WHO Surgical Site Infection Prevention Guidelines

Web Appendix 11

Summary of a systematic review on enhanced nutritional support

1. Introduction

Malnutrition, including protein-energy and micronutrient deficiencies, continues to be a major public health problem, particularly in developing countries. It affects also the rapidly growing elderly population in high-income countries *(1, 2)*. Nutritional status can have a profound impact on the immune system *(3)* and some studies have documented the relationship between malnutrition and an impaired host immune response *(2-4)*. These alterations in immunity may make patients more susceptible to postoperative infections and malnutrition was reported as a threat to surgical outcome *(2-7)*. Similarly, several studies found an association between poor preoperative nutritional status and poor surgical outcomes, including delayed recovery, higher rates of morbidity and mortality, prolonged hospital stay, increased health care costs and a higher early readmission rate *(2, 5, 7)*.

Some studies showed that early nutritional support can improve outcome and decrease the incidence of infectious complications following major surgery in selected malnourished or severely injured patients. The hypothesis is that the immune system may be modulated by the use of specific types of nutritional support *(2, 3, 7, 8)*. Furthermore, surgery induces an altered protein metabolism, marked by a negative nitrogen balance and changes in amino acid patterns in blood. In addition, inflammation is integral to recovery after stress, such as a surgical procedure. Therefore, nutritional support is being used more and more as a means to increase protein and caloric intake during the perioperative period, particularly by using formulas high in specific amino acids, antioxidants and anti-inflammatory nutrients *(9, 10)*.

Given the role of nutrition in the host response to surgery, many researchers believe that nutritional interventions would reduce surgical site infection (SSI) and related morbidity. However, an epidemiologic association between incisional SSI and malnutrition has been difficult to demonstrate consistently for all surgical subspecialties. Furthermore, there is very little consensus on the optimal timing and dosage of multiple nutrient-enhanced formulas, especially for the prevention of SSI.

There are currently no formal recommendations for nutrition supplementation for SSI prevention. Recent recommendations from the Society for Healthcare Epidemiology of America (SHEA)/Infectious Diseases Society of America (IDSA) state that the preoperative administration of parenteral nutrition should not delay surgery *(11)*.

2. PICO question

In surgical patients, should enhanced nutritional support be used for the prevention of SSI?

Population: inpatients and outpatients of any age undergoing surgical operations (any type of procedure)
Intervention: enhanced nutritional support (oral, enteral, parenteral)
Comparator: standard nutrition formula or no nutritional support
Outcomes: SSI or SSI-attributable mortality

3. **Methods**

The following databases were searched: Medline (PubMed); Excerpta Medica Database (EMBASE); Cumulative Index to Nursing and Allied Health Literature (CINAHL); Cochrane Central Register of Controlled Trials (CENTRAL); and WHO regional medical databases. The time limit for the review was between 1 January 1990 and 24 July 2015. Language was restricted to English, French and Spanish. A comprehensive list of search terms was used, including Medical Subject Headings (MeSH) (Appendix 1).

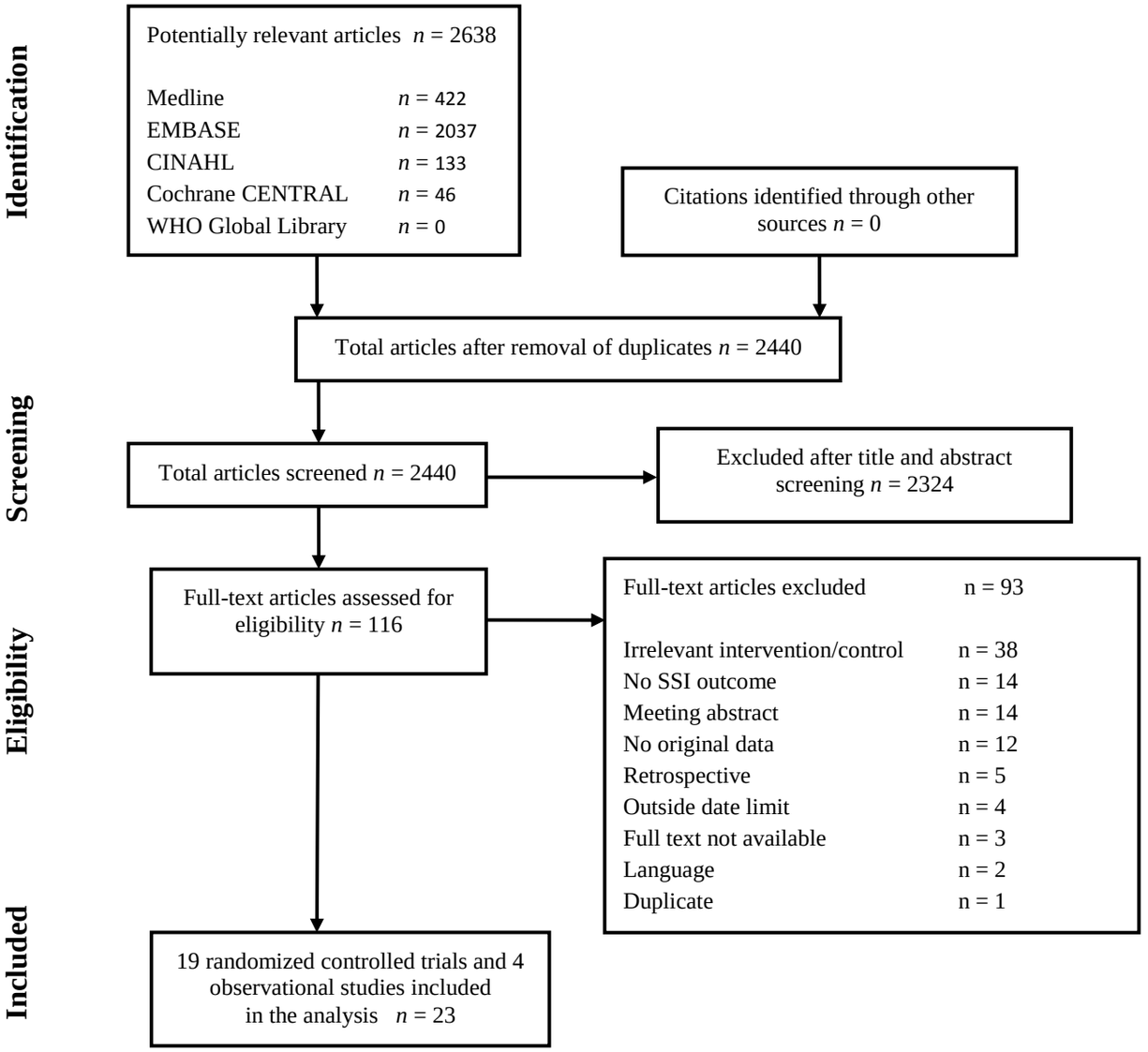
Two independent reviewers screened the titles and abstracts of retrieved references for potentially relevant studies. The full text of all potentially eligible articles was obtained and then reviewed independently by two authors for eligibility based on inclusion criteria. Duplicate studies were excluded.

Two authors extracted data in a predefined evidence table (Appendix 2) and critically appraised the retrieved studies. Quality was assessed using the Cochrane Collaboration tool to assess the risk of bias of randomized controlled trials (RCTs) *(12)* (Appendix 3a) and the Newcastle-Ottawa Quality Assessment Scale for cohort studies *(13)* (Appendix 3b). Any disagreements were resolved through discussion or after consultation with the senior author, when necessary.

Meta-analyses of available comparisons were performed using Review Manager version 5.3 *(14)* as appropriate (Appendix 4). Odds ratios (OR) with 95% confidence intervals (CI) were extracted and pooled for each comparison with a random effects model. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (GRADE Pro software, http://gradepro.org/) *(15)* was used to assess the quality of the body of retrieved evidence (Appendix 5).

4. **Study selection**

Flow chart of the study selection process



5. Summary of the findings and quality of the evidence

A total of 23 studies (19 RCTs and 4 observational) investigating the use of enhanced nutritional support and reporting SSI as an outcome were identified (Appendix 2). Nutrition administration routes varied between oral, enteral and/or parenteral, but these data were not always presented in a stratified manner. Nutritional formulas varied across studies as nutrients were not identical and contained different doses of single and/or multiple nutrients. Several studies used nutritional or inflammatory biomarkers as primary outcomes and addressed SSI as a secondary outcome and thus the assessment period was short for some studies.

