3. Grundlegende Fragen

3.1 Ist präoperative Nüchternheit notwendig?

Empfehlung 1

Patienten ohne besonderes Aspirationsrisiko soll vor einem chirurgischen Eingriff die Einnahme klarer Flüssigkeiten bis 2 h, die Einnahme von leicht verdaulichen, festen Speisen bis 6 h vor Beginn der Anästhesie erlaubt sein (BM, IE, QL).

Empfehlungsgrad A – Starker Konsens 100 % Zustimmung

<table>
<tr><th colspan="4">1. Brady M, Kinn S, Stuart P. Preoperative fasting for adults to prevent perioperative complications. Cochrane Database Syst Rev 2003;(4):CD004423.</th></tr>
<tr><th>Study Type/
Evidence Level</th><th>Study details/limitations</th><th colspan="2">Patient characteristics</th><th>Interventions</th></tr>
<tr><td>Systematic Review
1++</td><td>Countries: n/a
Centers: n/a
Setting: n/a
Funding Sources: n/a
Dropout rates: n/a
Study limitations: n/a</td><td colspan="2">Total no. patients: Not given
38 randomized controlled comparisons (made within 22 trials) were identified
Inclusion criteria:
Most of the trials were based on 'healthy' adult participants who were not considered to be at increased risk of regurgitation or aspiration during anesthesia.
Exclusion criteria: n/a</td><td>Randomized controlled trials which compared the effect on postoperative complications of different preoperative fasting regimens on adults were included.</td></tr>
<tr><td>Notes</td><td colspan="4">Author’s Conclusion:
There was no evidence to suggest shortened fluid fast results in an increased risk of aspiration, regurgitation or related morbidity compared with the standard 'nil by mouth from midnight' fasting policy. Permitting patients to drink water preoperatively resulted in significantly lower gastric volumes. Clinicians should be encouraged to appraise this evidence for themselves and when necessary adjust any remaining standard fasting policies (nil-by-mouth from midnight) for patients that are not considered 'at-risk' during anesthesia.</td></tr>
<tr><td>Outcome measures/results</td><td colspan="2">Effect of different preoperative fasting regimens (duration, type and volume of permitted intake) on perioperative complications and patient wellbeing (including aspiration, regurgitation and related morbidity, thirst, hunger, pain, nausea, vomiting, anxiety) in different adult populations.</td><td colspan="2">There was no evidence that the volume or pH of participants' gastric contents differed significantly depending on whether the groups were permitted a shortened preoperative fluid fast or continued a standard fast. Fluids evaluated included water, coffee, fruit juice, clear fluids and other drinks (e.g. isotonic drink, carbohydrate drink). Participants given a drink of water preoperatively were found to have a significantly lower volume of gastric contents than the groups that followed a standard fasting regimen. This difference was modest and clinically insignificant. There was no indication that the volume of fluid permitted during the preoperative period (i.e. low or high) resulted in a difference in outcomes from</td></tr>
</table>

		those participants that followed a standard fast. Few trials specifically investigated the preoperative fasting regimen for patient populations considered to be at increased risk during anesthesia of regurgitation/aspiration and related morbidity.

2. Fearon KC, Ljungqvist O, Von Meyenfeldt M, Revhaug A, Dejong CH, Lassen K, Nygren J, Hausel J, Soop M, Andersen J, Kehlet H Enhanced recovery after surgery: a consensus review of clinical care for patients undergoing colonic resection. Clin Nutr 2005; 24:466-477.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Consensus review 1++	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** Nutricia HealthcareNutricia Healthcare **Dropout rates:** n/a **Study limitations:** n/a	**Total no. patients:** n/a **Inclusion criteria:** n/a **Exclusion criteria:** n/a	Medline database was searched for all clinical studies/trials relating to enhanced recovery after colorectal resection. Relevant papers from the reference lists of these articles and from the authors' personal collections were also reviewed. A combination of evidence-based and consensus methodology was used to develop the resulting enhanced recovery after surgery (ERAS) clinical care protocol.
Notes	**Author's Conclusion:** Within traditional perioperative practice there is considerable evidence supporting a range of maneuvers which, in isolation, may improve individual aspects of recovery after colonic surgery. The present manuscript reviews these issues in detail. There is also growing evidence that an integrated multimodal approach to perioperative care can result in an overall enhancement of recovery. However, effects on major morbidity and mortality remain to be determined. A protocol is presented which is in current use by the ERAS Group and may provide a standard of care against which either current or future novel elements of an enhanced recovery approach can be tested for their effect on outcome.		
Outcome measures/results	Clinical care of patients undergoing colonic surgery differs between hospitals and countries. In addition, there is considerable variation in rates of recovery and length of hospital stay following major abdominal surgery. There is a need to develop a consensus on key elements of perioperative care for inclusion in enhanced recovery programs so that these can be widely adopted and refined further in future clinical trials.	Summary of core protocol elements • Patient information: Essential before admission for surgery. • Preoperative bowel preparation: No routine oral preparation for colon resections. • Preanesthetic medication: Not recommended. • Preoperative fasting and fluids: Patients should be allowed to drink clear fluids up to 2 h prior to initiation of anesthesia and should receive preoperative oral carbohydrate loading. • Standard an aesthetic protocol: Intraoperative mid-thoracic epidural analgesia (local an aesthetic+ low-dose opioid). Short-acting intravenous or inhalational an aesthetic agent, according to local traditions. • Prevention of intraoperative hypothermia: Warmed IV fluids and upper body air-warming device.	

		• Thromboembolic prophylaxis: Low-dose LMWH started about 2 h after placement of epidural catheter and continued until full mobilization. Nasogastric decompression tubes: Not recommended. • Prophylactic antibiotics: Indicated with two drugs (anaerobic and aerobic prophylaxis) given before skin incision and single dose, may be repeated when surgery43h. Incision: Short midline or transverse incisions recommended. • Drainage: Drains should not be used routinely in colonic surgery. • Urinary bladder catheterization: Suprapubic or urethral catheterization. Removal of catheter 24–48 h after surgery recommended. • Fluid therapy: Avoid excessive intravenous fluids. Vasopressors recommended for treatment of epidural-related hypotension. Discontinuation of IV fluids on postoperative day 1. • Ileus prophylaxis and promotion of GI motility: Continuous thoracic epidural analgesia for first 2 postoperative days (low-dose epidural local an aesthetic–opioid): Use of magnesium oxide twice daily recommended. • Postoperative analgesia: Continuous thoracic epidural analgesia for 2 days postoperatively (low-dose epidural local an aesthetic–opioid), paracetamol as routine oral analgesic and Epidural top up as rescue. Commence NSAIDs at end of epidural. Additional opioid only if other efforts fail. • Nutrition: Postoperative nutrition includes ONS from the day of operation in addition to normal food. Malnourished patients should continue ONS at home. • Early Mobilization: A care plan that facilitates patients being out of bed for 2 h on the day of surgery and 6 h thereafter is recommended. • Discharge Criteria: Good pain control with oral analgesics, taking solid food and no intravenous fluids, independently mobile, willing to go home. • Follow-up and audit: Patients should be contacted 1–2 days after discharge, reviewed clinically at 7–10 days postoperatively and reviewed finally at 30 days postoperatively. Audit of results/endpoints/adverse events and protocol compliance is essential.

3.2 Ist bei elektiven Eingriffen eine präoperative metabolische Vorbereitung mittels Kohlenhydratgabe sinnvoll?

Empfehlung 2

Vor großen elektiven abdominellen Operationen sollten gezielt die Kohlenhydratspeicher aufgefüllt werden. (B) (QL). Die flüssige Kohlenhydratgabe kann nach Beginn am Vortag bis 2 h vor Anästhesiebeginn gegeben werden (0) (QL).

Empfehlungsgrad B/0 – Starker Konsens 100 % Zustimmung

3. Awad S, Varadhan KK, Ljungqvist O, Lobo DN (2013) A meta-analysis of randomised controlled trials on preoperative oral carbohydrate treatment in elective surgery. Clin Nutr 32:34-44.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis 1++	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources**: Nottingham Digestive Diseases Centre; National Institute for Health Research Biomedical Research Unit; Enhanced Research After Surgery Society. **Dropout rates:** n/a **Study limitations:** Relatively weak design of many of the included studies whose quality, was assessed by GRADEpro®, was rated as low to moderate. There were small numbers and significant heterogeneity in the design and magnitude of surgery in many studies of preoperative carbohydrate treatment that precluded	**Total no. patients:** n = 1685 patients of Twenty-one randomized studies, (range 14 - 252 patients per study) • 733 in preoperative carbohydrate treatment group • 952 in control group **Inclusion criteria:** We included prospective studies that randomized adult patients undergoing elective surgery to either preoperative oral treatment with complex carbohydrates using ≥ 50 g oral carbohydrate in the preoperative morning serving of the drink or a control arm. The latter may have been either ingestion of an equivalent volume of placebo drink containing no nutrients or preoperative fasting. **Exclusion criteria:** Randomized controlled trials that administered intravenous carbohydrate, utilized ≤ 50 g oral	Preoperative carbohydrate treatment using 50 g oral carbohydrate (with or without additional additives) compared with control

	their inclusion in this metanalysis. The definitions of outcomes such as complications and reporting of events varied between studies. Similarly, insulin resistance was measured using different methods in the included studies, making it difficult to arrive at a common consensus, although most studies reported attenuation of postoperative insulin resistance in carbohydrate treated patients.	carbohydrate in the preoperative morning serving of the drink, that did not compare preoperative carbohydrate treatment against a placebo/preoperative fasting control arm, in which study outcomes were not measured, and those that included patients with diabetes mellitus were excluded. Additionally, non-randomized, case e control, retrospective, healthy volunteer studies, and other studies that did not fulfill the inclusion criteria were also excluded.	
Notes	The review question and inclusion criteria were clearly defined. Attempts were made to locate both published and unpublished data from various sources, and no language restrictions were applied during study selection. Efforts were also taken to minimize reviewer error and bias for the processes of study selection and quality assessment, though this was unclear for the process of data extraction. Suitable quality assessment criteria were employed; the results were variable across the included trials. The methods of synthesis were appropriate, although the inclusion of two very different treatments (fasting and placebo) as the control condition may have contributed to the heterogeneity observed in the meta-analyses. The authors acknowledged that the included trials had small sample sizes, and that there were differences between them with regards to definitions of outcomes and assessment methods for insulin resistance. They also acknowledged that the strength of the evidence ranged from low to moderate, due to imprecision and/or risk of bias. Given the limitations of the evidence base, the authors' conclusions regarding the reliability of the evidence appear suitably cautious. However, the apparent reduction in length of hospital stay amongst the subgroup of patients undergoing abdominal surgery may not be as robust as the authors suggest because of imprecision, heterogeneity, potential for risk of bias and problems associated with multiple testing. **Author's Conclusion:** Preoperative carbohydrate treatment may be linked to a reduced length of stay in patients who undergo major abdominal surgery, and attenuation of insulin resistance in all patients. However, the strength of the evidence was low to moderate.		
Outcome measures/results	**primary outcome measure:** The effect of preoperative carbohydrate treatment on length of primary hospital stay, (defined as number of postoperative days in hospital, until discharge). **Secondary outcome measures:**	No overall difference in length of stay was noted for analysis of all studies or subgroups of patients undergoing surgery with an expected hospital stay ≤ 2 days or orthopedic procedures. However, patients undergoing major abdominal surgery following PCT had reduced length of stay [mean difference, 95% confidence interval: -1.08 (-1.87 to -0.29); I^2 = 60%, p = 0.007]. PCT reduced postoperative insulin resistance with no effects on in-hospital complications over control (risk ratio, 95%	

	The effects of preoperative carbohydrate treatment on development of postoperative insulin resistance, occurrence of drink-related (vomiting, aspiration or pneumonia) and postoperative complications, and occurrence of postoperative nausea and vomiting.	confidence interval, 0.88 (0.50 - 1.53),I^2 = 41%; p = 0.640). There was significant heterogeneity amongst studies and, therefore, quality of evidence was low to moderate

4. Smith MD, McCall J, Plank L, Herbison GP, Soop M, Nygren J Preoperative carbohydrate treatment for enhancing recovery after elective surgery. Cochrane Database Syst Rev.2014 Aug 14;8: CD009161.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic Review 1++	**Countries**: Sweden, elsewhere in Europe, China, Brazil, Canada, New Zealand, **Centers**: Setting: hospitals providing elective surgery **Funding Sources:** n/a **Dropout rates:** Study limitations:	**Total no. patients:** n = 1976 • 935 received carbohydrate, • 595 received placebo • 446 were fasted preoperatively We included 27 trials involving 1976 participants **Inclusion criteria:** RCTs, we identified 27 studies and included the outcomes of 1976 participants. Studies investigated the outcomes of patients undergoing planned surgical procedures on the abdomen, the bones or joints, the heart or the thyroid gland. Eighteen studies compared carbohydrate supplements versus an identical appearing placebo drink that did not contain carbohydrates; in six of these studies, an additional group of patients had nothing to eat or drink for at least six hours before surgery. I n nine studies, taking carbohydrate supplements was	We included all RCTs of preoperative carbohydrate treatment compared with placebo or traditional preoperative fasting in adult study participants. Treatment groups needed to receive at least 45 g of carbohydrates within 4 hours before surgery or anesthesia start time.

		compared with having nothing to eat or drink for six hours before surgery. The primary outcomes of length of hospital stay and complication rate were reported by 19 and 14 studies, respectively. **Exclusion criteria:** not RCT, insufficient information to assess, incorrect participants, incorrect interventions, not reporting pre-specified outcomes, duplicate series, awaiting classification	
Notes	The overall quality of the evidence varied from very low to high. The quality of evidence in support of carbohydrate supplements resulting in a shorter hospital stay was very low because the included studies had important flaws in their design, a very wide range of results was described and evidence revealed that studies showing no differences in length of hospital stay may not have been published. When we looked only at well-conducted studies, we found that carbohydrate supplements had little or no effect on length of hospital stay. The quality of evidence to support the effects of carbohydrate supplements on complication rate was low because issues with study design were identified and results were not similar across studies. **Author's Conclusion:** Preoperative carbohydrate treatment was associated with a small reduction in length of hospital stay when compared with placebo or fasting in adult patients undergoing elective surgery. It was found that preoperative carbohydrate treatment did not increase or decrease postoperative complication rates when compared with placebo or fasting. Lack of adequate blinding in many studies may have contributed to observed treatment effects for these subjective outcomes, which are subject to possible biases.		
Outcome measures/results	**Primary outcomes** 1. Length of hospital stay: 2. Postoperative complication rate: as defined by trial authors. **Secondary outcomes:** 1. Aspiration pneumonitis rate 2. Insulin resistance or sensitivity 3. Fatigue 4. General well-being 5. Nausea 24 hours postoperatively 6. Vomiting within 24 hours postoperatively: 7. Return of intestinal function	Preoperative carbohydrate treatment was associated with a small reduction in length of hospital stay when compared with placebo or fasting in adult patients undergoing elective surgery. It was found that preoperative carbohydrate treatment did not increase or decrease postoperative complication rates when compared with placebo or fasting. Lack of adequate blinding in many studies may have contributed to observed treatment effects for these subjective outcomes, which are subject to possible biases.	

