2010;99:153-61.

46. Okamoto Y, Okano K, Izuishi K, Usuki H, Wakabayashi H, Suzuki Y. Attenuation of the systemic inflammatory response and infectious complications after gastrectomy with preoperative oral arginine and omega-3 fatty acids supplemented immunonutrition. *World J Surg* 2009;33:1815-21.

47. Daly JM, Reynolds J, Thom A, et al. Immune and metabolic effects of arginine in the surgical patient. *Ann Surg* 1988;208:512-23.

48. Fresenius Kabi AG. Intestamin® 2011: Product information. Available at: http://www.fresenius-kabi.com/1801.htm. Accessed 6th August 2011.

49. Chen DW, Wei Fei Z, Zhang YC, Ou JM, Xu J. Role of enteral immunonutrition in patients with gastric carcinoma undergoing major surgery. *Asian J Surg* 2005;28:121-4.

50. Braga M, Gianotti L, Cestari A, et al. Gut function and immune and inflammatory responses in patients perioperatively fed with supplemented enteral formulas. *Arch Surg* 1996;131:1257-64.

51. Wu GH, Zhang YW, Wu ZH. Modulation of postoperative immune and inflammatory response by immune-enhancing enteral diet in gastrointestinal cancer patients. *World J Gastroenterol* 2001;7:357-62.

52. Paccagnella A, Morassutti I, Rosti G. Nutritional intervention for improving treatment tolerance in cancer patients. *Curr Opin Oncol* 2011;23:322-30.

53. Kingham TP, Pachter HL. Colonic anastomotic leak: risk factors, diagnosis, and treatment. *J Am Coll Surg* 2009;208:269-78.

54. Higgins JP, Green S, eds. Appendix 8a Considerations and recommendations for figures in Cochrane reviews: Graphs of statistical data. Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 [updated September 2006]; Appendices. Chichester, UK: John Wiley & Sons Ltd., 2006.

55. Finco C, Magnanini P, Sarzo G, et al. Prospective randomized study on perioperative enteral immunonutrition in laparoscopic colorectal surgery. *Surg Endosc* 2007;21:1175-9.

56. Chopra SS. MSJAMA: Industry funding of clinical trials: benefit or bias? *JAMA* 2003;290:113-4.

57. Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *BMJ* 2003;326:1167-70.

58. Di Carlo V, Gianotti L, Balzano G, Zerbi A, Braga M. Complications of pancreatic surgery and the role of perioperative nutrition. *Dig Surg* 1999;16:320-6.

59. Gianotti L, Braga M, Vignali A, et al. Effect of route of delivery and formulation of postoperative nutritional support in patients undergoing major operations for malignant neoplasms. *Arch Surg* 1997;132:1222-9.

60. Braga M, Gianotti L, Vignali A, Cestari A, Bisagni P, Di Carlo V. Artificial nutrition after major abdominal surgery: impact of route of administration and composition of the diet. *Crit Care Med* 1998;26:24-30.

Figure 1 – PRISMA statement describing the identification, inclusion and exclusion of randomized controlled trials evaluating the effect of pharmaconutrition on postoperative clinical outcomes compared to standard nutritional provision.