After careful appraisal of the included studies, the research team and the Guidelines Development Group (GDG) decided to perform meta-analysis comparisons including only studies in which the oral and enteral routes were used and excluding those using the parenteral route. The main reason was that the parenteral route is very different from the oral and enteral routes and the experts considered it inappropriate to administer enhanced nutritional formulas only for the purpose of preventing SSI given the infectious risk related to intravenous access. According to the type of formula used, the following comparisons were possible:

1. **Single nutrient-enhanced nutrition**

   Six studies (5 RCTs *(16-20)* and one observational *(21)*) compared the use of nutritional formulas enhanced with a single nutrient (either arginine, glycine or branched chain amino acids) with the standard isocaloric, isonitrogenous enteral formula. These studies included adult patients with head and neck cancer, hepatocellular carcinoma and those with cardiac disease undergoing elective surgical procedures.

   Among the 5 RCTs, 2 studies *(16, 17)* reported that supplementing the enteral nutrition with a single nutrient may have some benefit, but the effect was not statistically significant. Two other studies *(18, 19)* reported no SSI events in both intervention and control groups. One study *(20)* estimated that single nutrient-enhanced nutrition may increase SSI, but the effect was not statistically different from the control group.

   Meta-analysis of these 5 studies showed that single nutrient-enhanced nutrition has neither benefit nor harm when compared to standard nutritional support in reducing the risk of SSI (OR: 0.61; 95% CI: 0.13–2.79) (Appendix 4). In addition, the observational study *(21)* showed a similar result with no difference between the two groups (OR: 0.29; 95% CI: 0.06 –1.39).

   The quality of the evidence for this comparison was very low for the RCTs due to the risk of bias and imprecision. Similarly, it was very low for the observational study due to imprecision (Appendix 5).

2. **Multiple nutrient-enhanced nutrition**

   Ten studies comprising 8 RCTs *(20, 22-28)* and 2 observational *(29, 30)* compared the use of nutritional supplements enhanced with multiple nutrients with the standard formula. Eight studies included adult patients undergoing elective surgical procedures for head and neck,

gastrointestinal, colorectal or gynaecological cancer. Two studies *(20, 28)* included cardiac surgical procedures. One study *(23)* included data from multiple centres. Patient conditions varied and included malnourished elderly persons as well as younger adult patients. The multiple nutrient-enhanced formulas used in the studies varied also and contained different combinations and doses of arginine, glutamine, omega-3 fatty acids and/or nucleotides. In most studies, it was observed that enteral tubal feeding was planned for most patients because of the nature of the surgery (for example, gastrointestinal resection) and not as part of the intervention.

The effect of the intervention varied among the 8 RCTs. Two studies *(26, 27)* showed that using multiple nutrient-enhanced nutrition has some benefit in reducing SSI compared to standard nutrition. Four studies *(22, 23, 25, 28)* showed similar results, but the effect was not statistically different from the standard nutrition group. One study *(24)* reported that multiple nutrient-enhanced formulas may increase SSI compared to standard nutrition.

Meta-analysis of these 8 studies showed a significant benefit of the use of multi-nutrient enhanced nutritional formulas in the risk of SSI compared to standard nutrition (OR: 0.53; 95% CI: 0.30–0.91) (Appendix 4). The test for funnel plot asymmetry among RCTs using multiple nutrient-enhanced formulas was not statistically significant (P=0.067), thus indicating the potential for publication bias. In addition, the meta-analysis of the 2 observational studies showed a similar result (OR: 0.07; 95% CI: 0.01–0.53).

The quality of the evidence for this comparison was very low due to risk of bias, inconsistency and publication bias for the RCTs. Similarly, it was very low for the observational studies due to imprecision (Appendix 5).

In conclusion, the retrieved evidence can be summarized as follows:

1. Overall, a very low quality of evidence (RCTs and one observational study) shows that single nutrient-enhanced nutrition is neither beneficial nor harmful in reducing SSI rates when compared to standard nutritional support.
2. Overall, a very low quality of evidence indicates that multiple nutrient-enhanced nutritional formulas are beneficial compared with standard nutrition in reducing the risk of SSI.

Some serious limitations can be observed within the available studies. Many studies were conducted by the same authors with or without commercial funding, which could potentially be a source of intellectual risk of bias. Studies reported that it was difficult to blind participants, clinical teams and/or outcome assessors, thus increasing the possible risk of bias.

6. **Other factors considered in the review**

The systematic review team identified the following other factors to be considered.

Potential harms

Oral administration of nutritional supplementation should not cause undesirable effects. Enteral feeding with either standard or enhanced formulas is generally well tolerated. There is an increased

possibility of discomfort from the location and insertion of gastric feeding tubes, as well as nausea and perforation from the tube itself.

The use of nutritional formulas may introduce some concern for accidental contamination during reconstitution, particularly in areas with limited access to potable water. Therefore, it is very important that infection prevention and control guidelines be followed while preparing these formulas. The use of enteral feeding tubes should be reserved for patients who will require their use, regardless of the administration of nutritional formulas. Some of the formulas studied were dairy-based, which may be problematic for individuals who avoid dairy products for dietary, ethical or cultural reasons.

Resource use

The use of enhanced nutrition support is expensive and requires additional work for health care providers. The availability of enhanced nutrition supplements may be limited, particularly in low- and middle-income countries. With nutritional interventions, there is an additional need for dietitians to be available in the clinic, including an increased need to train staff in the appropriate use and preparation of nutritional formulas. In addition to the added cost of multiple nutrient formulas, there is uncertainty that the benefits outweigh the costs due to the infrastructure and training needed to support such interventions.

7. **Key uncertainties and future research priorities**

Trials studying the efficacy and safety of enhanced nutritional support for the prevention of SSI were small and generally of low quality. They were also often conducted in populations at high risk for malnutrition (for example, gastrointestinal cancer), which may have more profound effects on healing and the immune response. Many studies are funded by manufacturers of proprietary formulas, thus increasing the potential for bias. Future studies should be conducted in larger populations of individuals undergoing a variety of general surgical procedures who may benefit from short-term nutritional support. The impact of nutritional support should be investigated further in populations with a high risk of malnutrition, such as in low- and middle-income countries. The optimal timing and duration of administration of nutritional support in relation to the time of surgery should be further assessed by well-designed RCTs. The effect of other nutrients (for example, iron and zinc) on reducing the risk of SSI should be investigated, either individually or combined.

APPENDICES

Appendix 1: Search terms

Medline (via PubMed)

1) (“nutrition therapy”[Mesh] OR “diet therapy”[Mesh] OR “caloric restriction”[Mesh] OR “diabetic diet”[Mesh] OR “diet, carbohydrate-restricted” [Mesh] OR “diet, fat-restricted”[Mesh] OR “diet, gluten-free”[Mesh] OR “diet, Mediterranean”[Mesh] OR “diet, Paleolithic”[Mesh] OR “diet, protein-restricted”[Mesh] OR “diet, reducing”[Mesh] OR “diet, sodium-restricted”[Mesh] OR “diet, vegetarian”[Mesh] OR “diet, macrobiotic”[Mesh] OR “ketogenic diet”[Mesh] OR “nutritional support”[Mesh] OR “enteral nutrition”[Mesh] OR “parenteral nutrition”[Mesh] OR “parenteral nutrition, total”[Mesh] OR “parenteral nutrition solutions”[Mesh] OR “amino acid”[TIAB] OR “arginine”[TIAB] OR “fish oil”[TIAB] OR “omega-3”[TIAB] OR “nucleotides”[TIAB] OR “ribonucleic acid”[TIAB] OR “nutritional support”[TIAB] OR “immune nutrition” OR “immune-nutrition” OR “immunonutrition” OR “immune-nutrition”[TIAB] OR “enhanced nutrition”[TIAB] OR “specialized nutrition”[TIAB] OR “fortified nutrition”[TIAB] OR “dietary supplements” [Mesh] OR “prebiotics”[Mesh] OR “probiotics”[Mesh] OR “synbiotics”[Mesh] OR “yeast, dried”[Mesh] OR “food, specialized”[Mesh] OR “food, formulated”[Mesh] OR “food, fortified”[Mesh] OR “functional food”[Mesh] OR “micronutrients”[Mesh] OR “trace elements”[Mesh] OR “vitamins”[Mesh] OR “nutritional requirements”[Mesh] OR “recommended dietary allowances”[Mesh] OR “nutritive value”[Mesh] OR “nutrition policy”[Mesh] OR “appetite regulation”[Mesh])
2) ("surgical wound infection"[MeSH] OR "surgical site infection" OR "surgical site infections" [TIAB] OR "wound infection" [TIAB] OR "wound infections" [TIAB] OR” surgical wound infection” [TIAB] OR “prosthesis-related infection” [TIAB] OR “prosthesis-related infections”[TIAB] OR “surgical site infection” [tiab] OR “surgical site infections” [tiab] OR SSI [tiab] OR SSIs [tiab])
3) #1 AND #2
4) LIMIT to 1990-Present