5. Amer MA, Smith MD, Herbison GP, Plank LD McCall JL. Network meta-analysis of the effect of preoperative carbohydrate loading on recovery after elective surgery. Br J Surg 2016.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-analysis 1++	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** Health Research Council of New Zealand Project Grant **Dropout rates:** n/a **Study limitations:** -most trials were of low to moderate quality, with the risk of performance and selection bias -lack of well designed, placebo-controlled trials (this led to the combination of placebo and water into one group for the main analysis) -moderate statistical heterogeneity, and inconsistency between the direct and indirect evidence for some outcomes (due to heterogeneity in trial design, endpoints measured and clinical settings) -Comparisons involving low-dose carbohydrate administration for some outcomes were informed by only one or two head-to-head RCTs (may affect the power and reliability of those effect estimates)	**Total no. patients:** n= 3110 (43 RCTs) **Inclusion criteria:** All randomized and quasi-randomized trials comparing the preoperative administration of at least 10 g carbohydrate (orally or intravenously) within 4 h of surgery start time, with fasting, water or placebo; adults undergoing any type of elective surgical procedure; Studies that co-administered other substances (such as glutamine), as long as the dose of carbohydrate was 10 g or more **Exclusion criteria:** Studies that administered carbohydrate more than 4 h before surgery; Studies including patients undergoing emergency surgery (defined as within 24 h of first physician contact)	This study employed multiple-treatments meta-analysis to determine the effects of preoperative carbohydrate administration on clinically relevant postoperative outcomes in adult patients undergoing elective surgery. Therefore, article databases were searched systematically for RCTs comparing preoperative carbohydrate administration with water, a placebo drink, or fasting. A four-treatment multiple-treatments meta-analysis was performed comparing two carbohydrate dose groups (low, 10–44 g; high, 45 g or more) with two control groups (fasting; water or placebo).
Notes	Studies included in qualitative synthesis n= 43, studies included in quantitative synthesis n= 41		

	Author's Conclusion: Carbohydrate loading before elective surgery conferred a small reduction in length of postoperative hospital stay compared with fasting, and no benefit in comparison with water or placebo.	
Outcome measures/results	**Primary outcome measures:** length of postoperative stay (in days), postoperative complication rate **Secondary outcome measures:** aspiration pneumonitis rate (defined as observed regurgitation or vomiting in association with abnormal chest imaging); vomiting within the first 24 h after surgery (measured as an incidence count); insulin resistance (measured by the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) method); insulin sensitivity (measured by the hyperinsulinemic–euglycemic clamp method); nausea at 24 h after surgery, postoperative general well-being and postoperative fatigue (all measured on ordinal, visual analogue or composite scales); return of intestinal function (number of postoperative days to first passage of flatus, and first bowel motion)	Some 43 trials involving 3110 participants were included. Compared with fasting, preoperative low-dose and high-dose carbohydrate administration decreased postoperative length of stay by 0·4 (95 percent c.i. 0·03 to 0·7) and 0·2 (0·04 to 0·4) days respectively. There was no significant decrease in length of stay compared with water or placebo. There was no statistically significant difference in the postoperative complication rate, or in most of the secondary outcomes, between carbohydrate and control groups.

6. Noblett SE, Watson DS, Huong H, Davison B, Hainsworth PJ, Horgan AF Pre-operative oral carbohydrate loading in colorectal surgery: a randomized controlled trial. Colorectal Dis 2006; 8:563-569.

Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
RCT 1+	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** n/a	**Total no. patients:** n = 35 The age distribution was similar in all 3 groups; fasting group mean age 55 years (range 21–79 years), water group mean age 59 years (range 32–71 years) and carbohydrate (CHO) group mean age 58 years (range 30–77 years). All groups had a median American Society of Anaesthesiologists (ASA) grade of 2. Stoma formation was similar in all groups, as was the distribution of colostomy and ileostomy formation. **Inclusion criteria:**	Three arms: – Carbohydrate group: 100g Precarb, dissolved in 800mL of water the night before surgery and 50g of Vitajoule dissolved in 400mL of water 3h before prior to surgery – Water group: 800mL of water the night before surgery and 400mL of water 3h prior to anesthesia – Fasted group: fasting from midnight the night before surgery

		36 patients undergoing elective colorectal resection **Exclusion criteria:** Patients with diabetes mellitus, gastro-esophageal reflux disease or disorders of gastric emptying were excluded from the study	
Notes	**Author's Conclusion:** We found that pre-operative administration of oral carbohydrate leads to a significantly reduced postoperative hospital stay, and a trend towards earlier return of gut function when compared with fasting or supplementary water.		
Outcome measures/results	**Primary outcome measure:** length of postoperative hospital stay; **Secondary outcome measure:** return of gastrointestinal function, grip strength		post-operative LOS: fasted 10d, water 13 d, CHO 7.5 d (CHO vs. Water p=0.019); median time first flatus: fasted 3 d, water 3 d, CHO 2d (ns.); median time 1st bowel movement: fasted 3.5 d, CHO 2 d (ns.) Grip strength as mean drop in %: fasted 11%, water 8%, CHO 5% (ns.). Oral CHO leads to a reduced postoperative hospital stay, and a trend towards earlier return of gut function.

7. Mathur S, Plank LD, McCall JL, Shapkov P, McIlroy K, Gillanders LK, Merrie AE, Torrie JJ, Pugh F, Koea JB, Bissett IP, Parry BR Randomized controlled trial of preoperative oral carbohydrate treatment in major abdominal surgery. Br J Surg 2010; 97:485-494.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries:** New Zealand **Centers**: Auckland City Hospital or Mercy Hospital, Auckland **Setting**: n/a **Funding Sources:** Financial support for this study was provided by Nutricia (NZ) Ltd. S.M. is the recipient of a Health Research Council Clinical Training Fellowship and a Foundation New Zealand Research Fellowship of the Royal	**Total no. patients:** n = 162 – CHO group: n = 80 – placebo group : n = 82 **Inclusion criteria:** Patients undergoing major elective colorectal surgery or hepatic resection **Exclusion criteria:** age below 18 or above 80 years, pregnancy, inability to consume clear fluids, gastrointestinal obstruction, liver cirrhosis, diabetes mellitus, corticosteroid treatment exceeding 5 mg/day and American Society of	Two arms: – CHO group: evening before surgery: between 19.00 and 24.00h 800mL PreOP solution (12.5% CHO, 50kcal/100mL, 290 Osm/kg); day of surgery: 400mL CHO drink, before scheduled induction of anesthesia to be taken over 20min. – Control group: at the same time same quantity of flavored water with artificial sweetener - identical in taste and appearance to the CHO drink

	Australasian College of Surgeons. **Dropout rates:** n/a **Study limitations:** A traditional overnight-fasted group was not included so it was not possible to determine whether CHO treatment or water may be beneficial compared with overnight fasting	Anesthesiologists (ASA) grade IV or higher	
Notes	**Author's Conclusion:** Preoperative CHO treatment did not improve postoperative fatigue or length of hospital stay after major abdominal surgery. A benefit is not ruled out when epidural blockade or laparoscopic procedures are not used.		
Outcome measures/results	**primary outcome measure:** postoperative fatigue and LOS; **secondary outcome measure:** residual gastric fluid volume (aspiration, dilution method), gastric pH, plasma glucose, serum insulin concentration		no significant difference in VAS and LOS; no significant difference in the postoperative course for insulin resistance (HOMA), grip strength, MAMC, TBP; significantly lower cortisol level in the CHO group on postoperative day 1 only

8. Yuill KA, Richardson RA, Davidson HI, Garden OJ, Parks RW The administration of an oral carbohydrate-containing fluid prior to major elective upper-gastrointestinal surgery preserves skeletal muscle mass postoperatively--a randomised clinical trial. Clin Nutr 2005; 24:32-37.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries**: UK **Centers**: n/a **Setting**: Royal Infirmary of Edinburgh **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** n/a	**Total no. patients:** n = 65 – CHO n = 31 – Control n = 34 **Inclusion criteria:** patients undergoing major, elective abdominal surgery **Exclusion criteria:** impaired renal function, liver cirrhosis, diabetes, metabolic abnormalities, gastric stasis/obstruction, emergency and laparoscopic procedures	Two arms: – CHOD group: 800 mL carbohydrate drink (12.6g carbohydrates /100mL + electrolytes) on the evening prior to surgery, approximately 12h before anesthesia and further 400mL 2-3h before the induction of anesthesia. No other food or fluid was permitted. – Control group: 800 mL placebo drink (fluid and electrolytes) on the evening before prior to surgery and 400 mL 2-3h before anesthesia. 18 months

Notes	**Author's Conclusion:** Preoperative consumption of carbohydrate-containing fluids is safe. Provision of a carbohydrate energy source prior to surgery may attenuate depletion of muscle mass after surgery. Further studies are required to determine if this preservation of muscle mass is reflected in improved function and reduced rehabilitation time.	
Outcome measures/results	**primary outcome measure:** tolerance of oral fluids; **secondary outcome measure**: effect of carbohydrate loading on body composition, biochemical parameters and length of hospital stay	Safety: No single perioperative aspiration occurred to preoperative fluid consumption. At discharge loss of muscle mass (arm muscle circumference) was significantly greater in the control group (-1.1+0.15cm) when compared with the CHOD group (-0.5+0.16cm). Baseline insulin and glucose were comparable in the two groups and did not differ postoperatively. There was no difference in postoperative morbidity and LOS.

9. Hausel J, Nygren J, Lagerkranser M, Hellstrom PM, Hammarqvist F, Almstrom C, Lindh A, Thorell A, Ljungqvist O A carbohydrate-rich drink reduces preoperative discomfort in elective surgery patients. Anesth Analg 2001; 93:1344-1350.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** n/a	**Total no. patients:** n = 252 **Inclusion criteria:** Patients who were able to intake clear fluids according to the guidelines of the Swedish Association of Anaesthetists **Exclusion criteria:** Conditions that impair gastrointestinal motility, gastroesophageal reflux, pregnancy, and the potential for difficult airway management; diabetes, ASA >III, suspected jaundice, or documented choledocholithiasis, operation after noon.	three arms: – CHO group: evening before surgery 800mL of PreOP drink (12.5% CHO, 50kcal/100mL); morning of surgery: 400mL of PreOP drink – Fasted group: fasting from midnight; premedication standardized at least two hours after morning drink, no glucose containing infusions before surgery, colorectal: unless contraindicated low-thoracic epidural analgesia. – Placebo group: flavored water (0kcal/100mL) at the same time points
Notes	The randomization is mentioned but method not specified. The patients were randomly assigned to one of three preoperative treatment groups: 1) preparation with CHO, 2) a placebo drink, or 3) fasting from midnight. The CHO and Placebo groups were double-blinded. To ensure that the taste of the drinks did not cause bias, a double-blinded pilot study (n 26, healthy volunteers) was performed. Each participant was given either CHO or placebo (flavored water). Of 26 subjects, 12 (46%) could correctly identify the drink received.		

	Author's Conclusion: The presently tested CHO had advantages over water (placebo) and overnight fasting by reducing preoperative discomfort in ASA I – II elective abdominal surgery patients. There were no adverse effects recorded from taking this drink in the preoperative period, GFVs were not increased, and gastric acidity was not affected. Thus, discomfort during the waiting period before elective surgery can be significantly reduced in a majority of patients by the simple use of a CHO.	
Outcome measures/results	**primary outcome measure:** preoperative discomfort according to VAS questionnaire with 11 variables (baseline, before intake of the drink on the morning of surgery, 40min and 90min after the morning drink; fasted group at the corresponding time points); **secondary outcome measure:** residual gastric fluid volume (aspiration, dilution method), gastric pH, plasma glucose, serum insulin concentration	No difference in VAS at any time point between laparoscopic cholecystectomy and colorectal surgery. After the morning drink (40 and 90 min) CHO less hungry ($p<0.05$) and less anxious ($p<0.05$) than the other groups, either drink less thirsty than the fasted group, CHO group less unfit (significant compared to fasted group), no difference with placebo. Over time: fasted group: trend to increasing preoperative discomfort in 5 of 11 variables (no change in other), CHO decreasing trend in 5 variables (no change in other), placebo: decreasing unfitness, malaise, but increasing nausea, tiredness, and ability to concentrate. Before morning drink no differences in plasma glucose and serum insulin between CHO, placebo and fasting; after the morning drink significant ($p<0.0001$) increase in CHO at 40 and 90min vs. placebo and fasting; at the induction of anesthesia: CHO group: glucose concentration slightly but significantly ($p<0.01$), and insulin concentration still larger ($p<0.05$) compared with placebo and fasting.

10. Breuer JP, von Dossow V, von Heymann C, Griesbach M, von Schickfus M, Mackh E, Hacker C, Elgeti U, Konertz W, Wernecke KD, Spies CD Preoperative oral carbohydrate administration to ASA III-IV patients undergoing elective cardiac surgery. Anesth Analg 2006; 103:1099-1108.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** n/a First, GFVs were measured by passive gastric reflux, and not the gold standard. Logistical problems and confounding factors such as intraoperative transesophageal	**Total no. patients:** n = 188 – CHO n = 56 – Placebo n = 60 – Control n = 44 **Inclusion criteria:** adult patients (>18years), including type II (non-insulin dependent) diabetes undergoing elective coronary artery bypass graft or valve replacement, who were able to intake clear fluids according to current national guidelines;	three arms: – CHO group: 800 mL 12.5% carbohydrate drink in the evening and 400 mL 2 h before surgery. – Placebo group: 800 mL flavored Water in the evening and 400 mL 2 h before surgery. – Fasted group: fasting overnight for surgery

	echocardiography restricted the sample size of patients undergoing GFV measurements. Second, nosocomial pneumonias were not diagnosed according to the recently published new guidelines of the American Thoracic Society. Finally, a possible CHO-associated effect on cardiac performance can only be indirectly suggested by the reduced inotropic requirements. Also, cardiac insufficiency was diagnosed only according to clinical variables. Even so, more than half of the CHO patients (55%) needed inotropic support during CPB weaning, and there was no difference in cardiovascular drug requirements at any other time.	**Exclusion criteria:** conditions likely to impair GI-motility or enhance gastroesophageal reflux, potentially difficult airway management, ASA >IV, nonelective or emergent surgery, infection, pregnancy, maltose or fructose intolerance, diabetes type I	
Notes	**Author's Conclusion:** CHO administration before elective cardiac surgery does not appear to influence PIR. The intake of clear fluids reduced preoperative thirst, and may be recommended as routine procedure for ASA physical status III–IV patients. As GFVs were not increased, and other adverse events or metabolic disorders did not occur, oral CHO administration can be considered safe for cardiac surgery patients, including noninsulin-dependent Type-2 diabetes patients.		
Outcome measures/results	**primary outcome measure:** postoperative insulin resistance (PIR) as indicated by lower insulin requirements **secondary outcome measure:** improvement of preoperative discomfort (VAS) without affecting gastric fluid volume (GFV) (passive reflux), morbidity as measured by organ function	PIR was not different, no difference in insulin administration and dose Patients with CHO and placebo were less thirsty than controls ($p<0.01$ and $p=0.06$) Ingested liquids did not cause increased GFV or other adverse events. No technical difference during surgery. CHO group: less intraoperative inotropic support after initiation of cardiopulmonary bypass weaning vs. placebo and fasting ($p<0.05$), no difference in morbidity	

11. Järvelä K, Maaranen P, Sisto T Pre-operative oral carbohydrate treatment before coronary artery bypass surgery. Acta Anaesthesiol Scand 2008; 52:793-797.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries**: Finland **Centers**: Heart Center of Tampere University Hospital **Setting**: n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** All our patients were elective CABG patients with uncompromised preoperative hemodynamics and hemodynamics was treated according to a protocol, but we did not record and analyze perioperative hemodynamics. Therefore, we cannot exclude the fact that circulatory differences may have influenced the glycemic balance of these patients.	**Total no. patients:** n = 101 - CHO: n=50 - control: n=51 **Inclusion criteria:** scheduled for elective coronary artery bypass graft **Exclusion criteria:** diagnosed diabetes, delayed gastric emptying for any reason	Two arms: – CHOD group: oral intake until the preoperative evening, fasting overnight, 400mL of PreOP drink (12.5% CHO, 50kcal/100mL) 2h before induction of anesthesia, – Control group: fasting overnight, no drink in the morning
Notes	**Author's Conclusion:** In this study patient population, a pre-operative oral carbohydrate drink did not reduce post-operative insulin resistance or post-operative nausea and vomiting. According to our findings, it is safe to allow cardiac surgery patients to drink clear fluids up to 2 h before induction of anesthesia, because gastric emptying of the drink was almost total and no aspiration occurred.		
Outcome measures/results	**primary outcome measure:** Postoperative insulin resistance (PIR) as indicated by lower insulin requirements **Secondary outcome measure:** Gastric drainage, postoperative nausea and vomiting		PIR was not reduced, no difference in blood glucose, postoperative and total drainage were greater (p=0.005) in the treatment group, but less than the amount of preoperative drink. Postoperative nausea and vomiting (PONV) were not reduced.