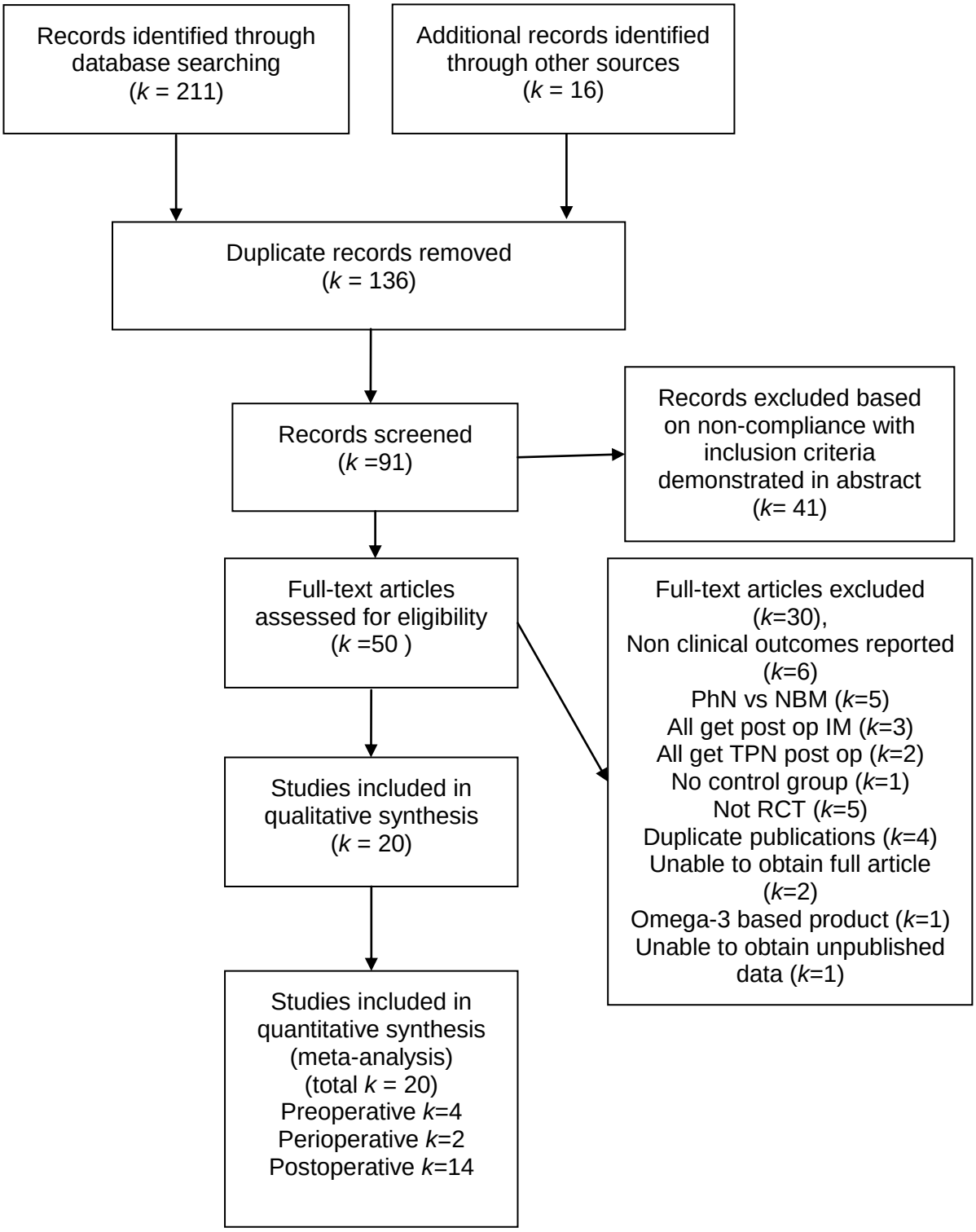


Figure 2A – Infectious complications: postoperative administration.

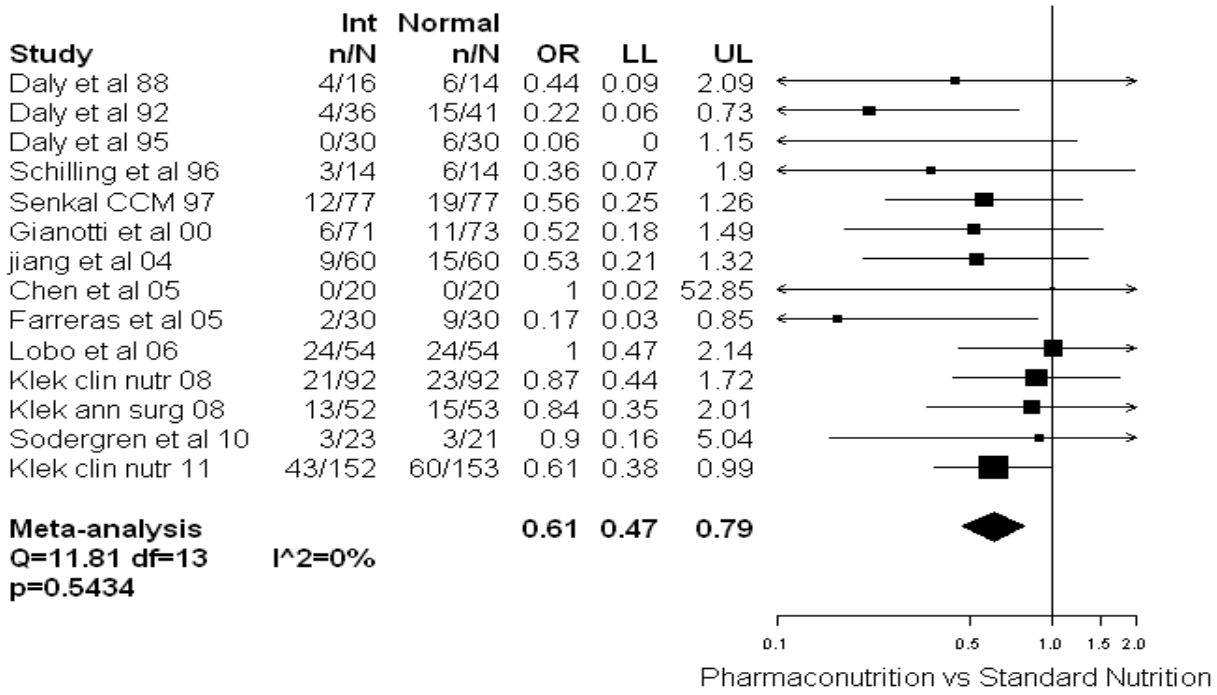
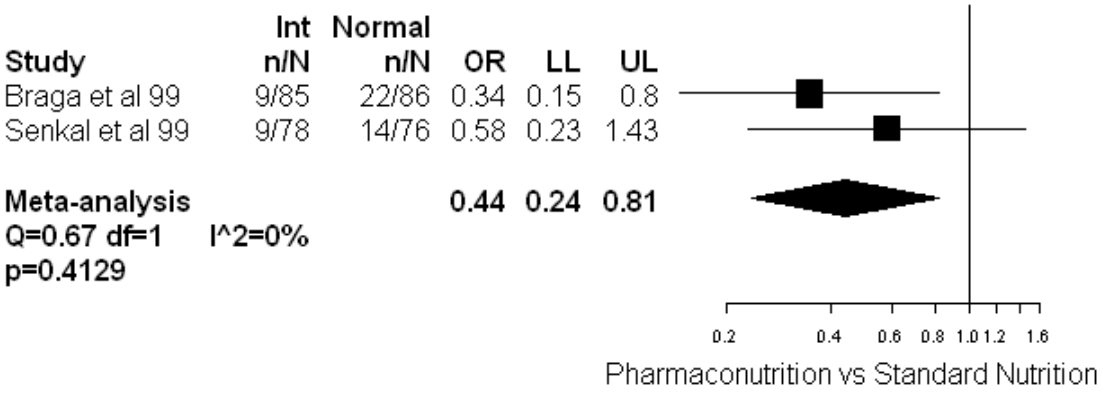


Figure 2B - Infectious complications: perioperative administration.