EMBASE

1) 'diet therapy'/exp OR 'amino acid'/exp OR 'fish oil'/exp OR 'RNA'/exp OR 'nucleotide'/exp OR 'trace element'/exp OR 'nutritional requirement'/exp OR 'nutritional value'/exp OR ('health care policy'/exp OR nutrition*:ti,ab) OR 'food intake'/exp OR 'nutritional science'/exp OR 'nutrition'/exp OR ‘nutrition therapy':ti,ab,de OR ‘diet therapy’:ti,ab,de OR ‘caloric restriction’:ti,ab,de OR ‘diabetic diet’:ti,ab,de OR ‘carbohydrate-restricted‘:ti,ab,de OR ‘fat-restricted’:ti,ab,de OR ‘gluten-free’:ti,ab,de OR ‘Mediterranean diet’:ti,ab,de OR ‘Paleolithic diet’:ti,ab,de OR ‘protein-restricted’:ti,ab,de OR ‘reducing diet’:ti,ab,de OR ‘sodium-restricted’:ti,ab,de OR ‘vegetarian diet’:ti,ab,de OR ‘macrobiotic diet’:ti,ab,de OR ‘ketogenic diet’:ti,ab,de OR ‘nutritional support’:ti,ab,de OR ‘enteral nutrition’:ti,ab,de OR ‘parenteral nutrition’:ti,ab,de OR ‘amino acid’:ti,ab,de OR ‘amino acids’:ti,ab,de OR ‘arginine’:ti,ab,de OR ‘fish oil’:ti,ab,de OR ‘fish oils’:ti,ab,de OR ‘fish oils’:ti,ab,de OR ‘omega-3’:ti,ab,de OR ‘nucleotides’:ti,ab,de OR ‘RNA’:ti,ab,de OR ’nucleotides’:ti,ab,de OR ‘ribonucleic acid’:ti,ab,de OR ‘nutritional support’:ti,ab,de OR ‘immune nutrition’:ti,ab,de OR ‘immune-nutrition‘:ti,ab,de OR ‘immunonutrition’:ti,ab,de OR ‘enhanced nutrition’:ti,ab,de OR ‘specialized nutrition’:ti,ab,de OR ‘fortified nutrition’:ti,ab,de OR ‘dietary supplements’:ti,ab,de ‘dietary supplements’:ti,ab,de OR ‘dietary supplement’:ti,ab,de OR ‘prebiotics’:ti,ab,de OR ‘probiotics’:ti,ab,de OR ‘synbiotics’:ti,ab,de OR ‘dried yeast’:ti,ab,de OR ‘formulated food‘:ti,ab,de OR ‘fortified food’:ti,ab,de OR ‘functional food’:ti,ab,de OR ‘formulated foods’:ti,ab,de OR ‘fortified foods’:ti,ab,de OR ‘functional foods’:ti,ab,de OR ‘micronutrients’:ti,ab,de OR ‘trace elements’:ti,ab,de OR ‘vitamins’:ti,ab,de OR ‘nutritional requirements’:ti,ab,de OR ‘recommended dietary’:ti,ab,de OR ’dietary allowances’:ti,ab,de OR ‘dietary allowance’:ti,ab,de OR ‘nutritive value’:ti,ab,de OR ‘nutrition policy’:ti,ab,de OR ‘appetite regulation’:ti,ab,de OR ‘appetite regulation’:ti,ab,de OR ‘micronutrients’:ti,ab,de OR ‘nutritional sciences’:ti,ab,de OR ‘nutritional physiological phenomena’:ti,ab,de OR ‘nutrition assessment’:ti,ab,de OR ‘nutrition therapy’:ti,ab,de OR diet:ti,ab,de OR diets:ti,ab,de OR nutrition:ti,ab,de OR nutritional:ti,ab,de OR nutritive:ti,ab,de
2) 'surgical infection'/exp OR 'surgical infection' OR 'surgical site infection':de,ab,ti OR 'surgical site infections':de,ab,ti OR ssis:de,ab,ti OR ssi:de,ab,ti OR 'surgical infection wound':de,ab,ti OR 'surgical infection wounds':de,ab,ti OR 'surgical infection':de,ab,ti OR 'postoperative wound infection':de,ab,ti OR 'postoperative wound infections':de,ab,ti OR 'post-operative wound infection':de,ab,ti OR 'post-operative wound infections':de,ab,ti OR ('wound infection':de,ab,ti OR 'wound infections':de,ab,ti AND (operation*:de,ab,ti OR surgical:de,ab,ti OR surger*:de,ab,ti OR postoperat*:de,ab,ti OR 'post-operative':de,ab,ti OR 'post-operation':de,ab,ti)) OR 'prosthesis related infections':de,ab,ti OR 'prosthesis related infection':de,ab,ti
3) #1 AND #2

CINAHL

1) (“nutrition therapy” OR “diet therapy” OR “nutritional support” OR “enteral nutrition” OR “parenteral nutrition” OR “parenteral nutrition, total” OR “parenteral nutrition solutions” OR “amino acid” OR “arginine” OR “fish oil” OR “omega-3” OR “nucleotides” OR “ribonucleic acid” OR “nutritional support” OR “immune nutrition” OR “immune-nutrition” OR “immunonutrition” OR “immune-nutrition” OR “enhanced nutrition” OR “specialized nutrition” OR “fortified nutrition” OR “dietary supplements” OR “prebiotics” OR “probiotics” OR “synbiotics” OR “food, specialized” OR “food, formulated” OR “food, fortified” OR “functional food”OR “micronutrients” OR “trace elements” OR “vitamins”)
2) ("surgical wound infection" OR "surgical site infection" OR "wound infection" OR “prosthesis-related infection” OR “SSI” OR “SSIs”))
3) #1 AND #2

Cochrane CENTRAL

"nutrition" AND ("surgical site infection" OR "wound infection" OR "surgical wound infection")

WHO Global Health Library

"nutrition" AND ("Surgical site infection" OR "surgical wound infection")

ti: title; ab: abstract

Appendix 2: Evidence table

Author, year, reference	Design, setting, population	Study objective	SSI definition	Type of surgery	Methods	Intervention	Results
Beattie, 2000 *(31)*	RCT United Kingdom Population: patients admitted for elective gastrointestinal or vascular surgery who had a body mass index of 20 kg/m^2 or less on admission, postoperatively, and/or weight loss of 5% or more during operative period.	To investigate changes in nutritional status and the influence of oral supplements on nutritional status, morbidity, and quality of life in postoperative surgical patients.	Not specified	Gastrointestinal or vascular	Randomization: computer-generated table Exclusion criteria: patients who required parenteral nutrition, those who were pregnant or lactating, those with terminal diseases, those with decompensated liver or renal disease. Follow-up: 10 weeks Amounts/timing: patients were encouraged to aim to consume 400 mL of the supplements in small frequent amounts between meals to increase nutrient intake.	C: routine nutritional management I: oral dietary supplement (Ensure Plus®, Ross Laboratories, Lake Bluff, IL, USA)	Wound infection C: 7/49 I: 4/52 RR=0.53 95% CI : 0.17 – 1.73 Chest infection C: 6/49 I: 2/52 RR=0.31 95% CI: 0.07 – 1.48
Burden, 2011 *(32)*	RCT unblinded Spain Population: adult patients undergoing elective curative surgery for colorectal cancer with a minimum of 10 days preoperatively.	To determine whether preoperative oral supplementation using a standard formulation reduces the number of postoperative complications.	CDC criteria and Buzby (CDC data used)	Colorectal cancer surgery	Randomization: block randomization with numerical blocks used to ensure that similar numbers were represented by each group. Weight loss was considered to be a prognostic variable at baseline; patients were weighed and divided into two strata for randomization – 0-9% weight loss and >10% weight loss. Opaque envelopes were used for allocation and a volunteer set up the procedure. Exclusion criteria: pregnancy, enrolment in	C: instructed to increase energy and protein from foods based on an information leaflet. Dietary intake diary recorded for compliance. I: 400 mL of an oral supplementary drink daily and dietary advice (see control). Milk-based supplements were given initially (630 kcal; 6 g protein), but replaced with fruit juice if not tolerated (630 kcal; 4 g protein).. Unblinded due to the nature of the study.	Wound infection: C: 17/62 I: 9/54 *P*= 0.145