12. Bopp C, Hofer S, Klein A, Weigand MA, Martin E, Gust R A liberal preoperative fasting regimen improves patient comfort and satisfaction with anesthesia care in day-stay minor surgery. Minerva Anestesiol 2011; 77:680-686.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries**: Germany **Centers**: University hospital, Heidelberg **Setting**: n/a **Funding Sources:** n/a **Dropout rates**:14 Patient **Study limitations:** The study was performed in a single university institution and, therefore, may not be applicable to other institutions. The absence of statistically significant differences between the two regimens in postoperative hunger may be due to the relatively small study sample size rather than a lack of effect of the preoperative drink.	**Total no. patients**: n = 109 – CHO: n=55 – control: n=54 **Inclusion criteria:** consecutive adult ASA I-III patients undergoing elective day-stay ophthalmological surgery; **Exclusion criteria:** nonelective surgery, pregnancy, GI obstruction, gastroesophageal reflux, diabetes mellitus, stomach hernia, obesity, potential difficult airway management could make their own choice about participation.	Two arms: – CHO group: oral food until midnight, 200mL PreOp drink (12.5% CHO, 50kcal/100mL) 2h before induction of anesthesia – control group: NPO with fasting from midnight
Notes	The randomization is mentioned but method not specified. **Author's Conclusion:** Standardized limited oral preoperative fluid intake increases patient comfort and satisfaction with anesthesia care and should be a part of modern day-stay ophthalmologic surgery.		
Outcome measures/results	**primary outcome measure:** pre- and postoperative discomfort **secondary outcome measure:** satisfaction with anesthesia		Patients in the CHO group were not as hungry ($p<0.05$), not as thirsty ($p<0.001$) preoperatively, and not as thirsty after surgery ($p<0.05$). Satisfaction with the premedication was comparable. Satisfaction with anesthesia care before discharge was significantly higher in the CHO group (<0.05).

13. Kaska M, Grosmanova T, Havel E, Hyspler R, Petrova Z, Brtko M, Bares P, Bares D, Schusterova B, Pyszkova L, Tosnerova V, Sluka M The impact and safety of preoperative oral or intravenous carbohydrate administration versus fasting in colorectal surgery--a randomized controlled trial. Wien Klin Wochenschr 2010; 122:23-30.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries**: n/a **Countries**: bicentric **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** The limitations of our study originate from the patient sample population. The patients were without any metabolic disease or significant comorbidity, and were aged 35–75 with BMI 20–30. Moreover, because of the bicentric nature of the study, with tests performed in two biochemical laboratories by two cardiologists and two physiotherapists, the conclusions should be generalized with caution. The study was underpowered to detect differences in complication rates and length of hospital stay.	**Total no. patients:** n = 221 - control n = 75 - CHO i.v. n= 72 - CHO orally n= 74 **Inclusion criteria:** age 35-70 years, no blood transfusion during surgery expected, BMI 20-30 kg/m², no metabolic disease, no diabetes, ASA<3, left ventricle dysfunction, moderate or severe valve disease, atrial fibrillation **Exclusion criteria:** n/a	Three arms: – control group A preoperative fasting from midnight before surgery – CHO i.v. group B: intravenously 500mL glucose 10% with 10mL of 7.45% KCl and 10mL of 20% MgSo4 twice: evening before surgery, between 6h and 2h before commencement of surgery – CHO orally group C: oral intake of 400mL PreOp (12.6% maltodextrin) twice evening and morning preoperative up to 2h before surgery
Notes	Blinding method: envelope method **Author's Conclusion:** Most patients having elective surgery can be allowed to drink a specific preparation containing carbohydrates and minerals up to two hours before anesthesia. The drink can reduce postoperative insulin resistance estimated one day postoperatively. Further substantial ad vantages include benefits in patients' psychosomatic status and better preservation of cardiac performance. Preoperative fasting in patients is not associated with any benefit for the		

	patients or the medical staff. In contrast, drinking an appropriate preparation of carbohydrates, water and minerals confers protection against surgical trauma.	
Outcome measures/results	**primary outcome measure:** hospital stay, complication rate **secondary outcome measure:** psychosomatic status (mod. Beck questionnaire), biochemical markers including insulin resistance (QUICKI index), gastric residual volume, muscle-grip-strength	No difference in length of stay and in the rate of complications between the three groups. Best preoperative psychosomatic conditions in group C ($p<0.029$) and significant better general perioperative clinical status of patients in group C and B. Significant rise in the index of insulin resistance (QUICKI) only in group A ($p<0.05$). Improved postoperative systolic and diastolic function of the left ventricle ($p<0.04$) and significantly higher postoperatively ejection fraction in group C ($p<0.03$). No significant difference in gastric residual volume in all groups.

14. Bisgaard T, Kristiansen VB, Hjortso NC, Jacobsen LS, Rosenberg J, Kehlet H Randomized clinical trial comparing an oral carbohydrate beverage with placebo before laparoscopic cholecystectomy. Br J Surg 2004; 91:151-158.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries**: Denmark **Countries:** Glostrup University Hospital **Setting**: **Funding Sources**: University of Copenhagen, the Danish Medical Research Council (journal number 9902757), and the Danish Hospital Foundation for Medical Research, Region of Copenhagen, the Faroe Islands and Greenland **Dropout rates**:8 Patients (8,5 %) **Study limitations**:	**Total no. patients**: 94 Data from 86 patients were available for statistical analyses, 43 in each treatment group **Inclusion criteria:** Age between 18-75 **Exclusion criteria:** American Society of Anesthesi-ologists grade III or IV, age below 18 or above 75 years, and patients who had papillotomy by endoscopic retrograde cholangiopancreatography less than 1 month before operation. Patients with diabetes, gastric disease or previous gastric surgery, chronic pain other than that associated with gallstone disease, or expected poor compliance (for example foreign language), and patients receiving opioids or tranquillizers for more than 1 week	Patients received 800 ml of an iso-osmolar 12.5 % carbohydrate-rich beverage the evening before operation (100 g carbohydrate) and another 400 ml (50 g carbohydrate) 2 h before initiation of anesthesia, or the same volume of a placebo beverage. 6 months

		before cholecystectomy. Because of possible attenuation of the metabolic effects of the beverage, patients were excluded if more than 5 h had elapsed between intake of the beverage and the initiation of anesthesia, or if the beverage protocol had been violated in any other way. Patients who developed surgical complications were also excluded as the occurrence of such complications might influence the chosen outcome variables.	
Notes	The randomization is mentioned but method not specified. **Author's Conclusion:** A preoperative carbohydrate beverage did not improve clinical outcome after laparoscopic cholecystectomy		
Outcome measures/results	**primary outcome:** General well-being the day after operation. Daily scores of general well-being, fatigue, appetite and pain, computerized measurements of physical activity and sleep (actigraphy), and subjective sleep quality were recorded. Nausea and vomiting were assessed twice within the first 24 h after surgery.	The present study showed that preoperative administration of a carbohydrate beverage did not improve clinical outcome after laparoscopic cholecystectomy. Preoperative carbohydrate had no influence on postoperative discomfort in terms of general well-being, fatigue, appetite, pain, and nausea and vomiting, and had no influence on sleep or physical activity levels compared with placebo	

15. Soop M, Nygren J, Thorell A, Weidenhielm L, Lundberg M, Hammarqvist F, Ljungqvist O Preoperative oral carbohydrate treatment attenuates endogenous glucose release 3 days after surgery. Clin Nutr 2004; 23:733-741.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries**: Sweden **Countries:** St. Göran Hospital, Stockholm **Setting**: n/a **Funding Sources**:	**Total no. patients**: 14 • CHO group: n = 8 • Control: n= 6 **Inclusion criteria:**	14 patients undergoing total hip replacement were double-blindly randomized to preoperative oral carbohydrate treatment (12.5%, 800 + 400 ml, n = 8) or placebo (n = 6).

	Swedish House of Nobility, the Karolinska Institute and the Stockholm County Council **Dropout rates**: 1 patient was excluded **Study limitations**: sample size, gender distribution in the two groups (only male in the control group)	Age:18-80 years, body mass index (BMI): 18-28 kg/m^2 **Exclusion criteria:** American Society of Anesthesiologists (ASA) physical status class 3-5, conditions or medication known to affect insulin sensitivity, symptoms or signs of upper Gl disease, fasting circulating concentrations of glucose, c-reactive protein, liver function tests and creatinine outside hospital laboratory reference limits, intolerance of non-steroidal anti-inflammatory drugs or epidural analgesia (EDA) and major complications which could be expected to affect the metabolic or clinical recovery.	
Notes	The randomization is mentioned but method not specified. The two beverages were supplied by the manufacturer in random order in coded lots given in consecutive order to study patients, and the code broken at the end of the study. **Author's Conclusion:** Whereas postoperative insulin resistance during the first 24 h after surgery is due mainly to a peripheral defect resulting in reduced glucose disposal, this study shows that insulin resistance is present mainly in the liver three days after surgery. Preoperative carbohydrate treatment attenuates endogenous glucose release on the third postoperative day. The attenuation of postoperative endogenous glucose release may be associated with reduced nitrogen losses.		
Outcome measures/results	Glucose and insulin concentrations were measured. Levels of glucose, insulin and stress hormones were studied pre-, per- and postoperatively. A gastric emptying test was performed.		The study group was insulin resistant on postoperative day one and two. The effects were explainable by the traumatic stress response. No adverse effect was noted from the carbohydrate drink. If glucose is administered intravenously during surgery, there is no obvious advantage of preoperative carbohydrate loading on insulin resistance or stress hormone response.

16. Rapp-Kesek D, Stridsberg M, Andersson LG, Berne C, Karlsson T Insulin resistance after cardiopulmonary bypass in the elderly patient. Scand Cardiovasc J 2007; 41:102-108.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries**: Sweden **Countries:** Uppsala University Hospital **Setting**: n/a **Funding Sources**: The Swedish Heart-Lung Foundation and the Research and Development Foundation of the Uppsala University Hospital **Dropout rates**: n/a **Study limitations**: A possible positive effect in this study group could have been counteracted by the fact that strong hormonal trauma response may obscure a beneficial effect, high levels of stress hormones in this study may be due to the fact that the patients are elderly	**Total no. patients**: n = 18 **Inclusion criteria:** Patients aged over 65, scheduled to undergo elective CABG were included in this investigation **Exclusion criteria:** known diabetes mellitus, other metabolic disease or severely impaired respiratory, circulatory or renal function.	Patients were assigned either to get a carbohydrate drink or to be controls. Perioperatively, glucose was administered.
Notes	The randomization is mentioned but method not specified. **Author's Conclusion:** All patients exhibited insulin resistance on the first postoperative days. We did not observe any clearly adverse or beneficial effects of oral carbohydrate drink on insulin resistance or stress hormone response. This could be due to the fact that all these patients were given an adequate glucose infusion.		
Outcome measures/results	Glucose and insulin concentrations were measured. Levels of glucose, insulin and stress hormones were studied pre-, per- and postoperatively. A gastric emptying test was performed.		The study group was insulin resistant on postoperative day one and two. The effects were explainable by the traumatic stress response. No adverse effect was noted from the carbohydrate drink. If glucose is administered intravenously during surgery, there is no obvious advantage of preoperative carbohydrate loading on insulin resistance or stress hormone response.

17. Hausel J, Nygren J, Thorell A, Lagerkranser M, Ljungqvist O Randomized clinical trial of the effects of oral preoperative carbohydrates on postoperative nausea and vomiting after laparoscopic cholecystectomy. Br J Surg 2005; 92:415-421.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries**: Sweden **Countries:** Karolinska, St Göran and Ersta Hospital **Setting**: n/a **Funding Sources**: Swedish Research Council (no. 09101), Karolinska Institutet, Stockholm County Council (EXPO-95) and from Numico Research. O.L **Dropout rates**: **Study limitations**: Relatively small sample sizes (about 50 per group). With such a small number of patients, the risk of a Type II error increases. Intravenous infusion volumes were about 2400 ml per 24 h in all three groups. These volumes may seem somewhat high in the light of recent findings. Such volumes may have obscured the hydration effects of the oral fluid given before surgery in the CHO and placebo groups.	**Total no. patients**: n = 172 **Inclusion criteria:** Adult patients scheduled for elective laparoscopic cholecystectomy, and who were eligible for intake of preoperative clear fluids according to the guidelines of the Swedish Society of Anaesthesia and Intensive Care, were considered for inclusion. **Exclusion criteria:** Patients with conditions (including pharmacological treatments) that might impair gastrointestinal motility, gastro-esophageal reflux and those who had the potential for difficult airway management, diabetes mellitus, American Society of Anesthesiologists physical status grade III or higher and pregnancy. Patients with suspected (jaundice or based on laboratory findings) or documented choledocholithiasis were not included, to allow standardization of the surgical trauma	Patients were randomized to either preoperative fasting, intake of carbohydrate-rich drink (CHO) (50 kcal/100 ml, 290 mOsm/kg) or placebo. The non-fasting groups were double-blinded; patients ingested 800 ml of liquid on the evening before surgery and 400 ml 2 h before anesthesia. 20 months
Notes	**Notes:** The patients, investigators and nursing staff were all blinded to the CHO and placebo treatments, whereas fasting patients were unblinded. CHO and placebo drinks have previously been shown to be indistinguishable in taste and the products were provided in identical packaging. **Author's Conclusion:**		

	The present data suggest that the metabolic setting at the onset of surgery influences late nausea and vomiting after elective laparoscopic cholecystectomy. CHO may therefore have a role in a multimodal approach to minimize PONV.	
Outcome measures/results	Nausea and pain scores on a visual analogue scale (VAS) and episodes of postoperative nausea and vomiting (PONV) were recorded up to 24 h after surgery.	The incidence of PONV was lower in the CHO than in the fasted group between 12 and 24 h after surgery (P = 0, 039). Nausea scores in the fasted and placebo groups were higher after operation than before admission to hospital (P = 0,018 and P < 0,001 respectively), whereas there was no significant change in the CHO group. No intergroup differences in VAS scores were seen. The use of an aesthetics, opioids, antiemetics and intravenous fluids was similar in all groups.

18. Meisner M, Ernhofer U, Schmidt J Liberalisation of preoperative fasting guidelines: effects on patient comfort and clinical practicability during elective laparoscopic surgery of the lower abdomen. Zentralbl Chir 2008; 33:479-485.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
1+	**Countries**: Germany **Countries:** **Setting**: n/a **Funding Sources**: n/a **Dropout rates**: n/a **Study limitations**: only female patients were included in this study	**Total no. patients**: 42 patients • LTNPO-group: n = 23 • STNPO-group: n = 19 **Inclusion criteria:** patients undergoing elective laparoscopic gynecological surgery **Exclusion criteria:** if patients had gastric emptying disorder, gastroduodenal passage obstacle, severe cardiovascular diseases, diabetes mellitus, decompensated renal insufficiency, or any diseases, previous operations or medication with an impact on the motility of the stomach, the amount of gastric juice as well as the tonus of the lower esophageal sphincter.	Patients undergoing elective laparoscopic gynecological surgery were randomized into two groups. Patients in the long-time NPO-group (LTNPO-group) had nothing per mouth after midnight whereas patients in the short-time NPO-group (STNPO-group) did not receive any oral nutrition after midnight but were allowed an unlimited intake of Pfrimmer Nutricia preOP up to 2 hours before scheduled surgery.
Notes	**Author's Conclusion:** The liberation of the national guidelines for preoperative fluid administration with unlimited intake of a carbohydrate drink offers the benefit of a significantly lower incidence of the preoperative item "feeling cold" and of the pre- and postoperative item "thirst / having a dry mouth". However, in daily clinical practice the length of fasting for fluids was conspicuously longer than that postulated by the new recommendations.		

Outcome measures/results	Patients were asked to assess the incidence of 12 symptoms of perioperative discomfort prior to and 4-6 hours after surgery using a standardized questionnaire. Gastric fluid volume, vital signs during the induction period of anesthesia and the actual duration of fasting were registered and compared.	The actual duration of fasting for solid nutrition was 11.3 h in the LTNPO-group and 10.9 h in the STNPO-group, respectively. The time of fasting for fluids was in the STNPO-group significantly shorter (4.5 h) compared to the LTNPO-group (11.3 h). The patients of the STNPO-group reported preoperatively a significant lower incidence of "feeling cold" and pre- and postoperatively of "thirst / having a dry mouth". No significant differences were reported between the groups with respect to heart rate, blood pressure, gastric volume, need of vasopressors and infusion requirements.