The boxes in Figure 2A and 2B represent individual studies with the size of each corresponding to the attributed weighting under a random effects model. Error bars represent 95% confidence intervals. The diamond represents the pooled effect size, with its length representing the width of the confidence interval. Vertical line represents the line of no effect (null hypothesis).

Figure 3A – LOS: postoperative administration.

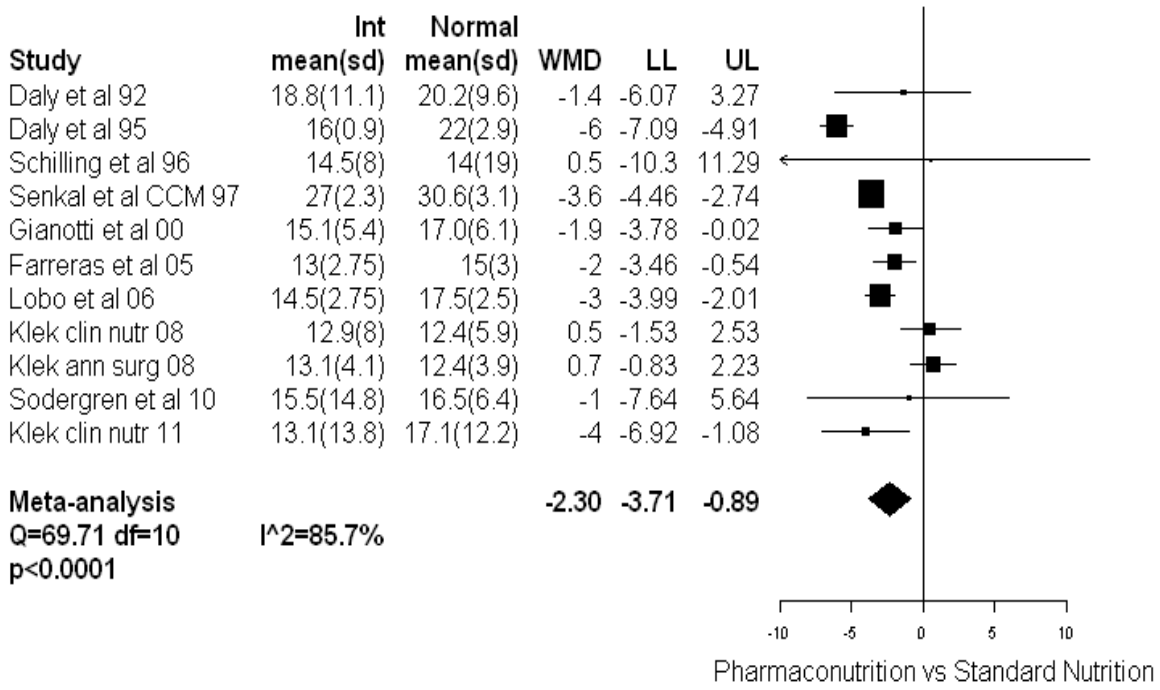
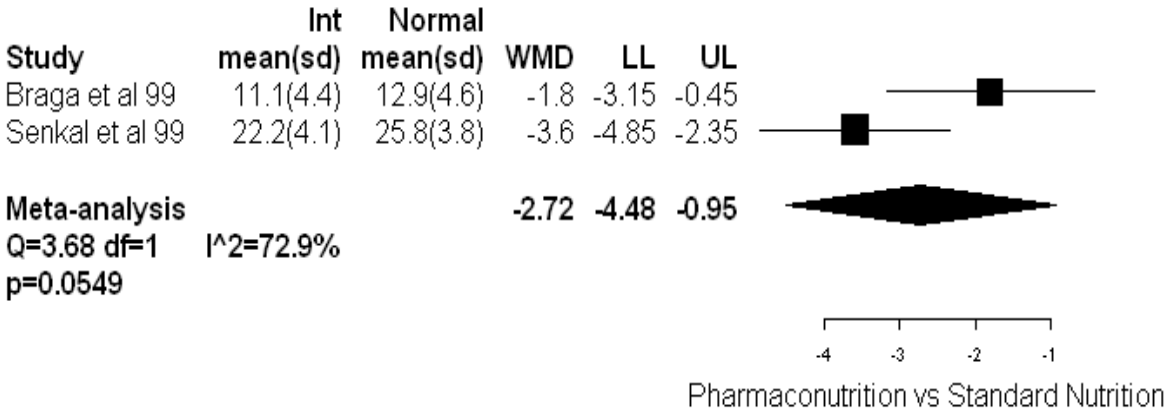
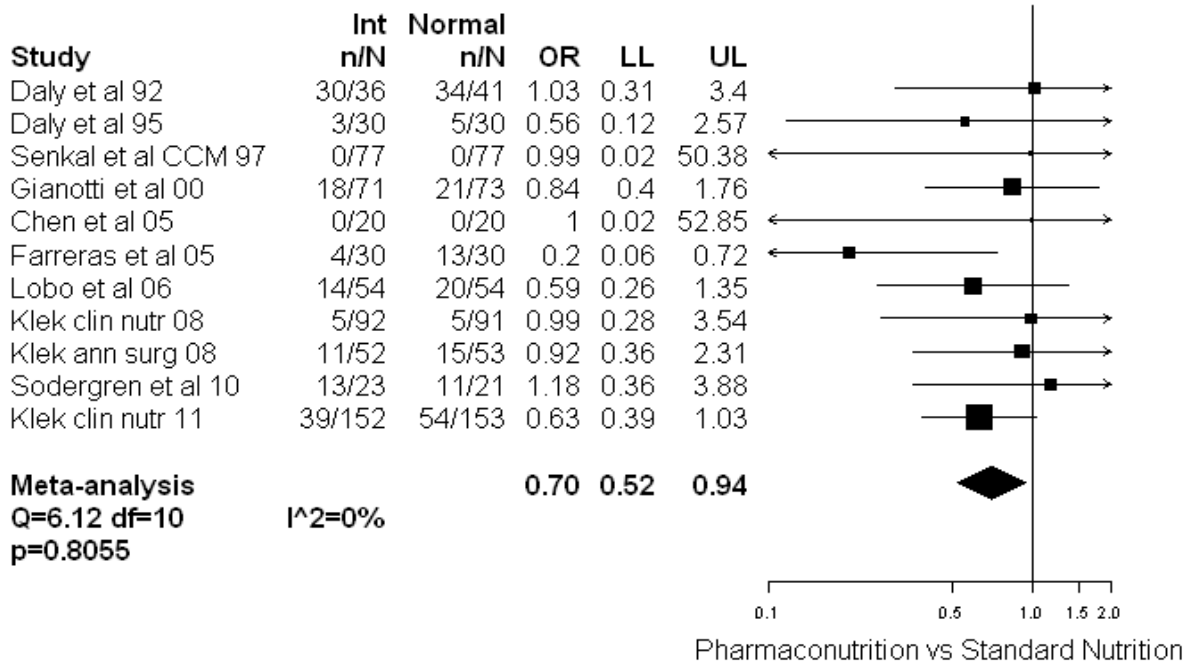