					another study, unable to give consent or inoperable tumour. Timing: time of enrolment (10+ days preoperatively) until surgery; not continued postoperatively. Follow-up: 3 months	Ward staff unaware of randomization.	
Casas-Rodera, 2008 *(16)*	RCT Spain Population: patients undergoing surgery for oral and laryngeal cancer.	Comparison of 2 immuno-enhanced enteral nutritional formulas with a control diet and evaluation of the effect on postoperative infections, length of stay and inflammatory markers.	Not specified	Head and neck cancer	Randomization: not specified. Exclusion criteria: severely impaired hepatic function, ongoing infection, autoimmune disorder, steroid treatment, nutritional oral supplementation in the previous 6 months. Amount/ timing: protein requirements were 1.5 g/kg/day. Enteral feeding was started within 12 hours of surgery. Infusion rate was progressively increased every 24 hours until the daily nutritional goal was reached on postoperative day 3. End point was a minimum oral intake of 1500 calories/day and 1 g/kg/day of protein without supplementation with a minimum of 7 days of enteral support.	Group 1: enteral diet supplemented with arginine. Group 2: standard polymeric enteral formula (control). Group 3: enteral diet supplemented with arginine, RN, and omega-3 fatty acids.	Wound infection Group 1: 1/15 Group 2: 2/15 Group 3: 1/14 Wound fistula Group 1: 3/15 Group 2: 2/15 Group 3: 1/14 General infection Group 1: 0/15 Group 2: 1/15 Group 3: 0/14 *P*=NS for all
Celik, 2009 *(22)*	RCT Turkey Population: patients with a diagnosis of gynaecological malignancy.	To assess the effect of immunonutrition on biochemical and haematological parameters, incidence of infection, postoperative	Not specified	Elective gynaecological oncologic surgery.	Randomization: blinded envelopes. Exclusion criteria: neoplasms treated with radio- or chemotherapy, chronic inflammatory bowel disease, renal insufficiency, cardiac insufficiency, hepatic	C: standard enteral nutrition formula orally (Ensure Standard®.) I: multiple nutrient enteral nutrition (Impact®, Nestlé Health Science SA, Vevey, Switzerland).	Wound infection C: 5/25 I: 1/25 *P*<0.05 Wound dehiscence C: 2/25

		complications, mortality rate and length of hospital stay.			insufficiency, severe respiratory insufficiency, current infection, diabetes mellitus and congenital or acquired immunodeficiency. Amount/timing: intervention group received 30 kcal/day of enhanced formula for 2 days before surgery and 7 days postoperatively.		I: 0/25 *P*<0.05
De Luis, 2002 *(17)*	RCT Spain Population: patients with oral and laryngeal cancer.	The aim of our study was to investigate whether postoperative nutrition of head and neck cancer patients using an arginine-enriched diet, could improve nutritional variables as well as clinical outcomes.	Respiratory tract infection: chest radiographic examination showed new or progressive infiltration, temperature >38.5°C and isolation of pathogens from the sputum or blood culture. Urinary infection: urine culture showed at least 10^5 colonies of a pathogen. *All compli-cations were assessed with standard methods by the same investigator.	Head and neck cancer	Randomization: not specified. Exclusion criteria: Severely impaired hepatic and renal function, ongoing infections, autoimmune disorders, steroid treatment, nutritional oral supplementation in the previous 6 months, and severely malnourished. Amount/timing: Postoperative: enteral feeding was started within 12 hours of surgery at a rate of 20 mL/hour. The infusion rate was progressively increased every 24 hours until the daily nutritional goal (32 kcal/kg; 1.7g protein/kg) was reached on day 4. Follow-up: 14 days	C: isocaloric, isonitrogenous enteral formula. I: enteral diet supplemented with arginine and dietary fibre.	Infectious complications C: 9/24 I: 9/23 *P*=NS Wound infection C: 3/24 I: 1/23 *P*=NS
De Luis, 2004 *(18)*	RCT Spain Population:	The aim of our study was to investigate whether postoperative	Respiratory tract infection: chest radiographic examination	Head and neck cancer	Randomization: not specified. Amount/timing: Postoperative: enteral	C: isocaloric, isonitrogenous enteral formula with dietary fibre.	Wound infection C: 0/45 I: 0/45 *P*=NS

	patients undergoing surgery for oral and laryngeal cancer	nutrition of head and neck cancer patients using an arginine enhanced formula could improve nutritional variables as well as clinical outcomes.	showed new or progressive infiltration, temperature >38.5°C and isolation of pathogens from the sputum or blood culture. Urinary infection: urine culture showed at least 10^5 colonies of a pathogen. *All complications were assessed with standard methods by the same investigator.		feeding was started within 12 hours of surgery at a rate of 20 mL/hour. The infusion rate was progressively increased every 24 hours until the daily nutritional goal (32 kcal/kg; 1.7 g protein/kg) was reached on day 4.	I: enteral diet supplement with arginine and dietary fibre.	Wound fistula C: 5/45 I: 2/45 *P*<0.05 General infection C: 4/45 I: 2/45 *P*=NS
De Luis, 2007 *(19)*	RCT Tertiary care, Spain Population: patients with oral and laryngeal cancer.	To investigate whether postoperative nutrition of head and neck cancer patients using a higher dose of arginine-enhanced diet (17 g/day) than previous studies could improve nutritional variables, as well as clinical outcomes, when compared with a control enteral diet.	General infections: respiratory tract infection was diagnosed when the chest radiographic examination showed new or progressive infiltration, temperature >38.5°C and isolation of pathogens from the sputum or blood culture. Urinary infection was diagnosed if the urine culture showed at	Head and neck cancer surgery	Randomization: not specified. Exclusion criteria: severely impaired hepatic and renal function, ongoing infection, autoimmune disorders, steroid treatment, nutritional oral supplementation in the previous 6 months and severely malnourished. Amount/timing: Postoperative: enteral feeding was started within 8-12 hours of surgery at a rate of 20 mL/hour. The infusion rate was increased every 24 hours until postoperative day 4 with 17 g/day of arginine.	C: isocaloric, isonitrogenous enteral formula. I: enteral diet supplements with arginine.	Wound infection C: 0/37 I: 0/35 General infection C: 2/35 I: 2/35 Wound fistula C: 7/37 I: 1/35

			least 10^5 colonies. Follow-up: 12 days				
Falewee, 2014 *(23)*	RCT, double-blind, placebo controlled, multicentre phase III 8 centres; France Population: patients aged 18-75 years with squamous cell carcinoma of the oral cavity, oropharynx, larynx, or hypopharynx with anticipated surgery and postoperative enteral feeding for a minimum of 7 days.	To investigate whether preoperative or perioperative immunonutrition could reduce postoperative infectious complications and surgical site infections in this population.	CDC	Head and neck cancer	Randomization: centralized and carried out by the *CS Randomization* module from Clinsight software (Clinsight, Poitiers, France). The stratification consisted of searching with an algorithm for the less often allocated treatment code among patients whose randomization criteria matched the ongoing patient. Blinding: The allocation of patients to trial groups was carried out independently by the pharmacy clinical trials units using randomization lists. Double-blinding with adequate labels was used to minimize bias with bedside physicians and nurses. Follow-up: 90 days Amount/timing: Preoperative: for 7 days before surgery, patients received 3 bags/day Postoperative: for 7-15 days, all patients received an increasing number of bottles of enteral nutrition (1 bottle day 1, 2 bottles day 2, etc.)	Group A (control): perioperative formula without immune nutrients (Impact®) Group B: preoperative formula with immune nutrients (multiple nutrient, Impact®) and postoperative standard diet. Group C: perioperative formula with immune nutrients (multiple nutrient, Impact®).	Infection (systemic, surgical site infection, or nosocomial pneumopathy). C: 35/64 Group B: 37/68 Group C: 33/73 *P*=0.44
Fujitani, 2012 *(24)*	Design: RCT Japan Population: patients	To investigate the impact of preoperative enteral immuno-nutrition on the incidence of	CDC	Gastrectomy	Randomization: carried out by data centre staff using the minimization method, with an algorithm that balanced the institution.	C: regular diet I: 1000 mL/day immunonutrient-enriched enteral feed (Impact®) for 5 days	SSI C: 23/120 Superficial: 7 Deep: 1 Organ/space: 15