19. Dock-Nascimento DB, de Aguilar-Nascimento JE, Magalhaes Faria MS, Caporossi C, Slhessarenko N, Waitzberg DL Evaluation of the effects of a preoperative 2-hour fast with maltodextrine and glutamine on insulin resistance, acute-phase response, nitrogen balance, and serum glutathione after laparoscopic cholecystectomy: a controlled randomized trial. JPEN J Parenter Enteral Nutr 2012; 36:43-52.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries**: Brazil **Countries:** Santa Rosa Hospital, Cuiabá **Setting**: n/a **Funding Sources**: n/a **Dropout rates**: n/a **Study limitations**: small number of surgical cases included, some biochemical variables, such as GSH and CRP, were not assayed before the induction of anesthesia. Therefore, comparisons only between data from the induction of anesthesia and the postoperative period may not reveal differences in the baseline characteristics of the patients. Thus, caution should be taken when	**Total no. patients**: n = 48 • fasted group; n = 12 • placebo group; n = 12 • GLN group; n = 12 • CHO group; n = 12 **Inclusion criteria:** Female patients admitted for elective laparoscopic cholecystectomy; age: 18-65 years **Exclusion criteria:** malnutrition (assessed by subjective global assessment), age <18 or >65 years, pregnancy, diabetes mellitus, liver cirrhosis, renal failure, gastroesophageal reflux, acute cholecystitis, use of corticosteroids up to 6 months previously, body mass index (BMI) ≤18 or ≥30 kg/m2 , hemoglobin <12 g/dL, surgery expected to last more than 120	standard fasting (control group) vs. fasting with 1 of 3 different beverages before video-cholecystectomy. Beverages were consumed 8 hours (400 mL; placebo group: water; GLN group: water with 50 g maltodextrin plus 40 g GLN; and CHO group: water with 50 g maltodextrin) and 2 hours (200 mL; placebo: water; GLN: water with 25 g maltodextrin plus 10 g GLN; and CHO: water with 25 g maltodextrin) before anesthesia.

	drawing conclusions regarding the effect of the treatments on GSH, CRP, and other measures, given that potential mean differences between groups before the treatments were administered are unknown.	minutes, American Society of Anesthesiologists (ASA) score >II, or any noncompliance or violation of the assigned protocol for preoperative fasting. The necessity of either opening the main biliary tract or other combined surgical procedures would also exclude enrollment in the study. Patients with abnormal baseline CRP values (CRP >6 mg/L) were excluded from the entire analysis.	
Notes	Subjects were kept blind about treatment allocation: Appropriately labeled sachets were distributed to the patients who were unaware of the contents or the number of sachets for each group. **Author's Conclusion:** We conclude that an abbreviated preoperative fast with a GLN plus CHO-enriched beverage beneficially altered the organic response to trauma, not only by decreasing acute-phase response and improving antioxidant defenses but by also ameliorating NB, suggesting the preservation of lean body mass after surgical trauma. These results support the use of GLN enriched-CHO beverages as a preoperative metabolic preconditioning medication. Further research is needed to elucidate and confirm our findings.		
Outcome measures/results	Blood samples were collected pre- and postoperatively. Primary end points: insulin resistance (IR) assessed by the HOMA-IR equation, CRP, prealbumin, albumin and IL-6.		Preoperative intake of a GLN-enriched CHO beverage appears to improve IR and antioxidant defenses and decreases the inflammatory response after video-cholecystectomy. The mean (SEM) postoperative homeostasis model assessment-insulin resistance was greater ($P < .05$) in control patients (4.3 [1.3]) than in the other groups (placebo, 1.6 [0.3]; CHO, 2.3 [0.4]; and GLN, 1.5 [0.1]). Glutathione was significantly higher ($P < .01$) in the GLN group than in both CHO and control groups. Interleukin-6 increased in all groups except the GLN group. The C-reactive protein/albumin ratio was higher ($P < .05$) in controls than in CHO and GLN groups. The nitrogen balance was less negative in GLN (-2.5 [0.8] gN) than in both placebo (-9.0 [2] gN; $P = .001$) and control (-6.6 [0.4] gN; $P = .04$) groups.

20. Braga M, Bissolati M, Rocchetti S, Beneduce A, Pecorelli N, Di Carlo V Oral preoperative antioxidants in pancreatic surgery: a double-blind, randomized, clinical trial. Nutrition 2012; 28:160-164.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1-	**Countries**: Italy **Countries:** San Raffaele University, Milan **Setting**: n/a **Funding Sources**: Fresenius Kabi **Dropout rates**: n/a **Study limitations**: plasma values only provide an approximation of the actual endogenous antioxidant defense status, Antioxidant supplementation was not prolonged after pancreaticoduodenectomy, which per se considerably affects the postoperative metabolic response and induces a high-magnitude oxidative stress.	**Total no. patients**: n = 36 • pONS group (n =18) • placebo group (n = 18) **Inclusion criteria:** elective pancreaticoduodenectomy (PD) for either pancreatic cancer or periampullary cancer, aged between 18 and 80 years, and written informed consent. **Exclusion criteria:** criteria were severe malnutrition (subjective global assessment (SGA) score C), impaired gastric emptying, uncontrolled diabetes mellitus, renal failure (serum creatinine > 3 mg/dL or hemodialysis), cardiovascular dysfunction (NYHA class > 3), respiratory dysfunction (PaO2< 70 mmHg), ongoing infection (including HIV and hepatitis), low plasma neutrophil level (<2.0 # 10^9/L), psychiatric diseases, epilepsy, suspicion of drug abuse, severe alcohol abuse, pregnancy, breast feeding or fertile women refusing to use contraceptives, allergy to any component of the investigational product(s), patient ’s inability to cooperate adequately, and enrollment in other studies.	Patients were randomized to receive either preconditioning oral nutritional supplement (pONS) or placebo twice the day before surgery and once 3 hours before surgery.

Notes	**Author's Conclusion:** In conclusion, short-term preoperative application of a novel oral nutritional supplement with high-dose antioxidants and glutamine was well tolerated in cancer patients undergoing elective pancreaticoduodenectomy. Treatment positively affected both total endogenous antioxidant capacity and plasma vitamin C levels, but did not reduce oxidative stress and systemic inflammation markers. Further studies are needed to identify the optimal dosage and duration of antioxidant supplementation.	
Outcome measures/results	Total endogenous antioxidant capacity (TEAC), plasma levels of vitamin C, vitamin E, selenium, zinc, F2-isoprostanes, and C-reactive protein were measured at baseline following the intake of pONS or placebo drink, a gastrointestinal tolerance questionnaire and a visual analogue scale (VAS) questionnaire on preoperative well-being including questions about feeling hungry, thirsty, anxious, weak, or nausea were completed by patients. Gastric residual volume was assessed through a routinely placed nasogastric suction tube immediately after the induction of anesthesia. On postoperative day (POD) 1, 3, and 7 the following variables were recorded: TEAC, CRP, vitamin E, vitamin C, selenium, zinc, hand grip strength, and SaO2 . F-2 isoprostanes were assessed on POD 1 and 3. On POD 1 both VAS and gastrointestinal tolerance questionnaires were completed by patients. On POD 30 hand grip strength and SaO2 were recorded	Perioperative pONS administration positively affected plasma vitamin C levels and improved TEAC shortly after surgery, but did not reduce oxidative stress and systemic inflammation markers. At surgery, the mean gastric residual volume (mL) was 54.2 in the pONS group versus 51.3 in the placebo group (P = NS). On POD 1 plasma levels of vitamin C (P = 0.001), selenium (P = 0.07), and zinc (P = 0.06) were higher in the pONS group compared to placebo. TEAC was improved on POD 1, 3, and 7 in the pONS group compared to placebo (P = 0.01). No difference was found in plasma C-reactive protein levels after surgery in both groups.

21. Yagci G, Can MF, Ozturk E et al. Effects of preoperative carbohydrate loading on glucose metabolism and gastric contents in patients undergoing moderate surgery: a randomized, controlled trial. Nutrition 2008; 24: 212-216. doi:10.1016/j.nut.2007.11.003			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries:** Turkey **Centers:** single-center, Gulhane Military Medical Academy **Setting:** Department of Surgery **Funding Sources:** n/a **Dropout rates:** 0%	**Total no. patients:** 70 **Inclusion criteria:** patients, with an American Society of Anesthesiologists score of I or II and scheduled for laparoscopic cholecystectomy or thyroidectomy **Exclusion criteria:** Patients with diabetes mellitus, a history of	Two groups: Intervention group (n=34): received a carbohydrate-rich beverage in doses of 800 mL on the evening before surgery and 400 mL 2 h before the induction of anesthesia Control group (n=36): underwent surgery after overnight fasting

	Study limitations: did not address the actual risk of aspiration or other complications; no determination if the use of the carbohydrate-rich drink was of any advantage in terms of ultimate patient outcome; results of our study may not be applicable to patients with conditions with even a small increased risk of delayed gastric emptying	delayed gastric emptying, severe hepatic or renal failure, or any endocrine disorder that might influence the metabolic parameters were excluded, patients requiring urgent or emergent surgery.	
Notes	**Author's Conclusion:** preoperative intake of carbohydrate-rich fluids does not appear to alter the amount or pH of gastric contents, suggesting that this is a safe procedure, in terms of aspiration risk. Furthermore, the intake of such fluid might prevent energy malnutrition		
Outcome measures/results	Glucose levels, Insulin levels, gastric volume and pH		- Plasma glucose levels were significantly higher in the treatment group (initial 86.06 ± 10.9 mg/dL, final 83.03 ± 8.2 mg/dL) than in the control group (initial 74.12 ± 24.1 mg/dL, final 70.85 ± 22.3 mg/dL) - insulin levels were elevated in the treatment group (17.08 ± 5.2 mU/L, P < 0.001) - the insulin levels were similar in the two groups immediately before surgery (treatment group 17.66 ± 7.0; control group 17.82 ± 9.9, P < 0.94) - mean volumes for gastric contents were 16.24 ± 18.5 and 18.46 ± 16.4 mL for the treatment and control groups, respectively (P < 0.61). - pH of gastric contents also was comparable (treatment group 3.53 ± 1.7, control group 2.85 ± 1.8, P < 0.29).

22.	**Tudor-Drobjewski BA, Marhofer P, Kimberger O et al. Randomised controlled trial comparing preoperative carbohydrate loading with standard fasting in paediatric anaesthesia. Br J Anaesth 2018; 121: 656-661. doi:10.1016/j.bja.2018.04.040**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1++ ROB 4/7	**Countries:** Austria **Centers:** single-center, Medical university of Vienna	**Total no. patients:** 120 **Inclusion criteria:** children between 2 and 18 years of age scheduled for elective endoscopic examinations (gastroscopy with or without	Two groups:

	Setting: Department of Pediatrics and Adolescent Medicine **Funding Sources:** Departmental sources **Dropout rates:** 0% **Study limitations:** Risk of Bias: moderate Inconsistency: n/a Indirectness: low Impreciseness: moderate Publication bias: n/a Caution should be exercised in interpreting these behavioral (OPS) and self-reported (VAS) scores, given that children of all ages have limited understanding of their disease and are usually distressed during the perioperative period.	colonoscopy) under general anesthesia **Exclusion criteria:** children <2 years; Patients at risk for aspiration (related to their underlying disease), on H_1 antagonist or corticoid therapy, or those refusing PreOp™	Intervention group (n=60): 5 ml kg^{-1} of a lemon-flavored carbohydrate beverage (PreOp™) was administered on the evening and exactly 2 h before the scheduled endoscopic procedure Control group (n=60): standard protocol of preoperative fasting [6 h for solid foods, 4 h for breast milk, 2 h for clear fluids (water, tea)
Notes	**Author's Conclusion:** Preoperative carbohydrates can reduce nausea and gastric content, the latter being a surrogate parameter for the risk and severity of gastric aspiration into the lungs during anesthesia. Our study adds knowledge for preoperative fasting guidelines in pediatric anesthesia		
Outcome measures/results	**Primary outcomes**: pH and volume of stomach content **Secondary outcomes**: preoperative thirst and hunger, postoperative nausea and vomiting		- Mean volume of gastric content (SD) (ml kg^{-1}): 0.41 (0.28) in control group; 0.28 (0.27) in intervention group, P=0.01 - Mean pH of gastric content (SD): 1.9 (0.5) in control, 2.0 (0.6) in intervention, P= n.s. - Preoperative thirst (% of patients): 32 in control, 30 in intervention, not significant - Preoperative hunger (% of patients): 30 in control, 33 in intervention, not significant - Postoperative nausea (% of patients): 25 in control, 10 in intervention, P= 0.028 - Postoperative vomiting (% of patients): 5 in control, 2 in intervention, not significant

23.	Lee JS, Song Y, Kim JY et al. Effects of Preoperative Oral Carbohydrates on Quality of Recovery in Laparoscopic Cholecystectomy: A Randomized, Double Blind, Placebo-Controlled Trial. World J Surg 2018; 42: 3150-3157. doi:10.1007/s00268-018-4717-4		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+ ROB 4/7	**Countries:** Korea **Centers:** single-center, Gangnam Severance Hospital, Yonsei University Health System, Seoul **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** 9% **Study limitations:** Risk of Bias: moderate Inconsistency: n/a Indirectness: high Impreciseness: high Publication bias: n/a timing of the QoR-40 questionnaire was not appropriate to assess the primary endpoint; baseline results of the preoperative evaluation were significantly different among groups that included patients at varying stages of acute cholecystitis progression; degree of position change may have been insufficient to compare the hemodynamic instabilities; study was underpowered	**Total no. patients:** 153 **Inclusion criteria:** American Society of Anesthesiologists (ASA) class I–II adults who had a Karnofsky Performance Status Scale greater than 70 **Exclusion criteria:** fasting glucose level greater than 120 mg/dL; type I or II diabetes; gastroesophageal reflux disease; history of previous upper gastrointestinal surgery; Patients with an ASA physical status of IV/V	3 groups: Group No-NPO (n=51): received 800 mL of a clear carbohydrate beverage; ingest 400 mL of this beverage on the evening before surgery (8:00–10:00 p.m.) and on the morning of surgery (400 mL) 2 h before any anesthetic medication was administered Group MN-NPO (n= 51): not allowed to drink any solution or fluid after midnight (MN) before surgery. Group Placebo (n=51): received the same quantity of flavored water at the same times as those in the No-NPO group.

Notes	**Author's Conclusion:** preoperative carbohydrate beverage did not improve quality of recovery using the QoR-40 questionnaire after general anesthesia for laparoscopic cholecystectomy compared to placebo or conventional fasting. However, the preoperative fasting group had a consistently increased heart rate during changes in body position that induced hypotension, which is likely a result of depletion of effective intravascular volume caused by traditional fasting over 8 h.	
Outcome measures/results	**Primary endpoint**: quality of recovery after general anesthesia, as assessed using the QoR-40 questionnaire **Secondary endpoint**: intraoperative hemodynamic changes induced by a pneumoperitoneum (12 mmHg) and reverse Trendelenburg position (15°)	- preoperative QoR-40 as the baseline data also showed differences between the groups; difference between the preoperative and postoperative QoR-40 scores with preoperative QoR-40 adjustment was not statistically significant - Group MN-NPO patients had elevated heart rates com- pared to patients in groups No-NPO and Placebo (P = 0.0412). There was no significant difference in mean arterial pressure between the three groups.