Figure 3B- LOS: perioperative administration.



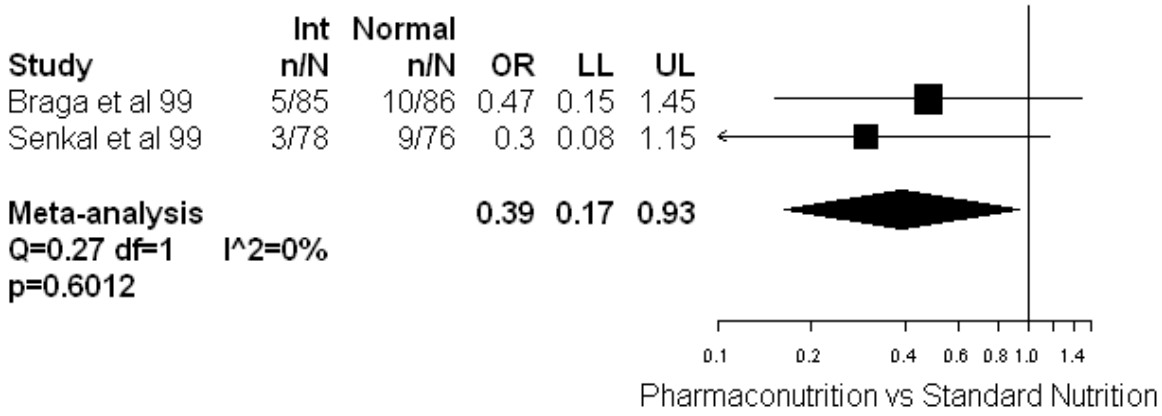
The boxes in Figure 3A and 3B represent individual studies with the size of each corresponding to the attributed weighting under a random effects model. Error bars represent 95% confidence intervals. The diamond represents the pooled effect size, with its length representing the width of the confidence interval. Vertical line represents the line of no effect (null hypothesis).

Figure 4 – Non-infectious complications: postoperative administration.