	with resectable primary gastric adenocarcinoma, aged no more than 80 years.	postoperative complications and C-reactive protein values (as a marker of inflammatory response) in patients undergoing elective total gastrectomy for gastric cancer.			Preoperative: immunonutrition group received 1000 mL/ day of immunonutrient-enriched enteral feed (Impact®) added to a normal diet for 5 days before surgery. Control group had regular diet without supplementation.	plus regular diet	I: 27/120 Superficial: 8 Deep: 5 Organ/space: 17 RR: 1.09 (0.66, 1.78) Wound infection or dehiscence C: 8/111 I: 13/120 *P*=0.369
Gianotti, 2002 *(25)*	RCT Italy Population: patients with histologically documented neoplasm of the gastrointestinal tract and planned major elective surgery.	To understand prospectively whether preoperative supplementation could be as efficacious as the perioperative approach and superior to conventional treatment (without artificial nutrition) in reducing postoperative infections and the length of hospital stay.	Not specified	Gastrointestinal tract cancer surgery	Randomization: computer programme generated list. Exclusion criteria: weight loss >10% in past 6 months, age <18 years, hepatic dysfunction, respiratory dysfunction, renal dysfunction, Karnofsky score <60, pregnancy, ongoing infections and immune disorder. Amount/timing: Group 1: 1 L/day for 5 days before surgery Group 2: 1 L/day for 5 days before surgery AND starting 12 hours after surgery.	C: no artificial nutritional supplement before surgery, intravenous solution of glucose 5% and electrolytes after surgery. Group 1: preoperative supplemented liquid diet (per os) (oral Impact®). Group 2: Preoperative supplemented liquid diet (per os) and postoperative supplemented liquid diet (enteral).	Wound infection C: 11/102 Group 1: 7/102 Group 2: 7/101
Horie, 2006 *(29)*	Prospective clinical study Japan Population: colorectal cancer patients undergoing elective surgery without malnutrition.	To ascertain the effects of preoperative enteral immunonutrition on SSI in patients with colorectal cancer without malnutrition.	CDC criteria	Elective colorectal (cancer)	Non-randomized: patients enrolled sequentially into either immunonutrition group or control group. Follow-up: 30 days after discharge Exclusion criteria: malnutrition, bowel obstruction, severe cardiopulmonary complication, diabetes,	I: supplement to normal preoperative diet with 3 packs of Impact® enteral immunonutrition/day (750 mL containing 9.6 g arginine, 2.49 g omega fatty acids, and 0.96 g RNA with a kcal:mL ratio of 1:1). C: unclear if placebo or no packets to supplement oral intake.	C: 5/34 I: 0/33 *P*= <0.05

					collagen disease or renal failure.		
Klek, 2008 *(33)*	RCT Poland Population: well-nourished patients undergoing gastrointestinal surgery.	To assess the clinical effect of immuno-stimulatory enteral and parenteral nutrition in patients undergoing resection for gastrointestinal cancer in well-nourished patients.	Wound infection: purulent exudate in the wound with positive bacterial culture	Major upper gastrointestinal surgery	Randomization: not specified; patients were randomly assigned in a 2x2 factorial design to 4 groups receiving immunostimulating *vs.* normal diets, and enteral *vs.* intravenous nutritional support. Exclusion criteria: patients requiring nutritional support, with disseminated tumours, serious comorbidities and renal or liver failure. Amount/timing: parenteral nutrition was commenced 20-24 hours postoperatively and continued for at least 7 days. Protein requirements were 0.15 g N/kg and covered by 10-15% amino acid solutions. Energy requirements were 150 kcal/g and covered by glucose and lipid emulsions.	Standard enteral nutrition (SEN). Immunostimulating enteral nutrition (IMEN). Standard parenteral nutrition (SPN). Immunostimulating parenteral nutrition (IMPN).	Wound infection SEN: 2/53 IMEN: 4/52 SPN: 2/49 IMPN: 1/51
Klek, 2011 *(26)*	RCT Poland Population: malnourished patients aged 18-85 years undergoing resection for pancreatic or gastric cancer.	To assess the impact of enteral immunonutrition in the postoperative period.	Wound infection: purulent exudate in the wound with positive bacterial culture. Collection of pus confirmed by percutaneous drainage or at reoperation. Sepsis: fever	Subtotal and total gastric resection with lympha-denectomy and pancreato-duodenectomy.	Randomization: computer generated randomization list managed by an external person not involved in the study Exclusion criteria: well-nourished patients or with metastatic disease, pregnant, poor general health status with recent history of severe heart, lung, kidney or liver failure, with history of allergies or drug	C: standard enteral nutrition, oligopeptide, isocaloric diet (Peptisorb). I: immunomodulating enteral nutrition (Reconvan).	Wound infection C: 27/153 I: 12/152 *P*=0.01077 Sepsis C: 2/153 I: 4/152 *P*=0.40498 Pneumonia C: 45/153

			>38°C, hypotension, or oliguria together with positive blood culture.		intolerance. Postoperative: enteral feeding was commenced 6 hours after surgery with glucose 5% solution at 20 mL/hour for the first 12 hours, followed by Peptisorb (Nutricia, Amsterdam, the Netherlands) or Reconvan (Fresenius-Kabi, Bad Homburg, Germany) at 20 mL/hour on day 1, 50 mL/hour on day 2, 75 mL/hour on day 3 and 100 mL/hour thereafter until the day 7.		I: 33/152 *P*=0.12322
Oguz, 2006 *(34)*	RCT Turkey Population: patients with a diagnosis of colorectal cancer.	To investigate the effect of L-alanine-L-glutamine (Gln) on the postoperative complication rate and duration of hospitalization in patients operated for colorectal cancer.	Wound infection: evidence of redness and tenderness of surgical wound with discharge of pus.	Colorectal	Randomization methods: not specified. Exclusion criteria: patients with metabolic disorders (hyperthyroidism, diabetes mellitus) and patients who had undergone an emergency surgery or abdominoperineal resection. Amounts/preoperative days given: patients received 1000 mL/day enteral nutrition for 5 days before surgery. Amounts/postoperative days given: 500 mL/day for the first 2 days and 1000 mL/day enteral nutrition after postoperative day 3. Follow up: NS. Outcomes collected: not specified.	C: enteral nutrition I: parenteral L-alanine-L-glutamine (Gln, Dipeptiven®, Fresenius-Kabi), 1 g/kg/day and enteral nutrition.	Wound infection C: 6/52 I: 1/57 *P*= 0.038 Abdominal abscess C: 4/52 I: 0/57 *P*= 0.044 Pulmonary tract infection C: 2/52 I: 1/57 *P*=NS Urinary tract infection C: 2/52 Intervention: 3/57 *P*=NS Wound dehiscence

							C: 4/52 I: 0/57 *P*= 0.044
Okabayashi, 2008 *(21)*	Prospective trial January 2000 to March 2007 Japan Population: 112 patients undergoing surgical management for hepatocellular carcinoma (84 men, 28 women).	To evaluate the clinical benefit of perioperative supplementation of a branched-chain amino acid-enriched nutrient mixture for patients undergoing liver resection for hepatocelllar carcinoma.	Not specified	Liver resection for hepatocellular carcinoma.	Randomization: not randomized. Exclusion criteria: not specified. Follow-up: 3-84 months (mean, 21 months).	C: no added dietary supplementation. I: patient diet was supplemented with branch-amino acids-rich soft-powder mixture (Aminoleban; Otsuka Pharmaceutical Company, Tokyo, Japan): 13 g free amino acids, 13 g, gelatin hydrolysate, 1 g casein, 62.1 g carbohydrate, 7 g lipid, glscyrrhizin, others with 420 kcal) at 100 g/day commencing at 2 weeks preoperatively.	SSI C: 11/72 I: 2/40 *P*=0.19
Roth, 2012 *(35)*	Prospective, randomized, single centre study September 2008 to March 2011 Switzerland Population: 169 consecutive bladder cancer patients scheduled.	To evaluate whether recovery can be improved with total parenteral nutrition in patients following extended pelvic lymph node dissection, cystectomy and urinary diversion.	Clavien-Dindo classification	Radical cystectomy	Randomization: prospectively randomly allocated by a computer based programme. Exclusion criteria: previous pelvic lymph node dissection, chronic inflammatory bowel disease, previous radiation therapy, prior bowel surgery, severe hepatic or cardiac dysfunction, inability to give fully informed consent. Timing: total parenteral nutrition commenced on postoperative day 1, continued for 5 consecutive days. Oral intake was started with clear fluids on the day of surgery with fluids started on postoperative day 1. Solid diet was resumed on the	C: oral alimentation was introduced on postoperative day 1 in both groups with a gastrostomy tube in place, which was initially left on drainage. Oral intake was started with clear fluids on the day of surgery with fluids started on postoperative day 1. Solid diet was resumed on the return of active bowel sounds and when fluids were well tolerated. The gastrostomy tube was removed after the patient passed stool and tolerated closure of the gastrostomy tube without nausea and vomiting for >24 hours. I: total parenteral nutrition (1500 mL/day;	Wound infection Control: 2/83 Intervention: 4/74