24. Helminen H, Branders H, Ohtonen P et al. Effect of pre-operative oral carbohydrate loading on recovery after day-case cholecystectomy: A randomised controlled trial. Eur J Anaesthesiol 2019; 36: 605-611. doi:10.1097/EJA.0000000000001002			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+ ROB 5/7	**Countries:** Finland **Centers:** multi-center Oulu University Hospital, Seinäjoki Central Hospital **Setting:** Department of Surgery and Anesthesia, Department of Surgery and Biostatistics **Funding Sources:** None **Dropout rates:** 0% **Study limitations:** Risk of Bias: moderate Inconsistency: n/a Indirectness: high Impreciseness: high Publication bias: n/a Could not standardize the exact timing of the pre-operative drink; did not	**Total no. patients:** 113 **Inclusion criteria:** Adults between 18 and 70 years old with ASA physical status I to II who were scheduled for day-case cholecystectomy **Exclusion criteria:** bleeding or coagulation disorders, BMI more than 40 kg m^{-2}, dementia and those suffering from insulin-treated diabetes, migraine, Meniere's disease or with history of alcohol or drug abuse	Two groups: Intervention group (n = 57): drink carbohydrate-rich drink at home before leaving for the hospital, or by 6 a.m. for surgery scheduled at 8 a.m. or 8 a.m. at the latest for later surgery Control group (n = 56): fasting overnight; take nothing by mouth after midnight on the night before surgery

	follow-up patients after discharge		
Notes	**Author's Conclusion:** carbohydrate loading as a single pre- operative drink in the morning did not show any clear advantages over fasting in the recovery after day-case cholecystectomy.		
Outcome measures/results	Visual analogue scales to score six forms of discomfort: the need for analgesia and antiemetics, the time to drinking, eating and first mobilization after surgery and the time to discharge. Any hospital re-admission was also recorded.		- No. patients given pain medication (n): 49 (86) in intervention, 52 (93) in control, P=0.094 - No. patients given opioids (n): 40 (70) in intervention, 42 (75) in control, P= 0.95 - No. patients given antiemetic medication (n): 18 (32) in intervention, 18 (32) in control, P= 0.84 - Able to drink (h): 2.0±1.1 in intervention, 2.2±1.0 in control, P= 0.57 - Able to eat (h): 3.4±1.1 in intervention, 3.4±1.0 in control, P= 0.80 - Able to ambulate (h): 3.4±1.1 in intervention, 3.4±1.0 in control, P= 0.47 - Time to discharge (h): 5.6±1.4 in intervention, 5.7±1.2 in control, P= 0.33

25. Hamamoto H, Yamamoto M, Masubuchi S et al. The impact of preoperative carbohydrate loading on intraoperative body temperature: a randomized controlled clinical trial. Surg Endosc 2018; 32: 4393-4401. doi:10.1007/s00464-018-6273-2			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+ ROB 4/7	**Countries:** Japan **Centers:** single-center, Osaka Medical College **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** 9% **Study limitations:** Risk of Bias: moderate Inconsistency: n/a Indirectness: high Impreciseness: high Publication bias: n/a Did not record the armpit temperature before intake of the carbohydrate-rich drink on the day of surgery; did not	**Total no. patients:** 70 **Inclusion criteria:** tumor location from cecum to recto- sigmoid, age 20–85 years, sufficient oral intake, American Society of Anesthesiologists physical status 1 or 2, and no intestinal obstruction **Exclusion criteria:** conversion from laparoscopic to open surgery, renal failure, history of thyroid diseases, dysautonomia, and body temperature above 37.5 °C on the day of surgery	2 groups: Intervention/CHO group (n=35): received 500 ml Arginaid Water® a carbo- hydrate-rich beverage, the night before surgery and 250 ml Arginaid Water® 2 h prior to induction of anesthesia Control group (n=35): not restricted regarding drinking clear water 2 h prior to induction of anesthesia

	include laparoscopic surgery for other carcinomas		
Notes	**Author's Conclusion:** preoperative carbohydrate loading had no effect on raising the intraoperative core temperature but did not have a negative impact on the perioperative outcome. preoperative carbohydrate loading prevented the loss of lower limb muscle mass, which may have a beneficial impact on postoperative recovery.		
Outcome measures/results	**Primary endpoint:** intraoperative esophageal temperature during the first 150 min after starting surgery **Secondary end points**: short-term outcomes and body composition change.		- armpit temperatures before surgery in each group were not significantly different (control vs. CHO: 36.27 ± 0.32 vs. 36.37 ± 0.36 °C, p = 0.1355) - core temperature of the CHO group 90, 120, and 150 min after starting surgery was significantly lower than that of the control group (control vs. CHO, respectively: 90 min; 36.26 ± 0.41 vs. 36.05 ± 0.43 °C, p = 0.0233, 120 min; 36.30 ± 0.44 vs. 36.06 ± 0.50 °C, p = 0.0283, 150 min; 36.33 ± 0.50 vs. 36.01 ± 0.56 °C, p = 0.0186). - first day of flatus, defecation, and solid food were not significantly different between the control and CHO groups - length of the hospital stay and the rate of complications were also not significantly different - significant difference in body weight loss (control vs. CHO, respectively: −1.6±0.8 vs. −0.9±1.4 kg, p=0.0304) and the loss of lower limb muscle mass (− 0.7 ± 0.7 vs. − 0.3 ± 0.6 kg, p = 0.0110) between the control and CHO groups, respectively - loss of lean body mass, total body water, skeletal muscle mass and upper limb muscle mass was not significantly different.

26. Rizvanovic N, Nesek Adam V, Causevic S et al. A randomised controlled study of preoperative oral carbohydrate loading versus fasting in patients undergoing colorectal surgery. Int J Colorectal Dis 2019; 34: 1551-1561. doi:10.1007/s00384-019-03349-4			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1++ ROB 6/7	**Countries:** Bosnia, Herzegovina **Centers:** Cantonal Hospital in Zenica **Setting:** Department of Anesthesiology, Intensive Care Unit and Department of Surgery **Funding Sources:** n/a	**Total no. patients:** 50 **Inclusion criteria:** American Society of Anesthesiologist (ASA) physical status of I-II, between 18 and 70 years of age and scheduled for elective open colorectal surgery	2 groups: FAST group = control group (n= 25): fasted for 8 h before surgery CHO group = intervention group (n=25): received 400 mL of a clear carbohydrate drink at 22 h on the evening before surgery and another 200 mL of the carbohydrate drink on the day of surgery, 2 h before anesthesia induction

	Dropout rates: 0% **Study limitations:** Risk of Bias: low Inconsistency: n/a Indirectness: moderate Impreciseness: high Publication bias: n/a Evaluated parameters were monitored up to the second postoperative day, longer would be better; results refer only to participants with ASA physical status grades I and II	**Exclusion criteria:** previous treatment for colorectal cancer, disseminated malignant disease, an increased risk of gastric con- tent aspiration, body mass index below 20 or above 30 kg/m^2 or an overall score ≥ 3 according to the Nutritional Risk Screening 2002; emergency colorectal surgery, diabetes mellitus, inflammatory bowel disease, immunomodulatory therapy, a history of allergy to any study drug	
Notes	**Author's Conclusion:** CHO supplement is a safe and effective practice in shortening preoperative fasting in open colorectal surgery. A CHO solution used the evening before surgery and 2 h before the induction of anesthesia reduces postoperative insulin resistance, attenuates the inflammatory response and improves subjective patient well-being. Additionally, a CHO drink allows for the faster return of gastrointestinal function, earlier independent ambulation and earlier postoperative discharge day		
Outcome measures/results	Clinical biochemical parameters, Subjective patient well-being and pain scores, Surgical outcomes		- Postoperative insulin resistance was 30% lower ($p < 0.03$) and insulin sensitivity was 15% higher ($p < 0.05$) in the CHO group than in the FAST group - Glasgow prognostic score was lower in the CHO group at postoperative day 1 ($p < 0.001$), postoperative day 3 ($p < 0.01$) and postoperative day 4 ($p < 0.004$) - IL-6 serum levels were lower at the analyzed postoperative time points in the CHO group ($p < 0.001$) - VAS well-being score was lower in the intervention group ($p < 0.001$); however, the VAS pain score was not significantly different between the groups - evaluated surgical outcomes appeared earlier in the CHO group ($p < 0.001$).

27.	**Gianotti L, Biffi R, Sandini M et al. Preoperative Oral Carbohydrate Load Versus Placebo in Major Elective Abdominal Surgery (PROCY): A Randomized, Placebo-controlled, Multicenter, Phase III Trial. Ann Surg 2018; 267: 623-630. doi:10.1097/SLA.0000000000002325**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+ ROB 7/7	**Countries:** Italy **Centers:** multi-center, 5 Italian university tertiary hospitals **Setting:** n/a **Funding Sources:** grant of the Surgical Infection Society-Europe. **Dropout rates:** 25% **Study limitations:** Risk of Bias: low Inconsistency: n/a Indirectness: high Impreciseness: moderate Publication bias: n/a no blinding of patients; glucose level was measured using blood capillary samples; role of blood glucose levels >180 mg/dL could not be ruled out from the design of the trial; results cannot be generalized; relatively low BMI of our patient population may not reflect the reality of other countries	**Total no. patients:** 662 **Inclusion criteria:** adult (age ≥ 18) patients who were candidates for elective major abdominal operation (duration ≥ 2 hours) for surgical diseases of the gastrointestinal tract and urinary tract, and for gynecological diseases **Exclusion criteria:** fasting glucose level >125 mg/dL, type 1 and 2 diabetes, gastro-esophageal reflux disease, hiatal hernia, pancreatic disease, American Society of Anesthesiologists (ASA) physical status classification >3, preoperative weight loss >10% of the usual body weight in the previous 6 months, ongoing cortico- steroid therapy, and any previous infection in the past 3 months	Two groups: Intervention group (n=331): oral intake of 800 mL of a water solution containing 12.6 g of CHO; instructed to start consumption of this solution from 8PM on the evening before the operation and stop consumption 2 hours before the planned time of operation. During this timeframe, the patients were not allowed to drink any other solution or fluid. Control/Placebo group (n=331): drink plain water (vehicle used in the treatment arm) with the same timing and volume as those in the treatment arm.
Notes	**Author's Conclusion:** Oral preoperative CHO load is effective for avoiding a blood glucose level >180mg/dL, but without affecting the risk of postoperative infectious complication.		
Outcome measures/results	**Primary outcome measure**: occurrence of at least 1 of the following postoperative infections: superficial or deep wound		- Composite postoperative infection occurred in 54 (16.3%) patients from the CHO group and in 53 (16.0%) patients from the placebo group (RR 1.019,

	infection, organ/space infection, urinary tract infection, pneumonia, sepsis, and septic shock. **Secondary outcome measures:** number of patients with at least 1 postoperative measurement of blood glucose >110 and <140mg/dL, or at least 1 postoperative measurement of blood glucose >140 and <180 mg/dL; number of patients needing intra- operative or postoperative insulin treatment; rate and duration of empiric antibiotic therapy after surgery; rate, severity, and duration of all postoperative complications; rate of reoperation; rate and duration of intensive care treatment; and length of postoperative stay.	95% CI 0.720 to 1.442; relative difference 0.003, 95% CI -0.053 to 0.059, P=1.00) - Preoperative CHO loading significantly reduced the rate of insulin administration - frequency of empiric antibiotic prescription and the duration of treatment did not differ between the groups. We did not observe any significant differences in the rate of overall surgery-related complications, their severity, and their duration between the groups - proportions of patients requiring reoperation and intensive care treatment were comparable between the groups. The median length of post- operative hospitalization was 11.0 days in both groups (RR 0, P =0.44).

28. Noba L, Wakefield A. Are carbohydrate drinks more effective than preoperative fasting: A systematic review of randomised controlled trials. J Clin Nurs 2019; 28: 3096-3116. doi:10.1111/jocn.14919			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic review 1++ AMSTAR II 9/16	**Countries:** Turkey, Poland, India, Serbia, Australia, Brazil, UK, China, Czech Republic, New Zealand, Finland, Sweden, Denmark **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** Overall confidence in the results of the review: Critically Low Risk of bias of single studies: moderate Inconsistency: n/a Indirectness: none Impreciseness: n/a	**Total no. Studies:** 22 **Inclusion criteria:** RCTs comparing the effectiveness of administrating oral preoperative carbohydrate drinks against placebo or standard care (fasting or clear water). **Exclusion criteria:** Non-English language studies plus those not using random experimentation, namely studies designated to be the following: quasi-experimental, case, crossover, or retrospective studies	Evaluation of the available evidence to establish whether oral preoperative carbohydrate drinks: shortened hospital length of stay, reduced insulin resistance and/or improved postoperative discomfort for adult patients.

	Publication bias: n/a Descriptive synthesis approach to summarize the findings; none of the trials included more than 100 participants in each intervention arm; excluded trials that included diabetic patients		
Notes	**Author's Conclusion:** Administration of preoperative carbohydrate drinks is safe and can be administered up to 2 hr. before surgery. Furthermore, preoperative carbohydrate drinks may reduce insulin resistance and improve post- operative discomfort especially in patients undergoing laparoscopic cholecystectomy		
Outcome measures/results	**Primary outcome**: Length of hospital stay or stay in intensive care unit, Insulin resistance **Secondary outcomes**: Postoperative nausea and vomiting, thirst, hunger, mouth dryness, tiredness, weakness, fatigue, malaise, anxiety, depression		- insufficient evidence to suggest whether preoperative carbohydrate drink shortens length of hospital stay - some evidence to suggest carbohydrate drinks can reduce insulin resistance. However, the results across the trials are inconsistent and some of the trials either used small samples or were assessed to be of low quality - Evidence suggests there is no effect on gastric volumes and pH, and carbohydrate drinks are safe - some evidence to suggest carbohydrate drink may reduce episode of nausea and vomiting - insufficient evidence to suggest preoperative carbohydrate drink can reduce postoperative pain - Evidence supports the notion carbohydrate drink may improve hunger, thirst and dry mouth - some evidence to suggest carbohydrate drink may improve tiredness, fatigue, weakness and malaise - some evidence to support the notion carbohydrate drinks may reduce anxiety and depression

29.	**Pachella LA, Mehran RJ, Curtin K et al. Preoperative Carbohydrate Loading in Patients Undergoing Thoracic Surgery: A Quality-Improvement Project. J Perianesth Nurs 2019; 34: 1250-1256. doi:10.1016/j.jopan.2019.05.007**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Controlled trial	**Countries:** USA	**Total no. patients:** 97	Two groups:

2+ NOS 6/9	**Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** 3% **Study limitations:** Risk of Bias: moderate Inconsistency: n/a Indirectness: moderate Impreciseness: moderate Publication bias: n/a Small sample size; liquids consumed before the arrival to the hospital not documented; occurrence of nausea and vomiting not directly measured	**Inclusion criteria:** patients undergoing thoracic surgery, older than 18 years, and undergoing lung resection for primary lung cancer or secondary metastasis. All standard surgical approaches for lung resection were included **Exclusion criteria:** other types of thoracic surgery; Patients who have higher risk of aspiration; those who have undergone prior esophageal surgery, benign motility disorders of the esophagus, and who reported nausea and vomiting before surgery; patients with DM	preintervention control group: received usual instructions to remain NPO after midnight, with the standard ERAS protocol allowing patients to take clear liquids up to 2 hours before reporting to the preoperative holding area postintervention group: self-administered the product Ensure Pre-Surgery Clear Nutrition Drink 2 hours before reporting to the preoperative holding area. This product meets the recommendations of Enhanced Recovery After Surgery Society guidelines to contain 50 g of carbohydrates
Notes	**Author's Conclusion:** carbohydrate loading is a nonpharmacologic intervention that can decrease nausea and pain in patients undergoing thoracic surgery, and should be incorporated into the ERAS protocol		
Outcome measures/results	occurrence of nausea and vomiting, Patient-reported pain scores (0-10) in the first 4 hours postoperatively and in the first 24 hours after surgery; morphine daily equivalent		- In the preintervention group, 15 of the 47 (32%) patients required antiemetic medication as opposed to the postintervention group, where 8 of the 50 (16%) patients required antiemetic medication. This was approaching statistical significance (P = .066) - no difference seen in the re- ported average pain score between the 2 groups during the first 4 hours after surgery, or during the first 24 hours postoperatively. There was no difference seen in MDE administered in the 24 hours after surgery - decrease in morphine daily equivalent in the postintervention group in the first 4 hours after surgery, which is statistically significant (P = .028)

30.	**Liu B, Wang Y, Liu S et al. A randomized controlled study of preoperative oral carbohydrate loading versus fasting in patients undergoing elective craniotomy. Clin Nutr 2019; 38: 2106-2112. doi:10.1016/j.clnu.2018.11.008**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT	**Countries:** China	**Total no. patients:** 120	Two groups:

1+ ROB 4/7	**Centers:** single-center, Tangdu Hospital (Xi'an, People's Republic of China) **Setting:** Department of Neurosurgery **Funding Sources:** China Natural Science Foundation **Dropout rates:** 0% **Study limitations:** Risk of Bias: moderate Inconsistency: n/a Indirectness: high Impreciseness: moderate Publication bias: n/a Lack of placebo of fluid balance preoperatively; non-blinding, groups could have been treated differently; primary endpoint measured via blood glucose and insulin levels, Insulin tolerance test could be better	**Inclusion criteria:** admitted for elective craniotomy; aged between 18 and 65 years-old, had a single intracranial lesion **Exclusion criteria:** intracranial trauma, pathology requiring emergent surgery, preoperative disturbance of consciousness, significant cognitive impairment who were unable to cooperate, and presence of a confounding condition (e.g., pregnancy) or disease that could potentially impact postoperative recovery (e.g., paralysis, spinal deformity, autoimmune diseases, myocardial infarction, severe infection, liver and renal malfunction, or severe psychological or mental illness), and those with diabetes or with a preoperative fasting glucose of greater than 7 mmol/L, those who were using steroids or immunosuppressants, those with history of abnormal gastric emptying or intestinal obstruction.	Intervention group (n=58): 400 mL of oral carbohydrate loading (i.e. Maltodextrin Fructose Solution, Xi'an, China; 12.6% carbohydrate, 0.5 kcal/ml, 260 mOsm/kg, pH 4.9) 2 h before surgery Control group (n=62): fasting 8 hours prior to surgery as routine management
Notes	**Author's Conclusion**: Oral carbohydrate loading given 2 h prior to surgery in patients undergoing elective craniotomy seems to be effective and safe in improving glucose homeostasis, handgrip strength and pulmonary function as well as reducing length of stay without increasing the risk of postoperative complications, compared with prolonged preoperative fasting		
Outcome measures/results	**Primary outcome**: glucose homeostasis **Secondary outcomes**: Handgrip strength, pulmonary function, postoperative complications		- Better glucose homeostasis (5.6 ± 1.0 mmol/L vs. 6.3 ± 1.2 mmol/L, P = 0.001) was achieved in patients who received preoperative oral carbohydrate loading compared to fasting - intervention group had better handgrip strength (25.3 ± 7.1 kg vs. 19.9 ± 7.5 kg, P < 0.0001) and pulmonary function (in terms of peak expiratory flow

		rate) (315.8 ± 91.5 L/min vs. 270.0 ± 102.7 L/min, P = 0.036) compared to the controls postoperatively - rates of postoperative surgical and non-surgical complications did not differ between the groups - Both postoperative and total hospital length of stay reduced significantly in the intervention group (-3d, P < 0.0001 and P = 0.004).