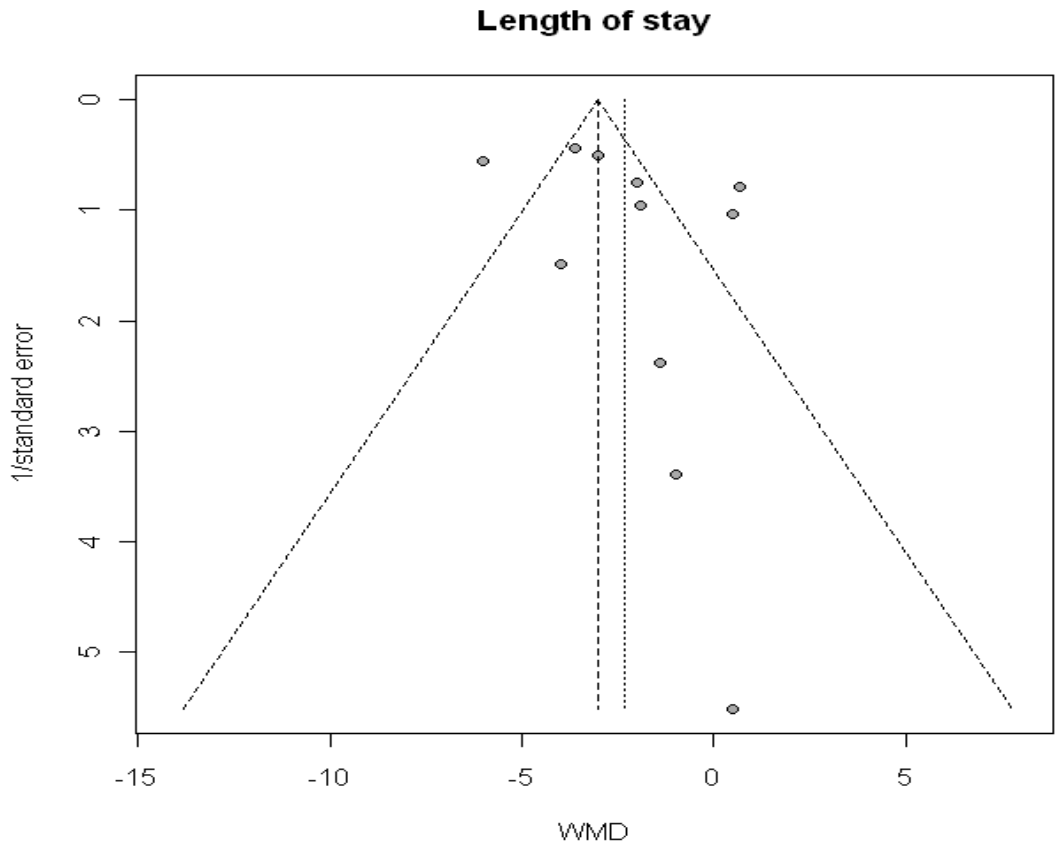
The boxes represent individual studies with the size of each corresponding to the attributed weighting under a random effects model. Error bars represent 95% confidence intervals. The diamond represents the pooled effect size, with its length representing the width of the confidence interval. Vertical line represents the line of no effect (null hypothesis).

Figure 5 – Anastomotic dehiscence: perioperative administration.



The boxes represent individual studies with the size of each corresponding to the attributed weighting under a random effects model. Error bars represent 95% confidence intervals. The diamond represents the pooled effect size, with its length representing the width of the confidence interval. Vertical line represents the line of no effect (null hypothesis).

Figure 6 – Funnel plot for LOS: postoperative administration.



The points correspond to the treatment effects (log WMD) from 11 individual studies, and the diagonal lines show the expected 95% confidence intervals around the pooled fixed effect log WMD estimate.

Table 1 – Pharmaconutritional Interventions of Included RCTs

Author Year	Timing of administration	Feeding protocol	Nutrition goal	Pharmaconutrition product	Control product
McCarter et al 1998[12]	Preoperative	Oral supplements in addition to normal meals for ≥7 days	750mL/d	Not stated	Not stated
Braga et al 2002[7]	Preoperative	Oral supplements in addition to normal diet for 5 days	1000mL/d	Oral Impact® (Novartis, Bern, Switzerland)	Not stated
Okamoto et al 2009[46]	Preoperative	Oral supplements in addition to standard hospital diet for 7 days	750mL/d	Impact® (Ajinomoto Pharm Co, Japan)	MEDIF® (Ajinomoto Pharm Co, Japan)
Gunerhan et al 2009[15]	Preoperative	7 days, route unspecified	Individual requirements (Harris-Benedict Equation)	Impact® (Novartis Nutrition, Switzerland)	Fresubin® (details not stated)
Senkal et al 1999[44]	Perioperative	Oral supplements ≥5 days in addition to normal hospital diet preoperatively; jejunal feeding commenced 12hrs postop continued until at least POD5	1000mL/d preop; 1920mL/d reached by POD5	Impact® (Novartis, Bern, Switzerland)	Not stated
Braga et al 1999[5]	Perioperative	Oral supplements for 7 days preoperatively in addition to normal food as desired; jejunal feeding 6hrs postoperatively and increased to goal by POD3. Oral intake from POD7, unclear when jejunal feeding ceased.	1000mL/d preoperatively; 1500mL postoperatively	Impact® (Novartis, Bern, Switzerland)	Not stated
Daly et al 1988[47]	Postoperative	Jejunal feeding commenced POD1 and continued to POD7. Clear fluids until POD7, oral intake recommenced POD7.	individual requirements (25kcal/kg)	Nutrisource Modular Diet® (Sandoz Nutrition, Minneapolis, MN) + 25g L-Arginine	Nutrisource Modular Diet® (Sandoz Nutrition, Minneapolis, MN) + 43g L-Glycine