					return of active bowel sounds and when fluids were well tolerated. Follow-up: 30 days	total 1860 kcal/day; 105 g polyamino acids/day; 360 g glucose/d; 0 g lipids/d) was administered continuously for 5 days starting on postoperative day 1. No intravenous supplementation of vitamins and trace elements was given. An additional 30 IU ActrapidHM (Novo Nordisk, Copenhagen, Denmark) and 1875 IU heparin (Liquemin; Drossapharm, Basel-Stadt, Switzerland) per 24 hours were added to the total parenteral nutrition solution.	
Snyderman, 1999 *(27)*	RCT USA Population: patients with stages II-IV squamous cell carcinoma of the oral cavity, pharynx or larynx undergoing oncologic surgery with curative intent and requiring postoperative nutritional supplementation.	To determine if perioperative nutritional supplementation with a multiple nutrient-enhanced formula is superior to a standard formula for the prevention of postoperative infectious complications.	Not specified	Head and neck cancer	Randomization: not specified. Follow-up: 1 month	Enhanced formula Group I: pre- and postoperatively Group II: postoperatively. Control formula Group III: pre- and postoperatively Group IV: postoperatively. Combined oral and enteral nutrition based on patient condition; patients assessed daily for intake/amount infused.	Postoperative infection C: 19/47 I: 10/82 *P*= 0.02 SSI data is for enhanced (all) vs. standard (all) nutrition
Suzuki, 2010 *(36)*	Prospective RCT May 2006 to January 2008 Japan Population: 30	To determine whether the use of multiple nutrient-enhanced formulas influences the following factors: cell-	Not specified	Pancreatico-duodenectomy	Exclusion criteria: under 18 or over 75 years of age, preoperative chemotherapy and/or radiation therapy, active preoperative infection, administration of corticosteroids or	Group A: oral supplementation for 5 days (1000 kcal/day) before operative resection with a formula enriched with arginine, omega-3 fatty acids, and RNA (oral Impact®, Ajinomoto Pharma Co.,	Wound infection: Group A: 0/10 Group B: 4/10 Group C: 2/10

	consecutive patients undergoing pancreatico-duodenectomy.	mediated immunity and differentiation, and the infectious complication rate after pancreatico-duodenectomy.			immunosuppressive agents, gastrointestinal obstruction, respiratory, cardiac or hepatic dysfunction, renal failure, history of recent immunosuppressive or immunologic disease and preoperative evidence of widespread metastatic disease.	Ltd, Tokyo, Japan) in addition to a half-amount of ordinary diet after surgery. Group B: postoperative group that underwent postoperative enteral infusion of the same enriched formula with no artificial nutrition before operative resection. Group C (control): total parenteral nutrition with no artificial nutrition before operative resection. Patients in groups B and C were allowed to consume an ordinary diet during the 5 days before operative resection. Enteral feeding started at 12-18 hours after surgery at a 10 mL/hour rate. The velocity was increased progressively by 20 mL/day until 25 kcal/kg/day was reached. Oral food intake was allowed on postoperative day 7. The 3 regimens were approximately isocaloric before and after.	
Takeuchi, 2007 *(30)*	Prospective case-control study Japan Population: consecutive patients	To test the hypothesis that preoperative, postoperative, or both, enteral multiple nutrient-enhanced	Incisional wound infection: evidence of purulent exudate in the wound and isolation of	Esophagectomy for thoracic esophageal squamous cell carcinoma.	Randomization: not specified. Amount/timing: control group received enteral diet during the first 14 postoperative days.	C: Enteral diet postoperatively I 1: enteral diet supplemented with multiple nutrient-enhanced formulas containing arginine,	Incisional wound infection C: 6/20 I 1: 2/6 I 2: 0/14 *P*= 0.067

	diagnosed with primary thoracic esophageal squamous cell carcinoma.	formulas supplemented with arginine, omega-3 fatty acids and RNA may reduce postoperative complications in patients undergoing esophagectomy for thoracic esophageal squamous cell carcinoma.	pathogenic organisms in the culture.		Intervention 1 received enhanced diet through the first 14 postoperative days. Intervention 2 received enhanced diet both 5 days pre- and 14 days postoperatively. Daily intake began at 250 kcal/ day and increased by 250 kcal/day until 1500 kcal/ day was reached for all groups.	omega-3 fatty acids, and RNA postoperatively. I 2: enteral diet supplemented with multiple nutrient enhanced formulas containing arginine, omega-3 fatty acids, and RNA pre- and postoperatively.	Sepsis/bacteraemia C: 2/20 I 1: 1/6 I 2: 0/14 *P*=0.36
Tepaske, 2001 *(28)*	RCT, double-blind, placebo-controlled The Netherlands Population: patients scheduled to undergo cardiac surgery who met one or more of the following criteria: age 70 years or older, ejection fraction less than 0·40, or replacement of mitral valve.	To ascertain whether an oral multiple nutrient-enhanced formula could improve preoperative host defence and subsequently lower postoperative infections and organ dysfunction in patients undergoing elective cardiac surgery who are at high risk of infection.	CDC	Cardiac	Randomization: blocks of 10 by closed envelope, done by a person not involved in the study. Exclusion criteria: less than 21 years, pregnant, insulin-dependent diabetes mellitus, severe renal and/or liver failure, known malignancy, use of immunosuppressive medication or non-steroidal anti-inflammatory drugs (except aspirin) on a long-term basis. Amount/ timing: all patients took a minimum of 5 L and a maximum of 10 L of the oral supplement in addition to their normal food intake during the 5-10 days before the operation. After surgery, patients who were on a ventilator and required tube feeding received either the intervention or control until extubation.	C: isocaloric, isocolaemic formula (placebo, Novartis Nutrition, Basel, Switzerland). I: pre-operative oral immune enhancing nutritional supplement (oral Impact®, Novartis Nutrition).	Wound infection C: 2/22 I: 0/23 *P*=0.233 Pneumonia C: 12/22 I: 3/23 *P*=0.047 Urinary infection C: 1/22 I: 2/23 *P*=1.000
Tepaske, 2007 *(20)*	RCT, double-blind, placebo-controlled, 3 arms	To determine whether addition of glycine to a standard	Infections were strictly scored according to CDC criteria.	Cardiac surgery	Randomization: opaque, sealed envelopes containing the assignments, performed by	C: isocaloric, isocolaemic formula (placebo, Novartis Nutrition).	Wound infection C: 0/24 I 1: 0/24 I 2: 1/22

	The Netherlands Population: patients were included if they were aged 70 years or older, had a compromised left ventricular function or were planned for mitral valve surgery.	preoperative oral multiple nutrient-enhanced formula improves outcome.			a person not involved in the study and patient care. Exclusion criteria: less than 21 years, pregnant, insulin-dependent diabetes mellitus, severe renal or liver failure, known malignancy, and use of immunosuppressive medication or nonsteroidal anti-inflammatory drugs.	I 1: standard oral multiple nutrient-enhanced formulas. I 2: glycine-enriched oral immune-enhancing nutrition Supplement.	*P*=0.02 Pneumonia C: 10/24 I 1: 4/24 I 2: 4/22 *P*=0.09 Urinary infection C: 4/24 I 1: 0/24 I 2: 2/22 *P*=0.12
Wei, 2014 *(37)*	Prospective RCT May 2007 to March 2008 People's Republic of China Population: adult patients undergoing a surgical operation for a gastric tumour.	To investigate the effect of omega-3 fish oil fat emulsion-based parenteral nutrition on nutritional state, immune function, inflammatory reaction, expression of tumour factors and the incidence of complications in patients after surgical resection for gastric cancer.	Not specified	Gastric resection	Randomization: not specified ("randomly allocated"). Exclusion criteria: age <18 years or >75 years, body mass index <16 or >30, hepatic insufficiency, abnormal renal function, ongoing infection and fever in the preceding month, major gastrointestinal disease (that is, Crohn's) autoimmune disorders, steroid treatment and medication that could modulate the metabolism or body weight, pregnancy or breast feeding, received total parenteral nutrition 2 months before the operation, severely malnourished. Timing: all patients received total parenteral nutrition for at least 6 consecutive postoperative days through a central venous catheter. Both groups were given	C: fat emulsion consisted of omega-6 lipid content. I: fat emulsion was partially replaced with omega-3 polyunsaturated fatty acids.	Incisional wound infection C:3/20 I:1/26 *P*= 0.303 Abdominal infection C: 1/20 I: 0/26 *P*= 0.435