31.	**Cakar E, Yilmaz E, Cakar E et al. The Effect of Preoperative Oral Carbohydrate Solution Intake on Patient Comfort: A Randomized Controlled Study. J Perianesth Nurs 2017; 32: 589-599. doi:10.1016/j.jopan.2016.03.008**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1- ROB 3/7	**Countries:** Turkey **Centers:** n/a **Setting:** general surgery clinic **Funding Sources:** n/a **Dropout rates:** 5% **Study limitations:** Risk of Bias: high Inconsistency: n/a Indirectness: moderate Impreciseness: moderate Publication bias: n/a	**Total no. patients:** 90 **Inclusion criteria:** adult patients undergoing an elective thyroid operation and American Society of Anesthesiologists (ASA) physical status I or II **Exclusion criteria:** aged below 18 or above 80 years, pregnancy, history of delayed gastric emptying, gastrointestinal obstruction, liver cirrhosis, diabetes mellitus, hypertension, severe hepatic or renal failure, or any endocrine disorder that might influence the metabolic parameters and patients requiring urgent or emergent surgery.	3 groups: Fasting group (n=33): Fasting from midnight before surgery Glucose group (n=32): received an IV injection of 1,000-mL dextrose (5% dextrose/water) between 12:00 a.m. and 2 hours before surgery. These patients were not given anything orally. CHD group (n=30): oral carbohydrate solution, 800 mL at 12:00 a.m. and 400 mL 2 hours before surgery.
Notes	**Author's Conclusion:** administering CHD (800 mL one night before surgery and 400 mL 2 hours before surgery) reduces preoperative discomfort (hunger, mouth dryness, tiredness, weakness, and headache) and the CHD group only experienced less postoperative early complications (vomiting and pain) compared with the fasting group. No differences were found with respect to the 5% glucose group.		

Outcome measures/results	Patients' Visual Analog Scale Scores in discomfort symptoms; preoperative, intraoperative, and postoperative blood glucose and vital signs	- In the preoperative assessment, hunger, thirst, mouth dryness, chill, and headache adjusted for age, gender, body mass index, and duration of the operation were all found to be significantly higher in the glucose and fasting groups than the CHD group (P < .01) - In the postoperative period, the fasting group experienced more vomiting, and pain compared with the CHD group (P < .05). - significant difference was found between the groups in terms of diastolic blood pressure and pulse rate in the preoperative and intra- operative periods (P <.05).

32.	**Doo AR, Hwang H, Ki MJ et al. Effects of preoperative oral carbohydrate administration on patient well-being and satisfaction in thyroid surgery. Korean J Anesthesiol 2018; 71: 394-400. doi:10.4097/kja.d.18.27143**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1- ROB 4/7	**Countries:** Korea **Centers:** single-center, Chonbuk National University Medical School and Hospital, Jeonju **Setting:** Department of Anesthesiology and Pain Medicine **Funding Sources:** n/a **Dropout rates:** 0% **Study limitations:** Risk of Bias: moderate Inconsistency: n/a Indirectness: none Impreciseness: moderate Publication bias: n/a Patients were not blinded to allocated group; confined the enrollment of participants only to those scheduled for	**Total no. patients:** 50 **Inclusion criteria:** 20–65 years with American Society of Anesthesiologists physical status I or II, who were scheduled to undergo open thyroidectomy under general anesthesia; Only patients who scheduled for the first operation in the morning **Exclusion criteria:** Patients with a history of type I or II diabetes mellitus, gastric emptying disorders including gastroesophageal reflux disease, contraindications for ketorolac or nefopam, or emergency surgery were excluded. Patients with fasting blood glucose ≥ 126 mg/dl or glycosylated hemoglobin ≥ 6.5% on pre-operative laboratory test, suggestive of hidden diabetes mellitus, were also excluded.	Two groups: Carbohydrate group (n=25): also fasted but received 400 ml of carbohydrate-rich drink 2 hours before induction of anesthesia Control group (n=25): obey traditional preoperative fasting after midnight prior to the day of surgery

	surgery at 8:30 am; degrees of patient well-being and satisfaction were favorable even in the control group, perhaps due to the short fasting time		
Notes	**Author's Conclusion:** preoperative oral carbohydrate administration does not appear to improve patient well-being and satisfaction compared with midnight fasting in patients undergoing thyroidectomy in the first schedule in the morning		
Outcome measures/results	**Primary endpoint**: Assessment of patient well-being and satisfaction **Secondary endpoints**: Oral Schirmer's Test, Blood glucose, preoperative fasting practice		The two groups were homogenous in-patient characteristics. Seven parameters representing patient well-being evaluated on NRS (0–10) and patient satisfaction scored on a 5-point scale were not statistically different between the two groups preoperatively and postoperatively. There were no statistically significant differences in secondary outcomes.

33. Wendling AL, Byun SY, Koenig M et al. Impact of oral carbohydrate consumption prior to cesarean delivery on preoperative well-being: a randomized interventional study. Arch Gynecol Obstet 2020; 301: 179-187. doi:10.1007/s00404-020-05455-z			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+ ROB 6/7	**Countries:** USA **Centers:** University of Florida College of Medicine **Setting:** n/a **Funding Sources:** I. Heermann Anesthesia Foundation **Dropout rates:** 30% **Study limitations:** Risk of Bias: low Inconsistency: n/a Indirectness: moderate Impreciseness: high Publication bias: n/a Nursing, obstetric, and anesthesiology staff were not always the same. Intraoperative intravenous	**Total no. patients:** 67 **Inclusion criteria:** ages 18–45, full-term pregnancy (≥ 37 weeks estimated gestational age), singleton gestation, and proficiency with the English language **Exclusion criteria:** pre-gestational or gestational diabetes mellitus, incomplete gestational diabetes screening test, his- tory of steroid administration within 7 days prior to planned delivery, history of magnesium sulfate administration in the setting of hypertensive disorder, current opioid use, fetuses with known congenital abnormalities or growth restriction, and women who were deemed American Society of	Three groups: CHO group (n=25): 710 mL of a clear CHO-rich beverage the evening prior to surgery and 355 mL the morning of surgery Group R (n=20): received an equal volume of commercial rehydration beverage at the same times Group F (n=22): Group F was instructed to have no oral intake for ≥ 8 h prior to surgery

	fluid and hemodynamic management was at the discretion of the treating team and could have varied	Anesthesiology physical class III or greater	
Notes	**Author's Conclusion:** Providing low-risk parturients presenting for scheduled cesarean delivery with either an oral high-dose CHO or common, commercial rehydration beverage improves patient well-being compared to prolonged fasting		
Outcome measures/results	**primary outcome**: assessed by visual analogue scales for hunger, thirst, anxiety, fatigue, and nausea administered on the morning of surgery prior to morning beverage consumption (time 1) and 60 min after the beverage (time 2) **Secondary outcomes**: intraoperative mean arterial pressure (MAP), total phenylephrine and ephedrine use, and postoperative satisfaction as assessed by the Quality of Recovery 40 questionnaire.	- both groups CHO and R showed improvements in the composite well-being score and with thirst, with no improvement in Group F - For hunger, group CHO showed some improvement after beverage consumption, while hunger worsened in group F - No differences were detected among groups regarding secondary outcomes except estimated blood loss for both intent-to-treat (p = 0.039) and as-treated (p = 0.038) analyses - Group CHO experienced the most estimated blood loss (863.3 ± 165.3), followed by group R (758.8 ± 215.2); group F (685.7 ± 151.2) had the lowest blood loss	

34.	**Yi HC, Ibrahim Z, Abu Zaid Z et al. Impact of Enhanced Recovery after Surgery with Preoperative Whey Protein-Infused Carbohydrate Loading and Postoperative Early Oral Feeding among Surgical Gynecologic Cancer Patients: An Open-Labelled Randomized Controlled Trial. Nutrients 2020; 12: 264. doi:10.3390/nu12010264**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1++ ROB 5/7	**Countries:** Malaysia **Centers:** single-center, National Cancer Institute, Putrajaya **Setting:** Surgical Gynecology Department **Funding Sources:** None **Dropout rates:** 0% **Study limitations:** Risk of Bias: moderate Inconsistency: n/a Indirectness: moderate Impreciseness: moderate Publication bias: n/a	**Total no. patients:** 118 **Inclusion criteria:** Ambulated Malaysian patients aged over 18 years and scheduled for elective surgery for suspected gynecologic cancer **Exclusion criteria:** Those who were allergic to soy or whey protein; diagnosed with chronic kidney diseases, ischemic heart disease or diabetes mellitus; or involved in other intervention studies	Two groups: Intervention group (n=62): standardized specially formulated drink in the evening 12 h before the operation and 3 h before operation. The drink that was provided in the evening before the operation consisted of 500 kcal, 100 g carbohydrate, and 18 g whey protein (total 474 mL), whilst the drink provided 3 h before the operation comprised 237 mL and provided 250 kcal, 50 g carbohydrate, and 9 g whey protein in a lactose-free, clear, tea-colored, fruit-flavored fluid. Control group (n=56): Their last meal was dinner, which was a minimum of 12 h before operation. Subjects started fasting from midnight on the day of operation

	Postoperative observation was limited to one-month, long-term effects not assessed; single-center study, and the protocol used might not be applicable to other hospitals.		
Notes	**Author's Conclusion:** high compliance on the multimodal ERAS with preoperative whey protein-infused CHO loading and postoperative early oral feeding shortened the length of postoperative hospital stay without increasing complications		
Outcome measures/results	**Primary outcomes:** postoperative outcomes (length of postoperative hospital stay, clear fluid toleration, food toleration, and bowel function return) between the intervention and control group **Secondary outcomes:** postoperative complications including postoperative nausea and vomiting, ileus, and infection		- trial found significant positive results which included shorter length of postoperative hospital stay (78.13 ± 33.05 vs. 99.49 ± 22.54 h); a lower readmission rate within one month PO (6% vs. 16%); lower weight loss (−0.3 ± 2.3 kg vs. −2.1 ± 2.3 kg); a lower C-reactive protein–albumin ratio (0.3 ± 1.2 vs. 1.1 ± 2.6); preserved muscle mass (0.4 ± 1.7 kg vs. −0.7 ± 2.6 kg); and better handgrip strength (0.6 ± 4.3 kg vs. −1.9 ± 4.7 kg) among CHO-P as compared with CO - no significant difference in mid-upper arm circumference and serum albumin level upon discharge

35. Onalan E, Andsoy, II, Ersoy OF. The Effect of Preoperative Oral Carbohydrate Administration on Insulin Resistance and Comfort Level in Patients Undergoing Surgery. J Perianesth Nurs 2019; 34: 539-550. doi:10.1016/j.jopan.2018.07.007			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+ ROB2 8/14	**Countries**: Turkey **Centers**: General Surgery Clinic of Karabuk University Training and Research Hospital **Setting**: Laparoscopic cholecystectomy **Funding Sources**: Scientific Research Project of Karab€uk University, project number KBÜ -BAP-15/2-YL-051 **Dropout rates**: 5.6%	**Total no. patients**: 53 **Inclusion criteria:** scheduled for laparoscopic cholecystectomy, age more than 18 years and less than 65 years, agreeing to participate in the study and signing the informed consent form. **Exclusion criteria:**history of diabetes (type 1 and 2), history of gestational diabetes, body mass index of 40 kg/m^2 or more, ASA group III or IV, administration if intravenous fluid before surgery,	<u>OCS (oral carbohydrate solution) group (n = 26)</u> The patients were given an oral glucose solution (Nutricia preop) containing 12.5% glucose, first 800 mL at 12 a.m., and then 400 mL at 6 a.m., 2 hours before the surgery. The solution was ingested in 10 minutes <u>Control group (n=27)</u> Food and water were cut off in the control group as of 12 a.m. the night before surgery. Both groups were not given intravenous fluid before surgery. The surgical intervention began between 8 and 9 a.m. in the morning in all patients. Surgery was conducted by the same surgeon.

	Study limitations: Risk of Bias: moderate Inconsistency: n/a Indirectness: low Impreciseness: moderate Publication bias: n/a Population did not include elderly patients, high-risk patients, or patients with an ASA Physical Status of III or higher; the safety and efficacy of preoperative OCS intake in these patients remain unclear.	liver and kidney failure, drug users whose blood glucose levels will be impacted, previous abdominal surgery, history of acute cholecystitis or acute pancreatitis, Patients for whom CO_2 insufflation is inconvenient in terms of anesthesia (heart failure, chronic obstructive pulmonary disease, and so forth), bleeding diathesis, immunosuppressive treatment, any infectious disease	
Notes	**Author's Conclusion:** This study indicates that OCS given before LC lowers the postoperative stress response and insulin resistance and improves patient comfort, and poses no risk at all. We believe that this study will contribute to future research, in that it is the first study to evaluate patient comfort using GCS in LC patients. However, if this view is to be supported, new randomized controlled clinical trials should be performed with a greater number of patients.		
Outcome measures/results	• Glucose and insulin levels 2 hours before, and at the first and third hour after the surgery. HOMA-IR was calculated from this. • General comfort scale • well-being, hunger, thirst, pain and anxiety by visual analog scales	Both groups were observed to have an increase in glucose levels over time. The increase in the glucose levels of the control group occurring over time was found to be statistically significant. In the control group, glucose levels at the third hour of surgery were significantly higher than baseline and those 2 hours before the operation. The mean insulin values measured at different times were not different from each other. In addition, no difference was found between patient groups regarding insulin levels. It was determined that there was no significant change in the HOMA-IR values in the OCS group over time, whereas a statistically significant increase was observed in the control group. The HOMA-IR values at the third hour of the surgical intervention in the control group were found to be significantly higher than those of baseline and those 2 hours before the surgery .The increase in HOMA-IR values of both groups was statistically significant. It was observed that hunger, thirst, anxiety, and pain were significantly lower in the OCS group.	

3.3 Ist eine Pause der oralen/enteralen Nahrungseinnahme nach einem chirurgischen Eingriff prinzipiell notwendig?

<u>Empfehlung 3</u>

Die orale/enterale Nahrungsaufnahme soll nach chirurgischen Eingriffen frühzeitig begonnen werden (BM, IE).

Empfehlungsgrad A

36. Willcutts KF, Chung MC, Erenberg CL, Finn KL, Schirmer BD, Byham-Gray LD Early oral feeding as compared with traditional timing of oral feeding after upper gastrointestinal surgery. Ann Surg 2016; 264: 54-63.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-analysis 1++	**Countries**: n/a **Centers**: n/a **Setting**: n/a **Funding Sources**: n/a **Dropout rates**: n/a **Study limitations**: -inherent clinical heterogeneity due to combining multiple types of upper GI surgery -methodological heterogeneity because of large variations of feeding start, composition of initial diet, the diet advancement regimen - supplemental nutrition support was provided in 4 studies (as their standard practice) -high risk of bias in one of the included studies	**Total no. patients**: n=2112 (15 trials) **Inclusion criteria:** adult patients undergoing (18 y of age) upper GI surgery p; allowed oral feeding early after surgery; report on least one of the following outcomes: postoperative nausea, postoperative vomiting, aspiration pneumonia, pneumonia, abdominal distention, anastomotic leak, anastomotic dehiscence, wound dehiscence, need for reinsertion of NGT, need for reoperation, tolerance of oral diet, time to return of bowel function, LOS, mortality, readmission rate, patient satisfaction, or quality of life; any study design; any language **Exclusion criteria:** Only children <18 y of age; Only non-upper GI surgery or combined upper GI surgery with other types of surgery and no subgroup analysis; Participants did not receive early oral feeding after surgery; Multimodal protocols; Review	We conducted a systematic review and meta-analysis to compare the effects of early oral feeding to traditional (or late) timing of oral feeding after upper gastrointestinal surgery on clinical outcomes.

		articles, protocol descriptions, comments; published before January 1, 1980	
Notes	**Author's Conclusion:** Early postoperative oral feeding as compared with traditional (or late) timing is associated with shorter hospital length of stay and is not associated with an increase in clinically relevant complications.		
Outcome measures/results	**Primary outcome measures:** anastomotic leaks, pneumonia, nasogastric tube reinsertion, reoperation, readmissions, mortality		Fifteen studies comprising 2112 adult patients met all the inclusion criteria. Mean hospital stay was significantly shorter in the early-fed group than in the late-fed group [weighted mean difference = -1.72 d, 95% confidence interval (CI) -1.25 to -2.20, P < 0.01). Postoperative length of stay was also significantly shorter (weighted mean difference = -1.44 d, 95% CI -0.68 to -2.20, P < 0.01). There was no significant difference in risk of anastomotic leak, pneumonia, nasogastric tube reinsertion, reoperation, readmission, or mortality in the randomized controlled trials (RCTs). The pooled RCT and non-RCT results, however, showed a significantly lower risk of pneumonia in early-fed as compared with late-fed group (odds ratio = 0.6, 95% CI 0.41-0.89, P = 0.01).