Daly et al 1992[41]	Postoperative	Jejunal feeding commenced POD1 and discontinued when patient could meet 'adequate' intake orally.	individual requirements (25kcal/kg)	Impact® (Sandoz Nutrition, Minneapolis, MN)	Osmolite HN® (Ross Laboratories, Columbus, OH)
Daly et al 1995[4]	Postoperative	Jejunal feeding commenced from POD1 and continued until fluids and foods taken by mouth.	individual requirements (25kcal/kg)	Impact® (Sandoz Nutrition, Minneapolis, MN)	Traumacal® (Bristol-Meyrs Squibb, Evansville, IN)
Schilling et al 1996[11]	Postoperative	Small bowel feeding commenced 'as early as possible'; Duration of feeding and time to goal rate not stated.	individual requirements (25kcal/kg)	Impact® (Sandoz Nutrition Ltd, Bern, Switzerland)	Fresubin® (Fresenius AG, Stans, Switzerland)
Senkal et al 1997[42]	Postoperative	Jejunal feeding commenced 12hrs postoperatively. Clear fluids commenced between POD5 and POD7. Unclear when jejunal feeds ceased.	individual requirements (25kcal/kg)	Impact® (Sandoz Nutrition, Bern, Switzerland)	Not stated
Gianotti et al 2000[6]	Postoperative	Jejunal feeding commenced 6hrs postoperatively and ceased when oral intake provided ~800kcal/d.	individual requirements (25kcal/kg)	Impact® (Sandoz Nutrition Ltd, Bern, Switzerland)	Not stated
Jiang et al 2004[43]	Postoperative	Jejunal feeding commenced POD1 and continued until POD7.	individual requirements (30kcal/kg)	Stresson Multifibre® (Nutricia, Holland)	Nutrison Multifibre® (Nutricia, Holland)
Chen et al 2005[49]	Postoperative	Jejunal feeds commenced POD2 postop continued to POD9	individual requirements (30kcal/kg)	Stresson® (Nutricia China, Shanghai, China)	Nutrison® (Nutricia, China, Shanghai, China)
Ferreras et al 2005[9]	Postoperative	Jejunal feeds commenced 12-18hrs postop continued to POD7.		Impact® (Novartis Consumer Health, Spain)	Isosource Protein® (Novartis Consumer Health, Spain)
Lobo et al 2010[39]	Postoperative	Jejunal feeds commenced 4hrs postop continued to POD10-15	75mL/hr over 20hrs/d.	Stresson® (Nutricia Ltd, Netherlands)	Nutrison High Protein® (Nutricia Ltd, Netherlands)
Klek et al	Postoperative	Jejunal feeds commenced 6hrs postop	2400mL/d	Reconvan® (Fresenius	Peptisorb® (Nutricia Ltd,

2008[13]		continued to POD7.		Kabi, Poland)	Poland)
Klek et al 2008[14]	Postoperative	Jejunal feeds commenced 6hrs postop continued to POD7.	2400mL/d	Stresson® (Nutricia Ltd)	Peptisorb® (Nutricia Ltd, Poland)
Sodergren et al 2010[45]	Postoperative	Jejunal feeds commenced POD1 and continued to POD5, with a possible extension period to a maximum of POD15.	individual requirements (25kcal/kg)	Prototype to Intestamin® (Fresenius-Kabi, Germany)	Not stated
Klek et al 2011[40]	Postoperative	Jejunal feeds commenced 6hr postop and continued until POD7.	~2000mL/d provided over 20-22hrs.	Reconvan® (Fresenius-Kabi, Poland)	Peptisorb® (Nutricia, Poland)

POD = Postoperative Day

Table 2 – Preoperative Pharmaconutrition study characteristics

Author (year) / Country	Study Population	Study Design	Std EN (n)	PhN EN (n)	Study Endpoints	Source of Funding	Mal-nutrition rates	Jadad score (R/B/W)
McCarter et al (1998) / USA[12]	Gastric, esophageal, pancreatic Ca	Std EN vs. high Arg EN vs. high Arg/EFAs EN	11	14	Not stated but appears to be immune and clinical outcomes	Supported in part by a grant from Novartis Nutrition Corporation, Minneapolis, MN	20%	4 (1/2/1)
Braga et al (2002) / Italy[7]	Colorectal Ca	Preop PhN oral + PhN EN postop vs. Preop PhN oral vs. Preop Std oral vs. no supplementation pre op, NBM postop	50	50	Not directly stated. Hypotheses involve immune-metabolic variables, morbidity and LOS.	Products provided by Novartis Consumer Health , Bern, Switzerland	10%	2 (2/0/0)
Okamoto (2009)/ Japan[46]	Gastric Ca	PhN EN vs. Std EN	30	30	Postoperative cellular immunity; postoperative infectious and non-infectious complications; SIRS.	N/R	N/R	2 (2/0/0)
Gunerhan et al (2009)/ Turkey[15]	Unspecified GIT Ca	PhN EN vs. Normal diet vs. Std EN	11	13	Nutritional parameters; cellular immunity	N/R	100%	2 (1/0/1)

GIT=gastrointestinal; UGI= upper gastrointestinal; Ca = cancer; SIRS = Systemic inflammatory response syndrome; Randomization (out of 2)/Blinding (out of 2)/Withdrawals (out of 1); PhN= Pharmaconutrition formulation; Std = standard composition formulation; EN= enteral nutrition; NBM= nil by mouth; N/R= not reported; LOS= length of stay; POD = Postoperative Day