					parenteral nutrition consisting of 104-125 kcal/kg/day of calories for energy with glucose and fat emulsion as the main sources of energy (35-50% fat emulsion and 0.15-0.20 g/kg.day of nitrogen). Glucose and exogenous insulin were provided at a ratio of 6:1, together with vitamins, water, electrolytes and trace elements (10-12 hours). Follow-up: followed by same investigator surgeon, recorded (range NS)		
Yeh, 2008 *(38)*	Prospective case-control study 2006 Taiwan (People's Republic of China) Population: 70 patients (20-85 years) undergoing gastrointestinal surgery by a single surgeon.	To evaluate the impact of a supplement of alanyl-glutamine dipeptide in parenteral nutrition on perioperative immune and nutritional changes and clinical outcomes for patients undergoing gastrointestinal operations.	Not specified	Gastrointestinal surgery	Non-randomized. Exclusion criteria: immunosuppressive condition, including acquired immunodeficiency syndrome, autoimmune disorders, organ transplantation, radiation therapy or chemotherapy within the previous 6 months and insulin-dependent diabetes. Timing: solution infused via a peripheral venous line started 1 day before operation and continued until postoperative day 6. Follow-up: discharge 6 days postoperative; mortality 1 month.	I: 500 cc amino acid 5% supplemented with 100 cc glutamine 20%. C: 500 cc amino acid 8% per day as nitrogen source.	Wound infection I: 2/35 C: 0/35 *P*= 1.0

SSI: surgical site infection; RCT: randomized controlled trial; C: control; I: intervention; CDC: Centers for Disease Control and Prevention; L: litre; Gln: L-glutamine; SEN: standard enteral nutrition; IMEN: immunostimulating enteral nutrition; SPN: standard parenteral nutrition; IMPN: immunostimulating parenteral nutrition.

Appendix 3: Risk of bias assessment of the included studies

Appendix 3a: Risk of bias assessment of included randomized controlled trials

RCTs author, year, reference	Sequence generation	Allocation concealment	Participants and personnel blinded	Outcome assessors blinded	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Beattie, 2000 *(31)*	LOW	UNCLEAR	HIGH	HIGH	LOW	LOW	UNCLEAR
Burden, 2011 *(32)*	LOW	LOW	HIGH	LOW	LOW	LOW	LOW
Casas-Rodera, 2008 *(16)*	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR
Celik, 2009 *(22)*	LOW	LOW	LOW	LOW	LOW	LOW	UNCLEAR
De Luis, 2002 *(17)*	UNCLEAR	UNCLEAR	LOW	LOW	LOW	LOW	UNCLEAR
De Luis, 2004 *(18)*	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW	UNCLEAR	UNCLEAR
De Luis, 2007 *(19)*	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW	UNCLEAR	UNCLEAR
Falewee, 2014 *(23)*	LOW	LOW	LOW	LOW	LOW	LOW	UNCLEAR
Fujitani, 2012 *(24)*	LOW	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW	LOW
Gianotti, 2002 *(25)*	LOW	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW	UNCLEAR
Klek, 2008 *(33)*	LOW	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW	UNCLEAR
Klek, 2010 *(26)*	LOW	UNCLEAR	LOW	LOW	LOW	LOW	LOW
Oguz, 2006 *(34)*	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW	UNCLEAR
Roth, 2012 *(35)*	LOW	UNCLEAR	HIGH	LOW	LOW	LOW	LOW
Snyderman, 1999 *(27)*	UNCLEAR	UNCLEAR	LOW	LOW	LOW	LOW	UNCLEAR

Suzuki, 2010 *(36)*	LOW	LOW	UNCLEAR	UNCLEAR	LOW	LOW	UNCLEAR
Tepaske, 2007 *(20)*	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Tepaske, 2001 *(28)*	LOW	LOW	LOW	LOW	LOW	LOW	UNCLEAR
Wei, 2014 *(37)*	UNCLEAR	UNCLEAR	LOW	UNCLEAR	LOW	LOW	LOW

RCT: randomized controlled trials.

Appendix 3b: Risk of bias assessment of the included non-randomized studies

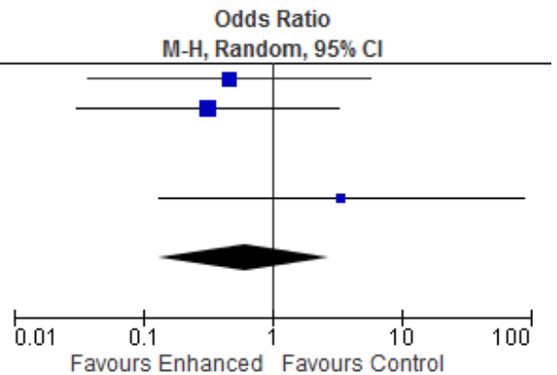
Cohort studies **Author, year, reference**	**Representativeness of cohort**	**Selection of non-exposed cohort**	**Ascertainment of exposure**	**Demonstration that outcome of interest was not present at start**	**Comparability of cohorts**	**Assessment of outcome**	**Follow-up long enough**	**Adequacy of follow-up of cohorts**
Horie, 2006 *(29)*	B(*)	A(*)	A(*)	B	B(*)	B(*)	A(*)	B(*)
Okabayashi, 2008 *(21)*	B(*)	A(*)	A(*)	B	AB(**)	D	A(*)	B(*)
Takeuchi, 2007 *(30)*	B(*)	A(*)	A(*)	B	AB(**)	A(*)	A(*)	A(*)
Yeh, 2008 *(38)*	B(*)	A(*)	A(*)	B	AB(**)	B(*)	B	A(*)

Appendix 4: Comparisons

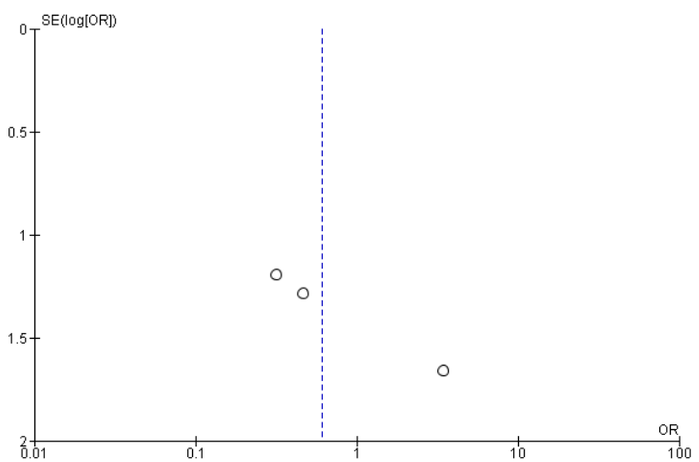
Comparison 1a: Single nutrient-enhanced nutrition (RCTs)

Study or Subgroup	Enhanced Events	Enhanced Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Casas-Rodera 2008	1	15	2	15	36.3%	0.46 [0.04, 5.75]
de Luis 2002	1	23	3	24	42.0%	0.32 [0.03, 3.31]
de Luis 2004	0	45	0	45		Not estimable
de Luis 2007	0	35	0	37		Not estimable
Tepaske 2007	1	22	0	24	21.7%	3.42 [0.13, 88.40]
Total (95% CI)		**140**		**145**	**100.0%**	**0.61 [0.13, 2.79]**
Total events	3		5			

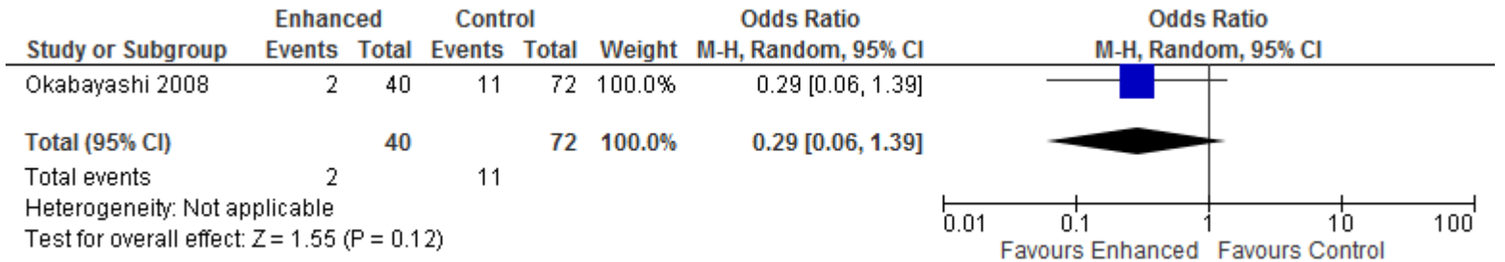
Heterogeneity: Tau² = 0.00; Chi² = 1.42, df = 2 (P = 0.49); I² = 0%
Test for overall effect: Z = 0.64 (P = 0.52)