37. Fearon KC, Ljungqvist O, Von Meyenfeldt M, Revhaug A, Dejong CH, Lassen K, Nygren J, Hausel J, Soop M, Andersen J, Kehlet H Enhanced recovery after surgery: a consensus review of clinical care for patients undergoing colonic resection. Clin Nutr 2005; 24:466-477.
See No. 2

38. 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; (4):CD004080.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis 1++	**Countries:** n/a **Centers:** n/a **Setting**: n/a **Funding Sources**: n/a **Dropout rates**: n/a **Study limitations**: see notes.	**Total no. patients**: 942 patients **Inclusion criteria:** Trials had to be published in a peer-reviewed indexed journal, only randomized or controlled clinical trials were eligible for meta-analysis. According to the ERAS working groups' recommendations, an ERAS program should incorporate 17 items. The difference in the number of	two separate study groups were used: first studies looking at laparoscopically operated patients that receive either ERAS or conventional aftercare; second, studies looking at laparoscopic versus open operative techniques while all patients are treated using ERAS.

		interventions used between the conventional and ERAS groups has to be large enough in order to judge the effect of the intervention named ERAS. **Exclusion criteria:** Dual publications or late follow-up from earlier trials was excluded from meta-analysis.	
Notes	Methodological quality of studies was moderate to poor overall with exception of the LAFA trial. Especially blinding of outcome assessors and clinicians was lacking. This could have resulted in observer bias, especially for outcome parameters like hospital stay. Time lag bias could have been introduced by the fact that trials significantly diverge in the time frame included trials were undertaken. Not all studies included used high number of ERAS items in their protocols, and some items (especially thoracic epidural analgesia) were used in the conventional protocol. Although all included studies satisfied the condition of using at least seven items in the ERAS protocol, this ranged between eight and almost all items. This could have introduced bias concerning the exact effect of ERAS as opposed to conventional care. The combination of these methodological limitations and bias could have influenced meta-analysis outcome and also the conclusions for clinical implications. **Author's Conclusion:** When laparoscopy and ERAS are combined, major morbidity and hospital stay are reduced. The reduction in morbidity seems to be due to laparoscopy rather than ERAS, so laparoscopy by itself offers independent advantages beyond ERAS care. Quality of included studies was moderate to poor, so conclusions should be regarded with some reservations.		
Outcome measures/results	**Primary outcome parameters:** Morbidity, Mortality, Readmissions, Length of hospital stay **Secondary outcome parameters:** Quality of life, Gastrointestinal function, Pain and pain medication, Cost **Other outcome parameters:** Protocol compliance	Primary search resulted in 319 hits. After inclusion criteria were applied, three RCTs and six CCTs were included in the meta-analysis. For laparoscopically operated patients with/without ERAS, no differences in morbidity were found and postoperative hospital stay favored ERAS (MD -2.34 [-3.77, -0.91], Z = 3.20, p = 0.001). When comparing laparoscopy and open surgery within ERAS, major morbidity was significantly reduced in the laparoscopic group (OR 0.42 [0.26, 0.66], Z = 3.73, p = 0.006). Other outcome parameters showed no differences. Quality of included studies was considered moderate to poor overall with small sample sizes.	

39. Greco M, Capretti G, Beretta L, Gemma M, Pecorelli N, Braga M. Enhanced recovery program in colorectal surgery: a meta-analysis of randomized controlled trials. World J Surg. 2014; 38:1531-41.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-analysis 1++	**Countries:** n/a **Centers:** n/a	**Total no. patients**: n=2376 (16RCTs)	We searched for RCTs comparing the ERAS pathway to conventional perioperative care.

	Setting: n/a **Funding Sources**: n/a **Dropout rates**: n/a **Study limitations**: n/a	**Inclusion criteria:** random allocation to treatment, colorectal surgery, and comparison between ERAS and standard treatment with no restriction on primary or secondary outcome **Exclusion criteria:** duplicate publications (in this case, only the article reporting the longest follow-up was abstracted), nonhuman experimental studies, other surgical settings, trials evaluating single aspects of ERAS, lack of data on principal outcomes	
Notes	**Author's Conclusion:** The ERAS pathway reduced overall morbidity rates and shortened the length of hospital stay, without increasing readmission rates. A significant reduction in nonsurgical complications was evident, while no significant reduction was found for surgical complications.		
Outcome measures/results	**Primary outcome measures:** overall morbidity rate, surgical complications (surgical site infections and anastomotic leakage), nonsurgical complications (cardiovascular, respiratory, urinary tract infections) **Secondary outcome measures:** LOS, readmission rate, mortality, and ileus.	A total of 2,376 patients in 16 RCTs were included in the analysis. The ERAS pathway was associated with a reduction of overall morbidity [relative ratio (RR) = 0.60, (95 % CI 0.46–0.76)], particularly with respect to nonsurgical complications [RR = 0.40, (95 % CI 0.27–0.61)]. The reduction of surgical complications was not significant [RR = 0.76, (95 % CI 0.54–1.08)]. The ERAS pathway shortened hospital stay (WMD = -2.28 days [95 % CI –3.09 to –1.47]), without increasing readmission rate.	

40. 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; 35:473-487.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis 1++	**Countries:** n/a **Centers:** n/a **Setting**: n/a **Funding Sources**: n/a **Dropout rates**: n/a **Study limitations**:	**Total no. patients**: 1240 patients **Inclusion criteria:** Only RCTs with primary comparisons between early and traditional feeding practices, Studies were required to have	Databases were searched to identify randomized controlled trials comparing the outcomes of early and traditional postoperative feeding. Trials involving gastrointestinal tract resection followed by patients receiving nutritionally significant oral or enteral intake within 24 hours after surgery were included for analysis.

	First, in an attempt to standardize the differences in reporting between articles, we contacted several authors for clarification of reported data or additional information within their published data. In cases where no response was returned, assumptions relating to the interpretation of various aspects of their published reports were made, such as the composition of the fluid diets reported or discrepancies in the reporting within the article. For these reasons, although every attempt has been made to ensure that analyzed studies met inclusion criteria and that other data are accurate, there may still be errors that confound the results obtained. Second, the studies that met inclusion criteria for this meta-analysis consistently yielded poor scores for methodological quality using the Jadad scoring system. Of a possible score of 5, a mean score of 1.9	reported clinically relevant outcomes and to have been conducted in adults (>18 years i.e., people older than) undergoing elective resectional surgery for whom early feeding was provided proximal to the anastomosis. **Exclusion criteria:** Unpublished studies and abstracts presented at national and international as well as duplicate publications	

	was achieved, with a maximum score of 3.		
Notes	**Author's Conclusion:** Early postoperative nutrition is associated with significant reductions in total complications compared with traditional postoperative feeding practices and does not negatively affect outcomes such as mortality, anastomotic dehiscence, resumption of bowel function, or hospital length of stay.		
Outcome measures/results	total complications (defined as any complication reported within the postoperative period, excluding mortality and nausea/vomiting;) anastomotic dehiscence; in-hospital mortality; days to passage of bowel motion; days to passage of flatus; hospital length of stay (LOS); and NG tube reinsertion		Fifteen studies involving a total of 1240 patients were analyzed. A statistically significant reduction (45%) in relative odds of total postoperative complications was seen in patients receiving early postoperative feeding (odds ratio [OR] 0.55; confidence interval [CI], 0.35 –0.87, P = .01). No effect of early feeding was seen with relation to anastomotic dehiscence (OR 0.75; CI, 0.39–1.4, P = .39), mortality (OR 0.71; CI, 0.32–1.56, P = .39), days to passage of flatus (weighted mean difference [WMD] –0.42; CI, –1.12 to 0.28, P = .23), first bowel motion (WMD –0.28; CI, –1.20 to 0.64, P = .55), or reduced length of stay (WMD –1.28; CI, –2.94 to 0.38, P = .13); however, the direction of clinical outcomes favored early feeding. Nasogastric tube reinsertion was less common in traditional feeding interventions (OR 1.48; CI, 0.93–2.35, P = .10).

41. Varadhan KK, Neal KR, Dejong CH, Fearon KC, Ljungqvist O, Lobo DN The enhanced recovery after surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: a meta-analysis of randomized controlled trials. Clin Nutr 2010; 29:434-440.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-analysis 1++	**Countries:** n/a **Centers:** n/a **Setting**: n/a **Funding Sources**: Research Fellowship from the Nottingham Digestive Diseases Centre NIHR Biomedical Research Unit, Fresenius Kabi **Dropout rates**: n/a **Study limitations**: n/a	**Total no. patients**: n= 452 (6 RCTs) **Inclusion criteria:** Studies comparing enhanced recovery programs with traditional perioperative care in patients undergoing major elective open colorectal surgery were selected from the initial search. RCTs documenting the individual elements of the ERAS pathway that were implemented, with a minimum of four elements covering the pre-, intra- and postoperative periods of the ERAS pathway	Medline, Embase and Cochrane database searches were performed for relevant studies published between January 1966 and November 2009. All randomized controlled trials comparing ERAS with conventional perioperative care were selected.

		Exclusion criteria: Non-randomized studies, case-controlled trials, cohorts, retrospective studies	
Notes	**Author's Conclusion:** ERAS pathways appear to reduce the length of stay and complication rates after major elective open colorectal surgery without compromising patient safety.		
Outcome measures/results	primary outcome measure: length of primary hospital stay secondary outcome measures: postoperative complications (total number of patients with complications in each group), readmission rates and mortality		Six randomized controlled trials with 452 patients were included. The number of individual ERAS elements used ranged from 4 to 12, with a mean of 9. The length of hospital stay [weighted mean difference (95% confidence interval): −2.55 (−3.24, −1.85)] and complication rates [relative risk (95% confidence interval): 0.53 (0.44, 0.64)] were significantly reduced in the enhanced recovery group. There was no statistically significant difference in readmission and mortality rates.

42. Lewis SJ, Andersen HK, Thomas S Early enteral nutrition within 24 h of intestinal surgery versus later commencement of feeding: a systematic review and meta-analysis. J Gastrointest Surg 2009; 13:569-575.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis 1++	**Countries:** n/a **Centers:** n/a **Setting**: n/a **Funding Sources**: n/a **Dropout rates**: n/a **Study limitations**: The13randomised trials identified were clinically heterogenous and most of them were small and of suboptimal methodological quality. Combining trials that differ in terms of underlying condition, operation and intervention may not be appropriate.	**Total no. patients**: n = 1173 patients of 13 trials **Inclusion criteria:** We defined early enteral nutrition as any oral caloric intake (i.e. normal diet or nutritional supplements) or any kind of tube feeding (gastric, duodenal or jejunal) commenced within 24 h of gastrointestinal surgery. The control arm is traditional management, defined as no caloric oral intake or tube feeding within 24 h post-operatively. **Exclusion criteria:** Studies on parenteral nutrition	We looked for randomized controlled trials comparing early commencement of feeding (within 24 h) with no feeding in patients undergoing gastrointestinal surgery.
Notes	Methods of randomization and blinding of outcome assessments were not described in sufficient detail, which means that the uncertainty regarding the methodological quality of trails remains.		

	Author's Conclusion: There is no obvious advantage in keeping patients "nil by mouth" following gastrointestinal surgery. Early enteral nutrition is associated with reduced mortality, though the mechanism is not clear. This review supports the notion that early commencement of enteral feeding may be of benefit.	
Outcome measures/results	Pneumonia, wound infections, intrabdominal abscess, anastomotic leakage, length of hospital stay and mortality within 30 days post-operatively. Adverse events such as nausea and vomiting	Mortality was reduced with early postoperative feeding. Early post-operative feeding increased vomiting. The direction of effect is suggestive of a reduction of risk of post-surgical complications and reduced length of hospital stay.

43. Mazaki T, Ebisawa K Enteral versus parenteral nutrition after gastrointestinal surgery: a systematic review and meta-analysis of randomized controlled trials in the English literature. J Gastrointest Surg 2008 12:739-755.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis 1++	**Countries:** n/a **Centers:** n/a **Setting**: n/a **Funding Sources**: n/a **Dropout rates**: n/a **Study limitations**: n/a	**Total no. patients**: n= 2552 (29 RCTs) **Inclusion criteria:** Randomized controlled trials (RCTs) that compared enteral nutrition with parenteral nutrition in adult patients following elective gastrointestinal surgery were eligible for inclusion in the review **Exclusion criteria:** trials that evaluated only nutritional or physiological outcomes; trials of home-based parenteral nutrition; trials that included patients undergoing transplantation surgery, chemotherapy, or radiotherapy; trials of critically-ill patients; and trials located in developing countries.	In all included trials, enteral nutrition commenced within six to 24 hours after surgery. The included patients underwent a variety of upper- and lower-gastrointestinal surgeries (including esophageal, gastric, pancreatic, colorectal, small/large bowel, and hepatic surgery). Most of the included trials were of patients with malignant, or malignant and benign conditions (where reported). Enteral nutrition was delivered mainly through a naso-jejunal or catheter jejunostomy. Control patients received total parenteral nutrition or peripheral parenteral nutrition. Five trials were conducted in the UK.
Notes	**Notes:** The review question was clear and was supported by potentially reproducible inclusion criteria for all aspects apart from outcomes, which appeared to be loosely defined. The search strategy included some relevant data sources. Unpublished data were included in the review. The language restriction to English papers might mean that relevant studies were missed, and language bias was a potential threat. The review process was poorly-reported, with only the data extraction process indicating that attempts were made to minimize error and bias.		

	Appropriate quality assessment components were applied to the included trials, and the results of this assessment were developed in the analysis. Trial characteristics were presented in sufficient detail. The chosen method of synthesis was appropriate. An extensive exploration of trial variation was carried out. The authors' conclusions reflected the evidence presented. The under-reporting of how trials were selected and quality assessed means that some caution is warranted when judging the reliability of this review. **Author's Conclusion:** Enteral nutrition after gastrointestinal surgery was associated with a significant reduction in the incidence of any complication, any infectious complication, anastomotic leaks, intra-abdominal abscesses, and length of stay in hospital.	
Outcome measures/results	primary outcomes: number of patients with any complication, any infectious complication and mortality. Secondary outcomes: were the number of patients with wound infections or dehiscence, anastomotic leaks, intra-abdominal abscesses, pneumonia, respiratory failure, urinary tract infections, renal failure, adverse effects, and length of hospital stay.	Twenty-nine trials, which included 2,552 patients, met the criteria. EN was beneficial in the reduction of any complication (relative risk (RR), 0.85; 95% confidence interval (CI), 0.74–0.99; P =0.04), any infectious complication (RR, 0.69; 95% CI, 0.56 – 0.86; P =0.001), anastomotic leak (RR, 0.67; 95% CI, 0.47 – 0.95; P =0.03), intraabdominal abscess (RR, 0.63; 95% CI, 0.41 – 0.95; P =0.03), and duration of hospital stay (weighted mean difference, − 0.81; 95% CI, − 1.25 – 0.38; P = 0.02). There were no clear benefits in any of the other complications.