Table 3 – Perioperative Pharmaconutrition study characteristics

Author (year)/ Country	Study Population	Study Design	Std EN (n)	PhN EN (n)	Study Endpoints	Source of Funding	Mal-nutrition rates	Jadad score (R/B/W)
Braga et al (1999) / Italy[5]	Gastric, pancreatic and colorectal Ca	PhN EN vs. Std EN	86	85	Reduction of infectious complications	Diets provided by Novartis Nutrition, Bern, Switzerland	23%	5 (2/2/1)
Senkal et al (1999) / Germany[44]	UGI and pancreatic Ca	PhN EN vs. Std EN	76	78	Primary outcome: Infectious complications after POD3 or POD5	Unclear – 4 organizations are thanked (including Nutricia, Bern, Switzerland) though reasons not stated	N/R	4 (1/2/1)

UGI= upper gastrointestinal; Ca = cancer; R/B/W=Randomization (out of 2)/Blinding (out of 2)/Withdrawals (out of 1); PhN= Pharmaconutrition formulation; Std = standard composition formulation; EN= enteral nutrition; TPN= total parenteral nutrition; N/R= not reported; POD = Postoperative Day

Table 4 – Postoperative Pharmaconutrtition Study characteristics

Author (year) / Country	Study Population	Study Design	Std EN (n)	PhN EN (n)	Study Endpoints	Source of Funding	Mal-nutrition rates	Jadad score (R/B/W)
Daly et al (1988) / USA[47]	UGI, pancreatic, colorectal Ca (97%), melanoma (3%)	Arginine supplemented Std EN vs. glycine supplemented Std EN	14	16	Not stated, but appears to be immune, metabolic and clinical outcomes.	Supported by Georgene S Harmelin Surgical Oncology Research Grant, and a grant from Sandoz Inc, and NIH Grant No 19525.	56%	3 (1/2/0)
Daly et al (1992) / USA[41]	UGI, pancreatic Ca	PhN EN vs. Std EN	44	41	Not stated, but appears to be nutritional, immune, metabolic and clinical outcomes.	Supported by Georgene S Harmelin Surgical Oncology Research Grant, and a grant from Sandoz Inc, and NIH Grant No 19525.	35%	3 (2/0/1)
Daly et al (1995) / USA[4]	UGI, pancreatic Ca	PhN EN (inpt ± outpt) vs. Std EN (inpt ± outpt) *Only inpatient data was used for this analysis*	30	30	Clinical outcome, white cell fatty acid composition, PGE_2 secretion	Supported by Georgene S Harmelin Surgical Oncology Research Fund, National institute of Health training grant 3-T32-CA-09619, and Sandoz Nutrition Inc	30%	3 (2/0/1)
Schilling et al (1996)/ Switzerland[11]	UGI, pancreatic or colorectal Ca	PhN EN vs. Std vs. low calorie/ low fat IV solution	14	14	Not stated, but appears to be immune function.	Supported in part by Sandoz Nutrition Ltd.	N/R	2 (1/0/1)
Senkal et al (1997) / Germany[42]	UGI, pancreatic Ca	PhN EN vs. Std EN	77	77	Not stated, but appears to be clinical outcome and costs.	Supported in part by Sandoz Nutrition Ltd.	N/R	5 (2/2/1)
Gianotti et al (2000) / Italy[6]	Pancreatic Ca	PhN EN vs. Std EN vs. Std TPN	73	71	Not stated, but appears to be immunometabolic parameters and clinical outcome	Partially supported by Novartis Nutrition, Bern, Switzerland	60%	2 (2/0/0)

Jiang et al (2004) / China[43]	UGI, colorectal Ca (81%), other Ca (7%), other diseases (12%)	PhN EN vs. Std EN	60	60	Not stated, but appear to be immune function, inflammatory response, and infectious complications	None stated	N/R	2 (1/0/1)
Chen et al (2005) / China[49]	Gastric Ca	PhN EN vs. Std EN	20	20	Inflammatory and immunological parameters	N/R	N/R	1 (1/0/0)
Ferreras et al (2005) / Spain[9]	Gastric Ca	PhN EN vs. Std EN	30	30	Primary: Postop wound healing Secondary: Infectious complications; morbidity, LOS.	Supported in part by Novartis Consumer Health, Spain	20%	5 (2/2/1)
Lobo et al (2006) / UK[39]	UGI Ca	PhN EN vs. Std EN	54	54	Primary: infectious complications. Secondary: non-infective complications; mortality; LOS.	Dr Lobo: Research Fellowship from Special Trustees of the University Hospital, Queen's Medical Centre, Nottingham. Dr Crowe: grant from Nutricia Clinical Care, UK. Feeds provided gratis by Nutricia Clinical Care, UK. States funding sources were not involved in the design or execution of the study or in the publication of the work.	N/R	5 (2/2/1)
Klek et al (2008) / Poland[13]	Gastric, pancreatic Ca	PhN EN vs. Std EN	91	92	Postoperative complications; LOS; liver/kidney/immune function; treatment tolerance.	Conflict of interest denied; funding source N/R	9%	3 (2/0/1)

Klek et al (2008) / Poland[14]	Gastric, pancreatic Ca	PhN EN vs. Std EN vs. PhN TPN vs. Std TPN	53	52	Infectious complications in well nourished patients	N/R	16%	3 (2/0/1)
Sodergren et al (2010) / UK[45]	UGI surgery (96%), Other (4%)	PhN EN vs. Std EN	21	23	Primary: C-Reactive Protein, prealbumin, retinol binding protein. Secondary: clinical, infections, safety, tolerance, biochemical	Fresenius Kabi Clinical Research Department (Bad Homberg, Germany) – actively involved in the randomization process.	N/R	3 (2/1/0)
Klek et al (2011) / Poland[40]	Gastric, pancreatic Ca	PhN EN vs. Std EN	153	152	Primary: postop complications Secondary: LOS, immune function, liver and kidney function	Conflict of interest denied; funding source N/R	100%	3 (2/0/1) States blinding in title but none described