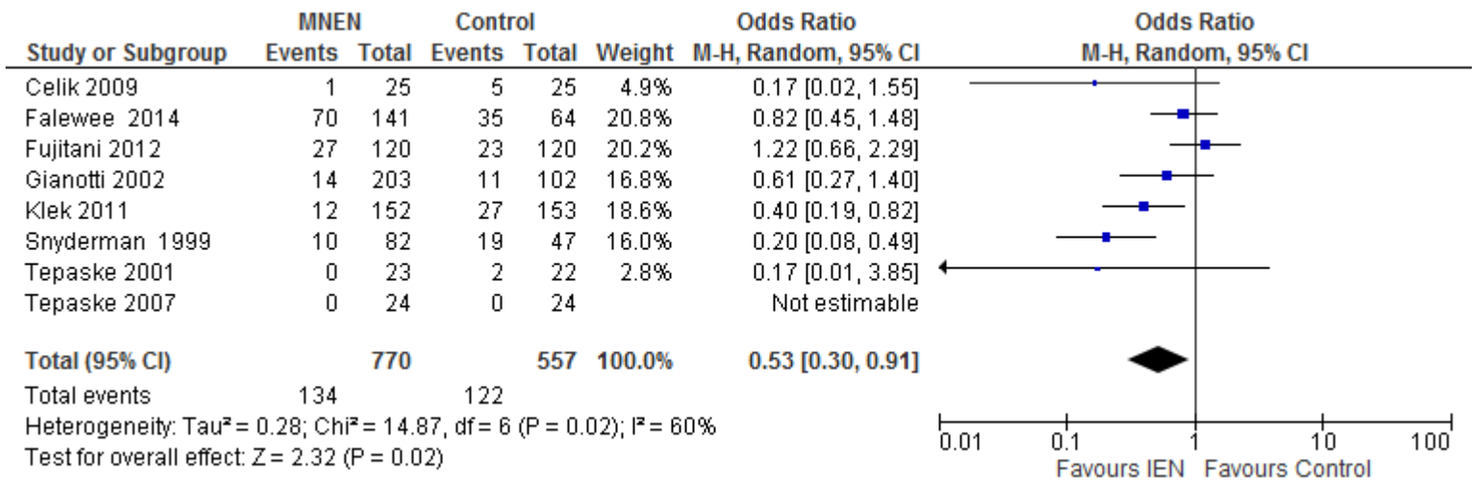
Funnel plot 1a: Single nutrient-enhanced nutrition (RCTs)



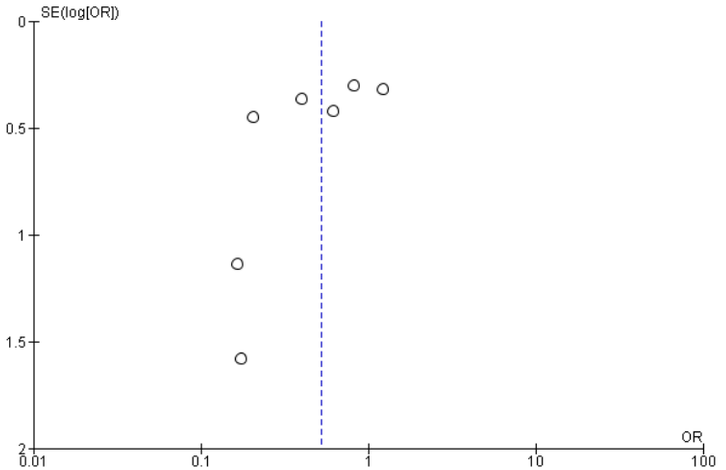
Comparison 1b: Single nutrient-enhanced nutrition (non-RCT)



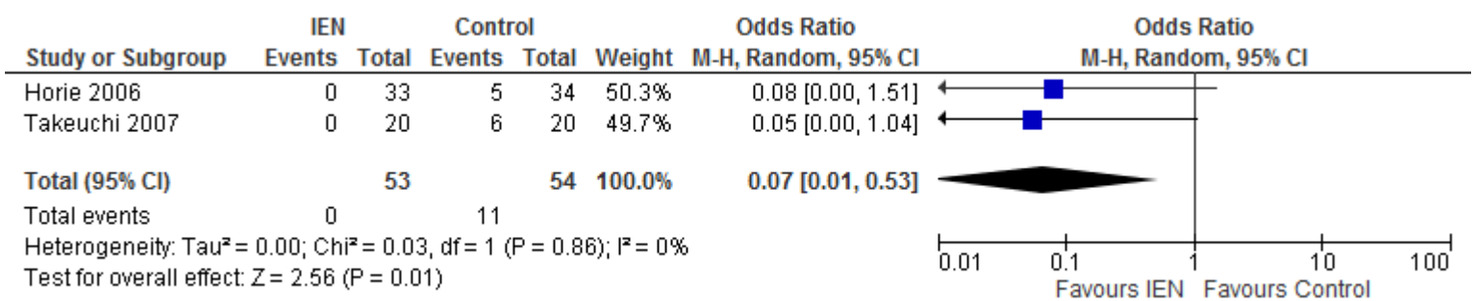
Comparison 2a: Multiple nutrient-enhanced nutrition (RCTs)



Funnel plot 2a: Multiple nutrient-enhanced nutrition (RCTs)



Comparison 2b : Multiple nutrient-enhanced nutrition (non-RCTs)



RCT: randomized controlled trial; M-H: Mantel-Haenszel (test*); CI*: confidence interval

Appendix 6: GRADE Tables

Comparisons 1a and 1b: Single nutrient-enhanced nutrition compared to standard nutrition support for the prevention of SSI

Quality assessment							№ of patients		Effect		Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single nutrient-enhanced nutrition	Standard nutrition support	Relative (95% CI)	Absolute (95% CI)	
Surgical site infection											
5	RCTs	serious [1]	not serious	not serious	very serious [2]	none	3/140 (2.1%)	5/145 (3.4%)	OR: 0.61 (0.13-2.79)	13 fewer per 1000 (from 30 fewer to 56 more)	⊕◯◯◯ VERY LOW
Surgical site infection											
1	Observational	not serious	not serious	not serious	very serious [2,4]	none	2/40 (5.0%)	11/72 (15.3%)	OR: 0.29 (0.06. 1.39)	103 fewer per 1000 (from 48 more to 142 fewer)	⊕◯◯◯ VERY LOW

1. Risk of selection bias and detection bias
2. Optimal information size not met and CI includes both appreciable benefit and harm (RR and RRR of 25%)

RCT: randomized controlled trial; CI: confidence interval; OR: odds ratio; RR: relative risk; RRR: relative risk reduction.

Comparisons 2a and 2b: Multiple nutrient-enhanced formula compared to control for the prevention of SSI

Quality assessment							№ of patients		Effect		Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multiple nutrient-enhanced formula	Control	Relative (95% CI)	Absolute (95% CI)	
Surgical site infection											
8	RCTs	serious [1]	serious [2]	not serious	serious [3]	publication bias strongly suspected [4]	134/770 (17.4%)	122/557 (21.9%)	OR: 0.53 (0.30-0.91)	90 fewer per 1000 (from 16 fewer to 141 fewer)	⊕◯◯◯ VERY LOW
Surgical site infection											
2	Observational	not serious	not serious	not serious	serious [3]	none	0/53 (0.0%)	11/54 (20.4%)	OR: 0.07 (0.01-0.53)	186 fewer per 1000 (from 84 fewer to 201 fewer)	⊕◯◯◯ VERY LOW

1. Most studies with unclear allocation concealment and clear blinding of outcome assessors
2. High heterogeneity, $I^2 = 60\%$
3. Optimal information size not met
4. Industry funding and intellectual bias suspected

RCT: randomized controlled trial; CI: confidence interval; OR: odds ratio.

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