UGI= upper gastrointestinal; Ca = cancer; SIRS = Systemic inflammatory response syndrome; inpt= inpatient; outpt= outpatient
Randomization (out of 2)/Blinding (out of 2)/Withdrawals (out of 1); PhN = Pharmaconutrition formulation; Std = standard composition formulation; EN= enteral nutrition; TPN= total parenteral nutrition; NBM= nil by mouth; N/R= not reported; LOS= length of stay; POD = Postoperative Day;

Table 5 – Pharmaconutrition products utilized within included studies

Product	Energy (per L)	Protein (per L)	Pharmaconutrients (per L)
Oral Impact®	1010kCal	56g	12.5g Arginine, 3.3 omega-3 fatty acid, RNA quantity not stated
Impact®	1000kCal or 1015kcal	56g or 59g	12.5g Arginine, 3.3 omega-3 fatty acid, 1.2g RNA
Nutrisource Modular Diet® + 25g L-Arginine	1090kCal	45g	25g additional Arginine
Stresson Multifibre® or Stresson®	1250kcal	75g	8.9g Arginine 13g Glycine Omega-6:omega-3 ratio 3.45:1
Reconvan®	1000kcal	55g	Not stated
Prototype to Intestamin®	n/s	n/s	arginine, glutamine, omega 3, tributyrin, Vitamins C, E, B-carotene and micronutrients

n/s = not stated

Table 6 – Standard nutrition products utilized within included studies

Product	Energy (per L)	Protein (per L)
MEDIF®	Isocaloric	isonitrogenous
Fresubin®	1000kcal	38g
Nutrisource Modular Diet® + 43g L-Glycine	1090kCal	45g
Osmolite HN®	1070kcal	45g
Traumacal®	1115kcal	62g
Nutrison Multifibre®	1000kcal	40g
Nutrison®	1000kcal	40g
Isosource Protein®	1220kcal	66g
Nutrison High Protein®	1250kcal	75g
Peptisorb®	1000kcal	40g

Table 7: Summary of pooled data of Preoperative Pharmaconutrition versus Standard Nutrition

Outcome Variables	Pooled OR WMD (95% CI)	Test for overall effect		Test for heterogeneity		
		Z	***p* value**	***Q***	***p* value**	***I²* index**
Mortality	1.21 (0.22; 6.64)	0.22	0.82	0.27	0.99	0% [0%; 0%]
Infective complications	0.56 (0.22; 1.47)	-1.17	0.24	7.2	0.12	44.5% [0%; 79.6%]
Anastomotic dehiscence	0.79 (0.30; 2.08)	-0.47	0.64	2.2	0.53	0% [0%; 79.1%]
Non-infective complications	1.97 (0.78; 4.94)	1.44	0.15	0.49	0.97	0% [0%; 0%]
Length of stay	1.21 (-2.31; 4.74)	0.67	0.50	28.47	<0.01	89.5% [75.8%; 95.4%]
Intolerance symptoms	0.66 (0.30; 1.44)	-1.04	0.30	1.92	0.38	0% [0%; 89.2%]

Table 8: Summary of pooled data of Perioperative Pharmaconutrition versus Standard Nutrition

Outcome Variables	Pooled OR WMD (95% CI)	Test for overall effect		Test for heterogeneity		
		Z	***p* value**	***Q***	***p* value**	***I*² index**
Mortality	0.51 (0.04; 6.17)	-0.53	0.60	0.17	0.68	0%
Infective complications	0.44 (0.24; 0.81)	-2.62	0.00	0.67	0.41	0%
Anastomotic dehiscence	0.39 (0.17; 0.93)	-2.13	0.03	0.27	0.60	0%
Non-infective Complications	0.79 (0.29; 2.17)	-0.45	0.65	0.34	0.56	0%
Length of stay	-2.57 (-3.70; -1.44)	-3.02	0.00	3.68	0.05	72.9%

Table 9: Summary of pooled data of Postoperative Pharmaconutrition versus Standard Nutrition

Outcome Variables	Pooled OR WMD (95% CI)	Test for overall effect		Test for heterogeneity		
		Z	***p* value**	***Q***	***p* value**	***I²* index**
Mortality	0.85 (0.45; 1.59)	-0.51	0.61	6.04	0.95	0% [0%; 3.3%]
Infective complications	0.61 (0.47; 0.79)	-3.80	<0.01	11.81	0.54	0% [0%; 50.5%]
Anastomotic dehiscence	0.72 (0.37; 1.40)	-0.96	0.34	0.73	0.99	0% [0%; 0%]
Non-infective complications	0.70 (0.52; 0.94)	-2.38	0.02	6.12	0.80	0% [0%; 35%]
Length of stay	-2.30 (-3.71; -0.89)	-3.20	0.00	69.71	<0.01	85.7% [76.1%; 91.4%]
Gastrointestinal intolerance symptoms	0.69 (0.44; 1.08)	-1.63	0.10	2.7	0.61	0% [0%; 69.2%]