44. Lewis SJ, Egger M, Sylvester PA, Thomas S Early enteral feeding versus "nil by mouth" after gastrointestinal surgery: systematic review and meta-analysis of controlled trials. BMJ 2001; 323:773-776.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis 1++	**Countries:** n/a **Centers:** n/a **Setting**: n/a **Funding Sources**: n/a **Dropout rates**: n/a **Study limitations**: n/a	**Total no. patients**: n = 837 patients (11 RCTs) **Inclusion criteria:** Clinical trials were eligible if patients had undergone elective gastrointestinal surgery and were randomly allocated to receive either enteral feeding (within 24 hours after surgery) or the traditional management of nil by mouth and intravenous fluids with introduction of enteral fluids and diet as tolerated. **Exclusion criteria:** n/a	A Systematic review and meta-analysis of randomized controlled trials comparing any type of enteral feeding started within 24 hours after surgery with nil by mouth management in elective gastrointestinal surgery was conducted to assess the evidence on benefit and harm of early enteral feeding.
Notes	**Author's Conclusion:**		

	There is little evidence from these trials that keeping patients nil by mouth is beneficial after elective gastro-intestinal resection. Although the data are clearly insufficient to conclude that early feeding is of proved benefit, we believe that there is a good case for an adequately powered clinical trial to assess early enteral feeding in such patients. With anastomotic dehiscence as the primary end point, such a trial would need to enroll about 1000 patients in each arm and would therefore involve several Centers.	
Outcome measures/results	Anastomotic dehiscence, infection of any type, wound infection, pneumonia, intra-abdominal abscess, length of hospital stay, mortality	Early feeding reduced the risk of any type of infection (relative risk 0.72, 95% confidence interval 0.54 to 0.98, P = 0.036) and the mean length of stay in hospital (number of days reduced by 0.84, 0.36 to 1.33, P = 0.001). Risk reductions were also seen for anastomotic dehiscence (0.53, 0.26 to 1.08, P = 0.080), wound infection, pneumonia, intra-abdominal abscess, and mortality, but these failed to reach significance (P > 0.10). The risk of vomiting was increased among patients fed early (1.27, 1.01 to 1.61, P = 0.046).

45. Elmore MF, Gallagher SC, Jones JG, Koons KK, Schmalhausen AW, Strange PS Esophagogastric decompression and enteral feeding following cholecystectomy: a controlled, randomized prospective trial. JPEN J Parenter Enteral Nutr 1989; 13:377-381.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries:** USA **Centers:** St. Francis Hospital Center Beech Grove, Indiana **Setting**: n/a **Funding Sources**: n/a **Dropout rates**: n/a **Study limitations**: n/a	**Total no. patients**: n= 114 **Inclusion criteria:** n/a **Exclusion criteria:** n/a	Group I: as control (patients received only intravenous fluids postoperatively and ate, when they were able to) Group II: intravenous fluids and esophagogastric decompression Group III: esophagogastric decompression and enteral sterile water through the duodenal feeding lumen Group IV: esophagogastric decompression and infusion of an elemental diet through the feeding lumen decompression Type of Surgery: cholecystectomy
Notes	**Author's Conclusion:** It is concluded that there is no objective benefit to the routine use of esophagogastric decompression with or without enteral nutrition in elective cholecystectomy patients.		
Outcome measures/results	cholecystectomy		The results of the study indicated no statistically or clinically significant differences among any of the treatment groups regarding. It is concluded that there is no objective benefit to the routine use of esophagogastric decompression with or without enteral nutrition in elective cholecystectomy patients.

46. Feo CV, Romanini B, Sortini D, Ragazzi R, Zamboni P, Pansini GC, Liboni A Early oral feeding after colorectal resection: a randomized controlled study. ANZ J Surg 2004; 74:298-301.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries:** Italy **Centers:** Department of Surgery of a public University teaching hospital **Setting**: n/a **Funding Sources**: n/a **Dropout rates**: n/a **Study limitations**: n/a	**Total no. patients**: n = 100 **Inclusion criteria:** All patients who underwent an elective colorectal resection for cancer at our institution between March 2000 and July 2002 **Exclusion criteria:** all patients with previous abdominal operations, cancer of the lower rectum, requiring low anterior or abdominal-peritoneal resection, metastatic disease	Group A: NG catheter and fasting until passage of flatus, followed by liquid diet advanced to soft-solid Group B: No NG tube, clear liquids the day after surgery, followed by soft-solid food. Type of Surgery: colorectal resection
Notes	**Author's Conclusion:** In conclusion, our data show that the majority of patients undergoing elective colorectal resection for cancer can be managed postoperatively without NG decompression and can be started on oral feeding as early as the first postoperative day. Albeit, no reduction in postoperative hospital stay or patients' well-being could be shown, elimination of postoperative NG tubes with early oral feeding was a safe approach, with only a minority of patients requiring NG catheter insertion because of repeated vomiting.		
Outcome measures/results	the effect of early oral feeding without NG decompression following elective colorectal resection for cancer The endpoints were: (i) morbidity; (ii) resumption of intestinal function; (iii) length of hospital stay; (iv) patients' well being evaluated by short-form health survey (SF-36).		Twelve complications occurred in group A (50 patients) and 13 in group B (50 patients) (P = NS). Seven patients developed vomiting in group A as compared to 16 in group B (P< 0.05). Twenty per cent of patients required NG decompression in group B hence 80% did not need NG tubes. Resumption of intestinal function occurred after 4 days, and length of hospital stay was 7 days in both groups. No significant difference was detected between groups (P = NS) in the SF-36 score change before and after the operation.

47. Reissman P, Teoh TA, Cohen SM, Weiss EG, Nogueras JJ, Wexner SD Is early oral feeding safe after elective colorectal surgery? A prospective randomized trial. Ann Surg 1995; 222:73-77.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries:** n/a **Centers:** n/a	**Total no. patients**: n = 161 **Inclusion criteria:**	group 1: early oral feeding group 2: regular feeding

	Setting: n/a **Funding Sources**: n/a **Dropout rates**: n/a **Study limitations**: n/a	All consecutive patients who underwent elective laparotomy with Bowel resection between November 1992 and April 1994 **Exclusion criteria:** n/a	The nasogastric tube was removed from all patients in both groups immediately after surgery. Type of surgery: laparotomy with either colon or small bowel resection
Notes	The randomization is mentioned but method not specified and will downgrade the study **Author's Conclusion:** Early oral feeding after elective colorectal surgery is safe and can be tolerated by the majority of patients. Thus, it may become a routine feature of postoperative management in these patients.		
Outcome measures/results	To prospectively assess the safety and tolerability of early oral feeding after elective "open" abdominal colorectal operations.		One Hundred sixty-one consecutive patients were studied, 80 Patients in group 1 (34 males and 46 females, mean age 51 years [range 16-82 years]), and 81 patients in group2 (43males and38 females, mean age 56 years [range 20-90 years]). Sixty-three patients (79%) in the early feeding group tolerated the early feeding schedule and Were advanced to regular diet within the next 24 to 48 hours. There were no significant differences between the Early and regular feeding groups in the rate of vomiting (21% vs. 14%), nasogastric tube reinsertion (11%vs. 10%), length of ileus (3.8 ± 0.1 days vs. 4.1 ± 0.1 days), length of hospitalization (6.2 ± 0.2 days vs. 6.8 ± 0.2 days), or overall complications (7.5% vs. 6.1%), respectively, (p = NS for all). However, the patients in the early feeding group tolerated a regular diet significantly earlier than did the patients in the regular feeding group (2.6 ± 0.1 days vs. 5 ± 0.1 days; $p < 0.001$).

48. Barlow R, Price P, Reid TD, Hunt S, Clark GW, Havard TJ, Puntis MC, Lewis WG Prospective multicentre randomised controlled trial of early enteral nutrition for patients undergoing major upper gastrointestinal surgical resection. Clin Nutr 2011; 30:560-566.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries:** UK **Centers:** three NHS Trusts, which were part of the South East Wales Upper Gastrointestinal Cancer Network **Setting**: n/a **Funding Sources**: This trial was funded by a grant awarded to Dr. Rachael	**Total no. patients**: n = 121 • ENN = 64 • CON = 57 **Inclusion criteria:** All adult patients admitted with a suspected upper gastrointestinal malignancy and referred for major elective surgery **Exclusion criteria:**	121 patients with suspected operable upper GI-cancer (54 esophageal, 38 gastric, 29 pancreatic) were randomized to receive EEN (n = 64) or Control management postoperatively (nil by mouth and IV fluid, n = 57). Type of surgery: major upper gastrointestinal surgical resection

	Barlow; Leading Practice Through Research from The Health Foundation, London, United Kingdom **Dropout rates**: n/a **Study limitations**: The heterogeneous nature of the patients diagnoses and surgery; Treatment allocation was not concealed; No placebo was used because of the risk of placebo associated physiological effect	age under 18 years; unable or unwilling to give informed consent; pregnancy; pre-operative infection; previous intestinal surgery resulting in residual small intestine length of less than 100 cm.	
Notes	**Author's Conclusion:** This randomized clinical trial has shown an important, clinically and statistically significant improvement in outcomes associated with EEN by means of feeding jejunostomy in patients undergoing major upper gastrointestinal surgical resection, with major clinical implications for individual tailored integrated care pathways and broader economic implications for healthcare networks and systems. EEN was associated with significantly shortened length of hospital stay and improved clinical outcomes. These findings reinforce the potential benefit of early oral nutrition in principle and as championed within enhanced recovery after surgery programs.		
Outcome measures/results	**Primary outcome measures:** Length of hospital stay (LOHS) **Secondary outcome measures:** were operative morbidity and mortality, including minor and major complications; patients were reviewed at 6 and 12 weeks post-discharge, and readmission rates during that period were documented.	Operative morbidity was less common after EEN (32.8%) than Control management (50.9%, p = 0.044), due to fewer wound infections (p = 0.017), chest infections (p = 0.036) and anastomotic leaks (p = 0.055). Median length of hospital stay was 16 days (IQ = 9) after EEN compared with 19 (IQ = 11) days after Control management (p = 0.023).	

49. Han-Geurts IJ, Hop WC, Kok NF, Lim A, Brouwer KJ, Jeekel J Randomized clinical trial of the impact of early enteral feeding on postoperative ileus and recovery. Br J Surg 2007; 94:555-561.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1++	**Countries:** Netherland **Centers:** two teaching and one non-teaching hospitals **Setting**: n/a	**Total no. patients**: n = 128 • Free diet group n= 61 • Conventional group n= 67 **Inclusion criteria:**	67 were randomized to a conventional return to diet, and 61 to a regimen allowing resumption of an oral diet as soon as tolerated (free diet group). Type of surgery: open colorectal or abdominal vascular surgery

	Funding Sources: n/a **Dropout rates**: n/a **Study limitations**: fewer patients were recruited than expected, which affects the level of significance of the results; Furthermore, the group size was too small for anastomotic leakage to be attributed to diet.	Patients awaiting elective open colorectal or aortic aneurysm surgery were enrolled in the trial; patients at age of >18 years and were not participating in another study at the time patients were all mentally competent, able to speak and understand the Dutch language gave written informed consent to participate **Exclusion criteria:** n/a	
Notes	**Author's Conclusion:** In conclusion, most patients tolerate early resumption of oral intake after operation, despite incomplete recovery of gastrointestinal function, and this does not lead to a higher postoperative complication rate. There appears to be no reason to withhold oral intake following open colorectal or abdominal vascular surgery.		
Outcome measures/results	**Primary outcome measures:** reinsertion of a nasogastric tube. **Secondary outcome measures:** interval between operation and tolerance of a normal diet, duration of hospital stay and complications. Bowel function was assessed by time to first bowel sound, flatulence and time to first defecation.	Early resumption of oral intake does not diminish the duration of postoperative ileus or lead to a significantly increased rate of nasogastric tube reinsertion. Tolerance of oral diet is not influenced by gastrointestinal functional recovery. As there is no reason to withhold oral intake following open colorectal or abdominal vascular surgery, postoperative management should include early resumption of diet.	

50. Carrere N, Seulin P, Julio CH, Bloom E, Gouzi JL, Pradere B Is nasogastric or nasojejunal decompression necessary after gastrectomy? A prospective randomized trial. World J Surg 2007; 31:122-127.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries:** France **Centers:** single center study, Department of Gastrointestinal Surgery (Pr Prade re), Purpan University Hospital, CHU de Toulouse **Setting**: n/a **Funding Sources**: n/a	**Total no. patients**: n = 84 **Inclusion criteria:** patients undergoing elective partial or total gastrectomy for carcinoma or benign disease **Exclusion criteria:** patients with emergency surgery, history of abdominal irradiation, additional resection of adjacent	Group 1 with postoperative nasogastric or nasojejunal tube (Tube Group, n = 43) vs. group 2 without a tube (No-tube Group, n = 41). Type of Surgery: partial or total gastrectomy

	Dropout rates: n/a **Study limitations**: this study was underpowered to demonstrate any differences in complication rate	organs, or technical operative difficulties (duodenal, pancreatic, or vascular injury)	
Notes	Downgrading to + because of small sample size **Author's Conclusion:** Routine prophylactic postoperative nasogastric decompression is unnecessary after elective gastrectomy.		
Outcome measures/results	Gastrointestinal function, postoperative course (time to first passage of flatus, first oral intake, duration of postoperative perfusions, postoperative hospital stay) and complications were assessed.		No significant differences in postoperative mortality or morbidity, especially fistula or intra-abdominal sepsis, were observed between the groups. Passage of flatus ($P < 0.01$) and start of oral intake ($P < 0.01$) were significantly delayed in the Tube Group. Duration of postoperative perfusion ($P = 0.02$) and length of hospital stay ($P = 0.03$) were also significantly longer in the Tube Group. Rates of nausea and vomiting were similar in the two groups. Moderate to severe discomfort caused by the tube was observed in 72% of patients in the Tube Group. Insertion of a nasogastric or nasojejunal tube was necessary in 5 patients in the No-tube Group (12%).

51. Lassen K, Kjaeve J, Fetveit T, Tranø G, Sigurdsson HK, Horn A, Revhaug A Allowing normal food at will after major upper gastrointestinal surgery does not increase morbidity: a randomized multicenter trial. Ann Surg. 2008; 247:721-729.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries:** Norway **Centers:** n/a **Setting**: n/a **Funding Sources**: n/a **Dropout rates**: n=6 (1.32%) **Study limitations**: - group heterogeneity within subgroup analysis - 17 percent of the patients were lost to post discharge follow-up at 8 weeks	**Total no. patients**: n=453 • EFT group n=227 • Normal food at will group n=220 **Inclusion criteria:** Adults undergoing both scheduled and emergency major upper gastrointestinal surgery (hepatic, pancreatic, esophageal, and gastric resections, bilioenteric and gastroenteric bypass procedures, and miscellaneous procedures	EFT (enteral tube feeding by needle-catheter jejunostomy) group -enteral feeding starting on postoperative day 1; maximum of 450 mL of water per day was allowed by mouth; At postoperative day 6 the patients were allowed food at will and enteral infusion halted Normal diet group - allowed normal food at will

		(e.g., ileus with gross small bowel distension and severe contamination of the upper abdominal cavity after gut perforation) where tradition would indicate nil-by-mouth postoperatively) **Exclusion criteria:** Patients with severe extra-abdominal disease or trauma, life expectancy less than 3 months, short bowel or other undisputed indication for parenteral nutrition	
Notes	All patients were invited to a physical follow-up about 8 weeks after discharge to assess trial outcome. **Author's Conclusion:** Allowing patients to eat normal food at will from the first day after major upper GI surgery does not increase morbidity compared with traditional care with nil-by-mouth and enteral feeding.		
Outcome measures/results	**Primary outcome measures:** major complications and death during hospital stay and within 8 week **Secondary outcome measures:** minor complications, adverse events, gut-recovery indicators (time to bowel movement and selective use of nasogastric tube), indicators for underfeeding (clinically indicated selective use of parenteral nutrition and weight loss), length of stay	Four hundred fifty-three patients who underwent major open upper GI surgery in 5 centers were enrolled between 2001 and 2006. Four hundred forty-seven patients were correctly randomized. Of 227 patients 76 (33.5%) had major complications in the ETF group compared with 62 (28.2%) of 220 patients allowed normal food at will (P = 0.26, 95% CI for the difference in rate from -3.3 to 13.9). In the ETF group, 36 (15.9%) patients were reoperated compared with 29 (13.2%) in the group allowed normal food at will (P = 0.50) and 30-day mortality was 10 (4.4%) of 227 and 11 (5.0%) of 220 patients, respectively (P = 0.83). Time to resumed bowel function was significantly in favor of allowing normal food at will (P = 0.01), as were the total number of major complications, length of stay, and rate of postdischarge complications.	

52. Hur H, Kim SG, Shim JH, Song KY, Kim W, Park CH, Jeon HM Effect of early oral feeding after gastric cancer surgery: a result of randomized clinical trial. Surgery 2011; 149:561-568.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries:** Korea **Centers:** n/a	**Total no. patients**: n= 54 • Early feeding group n= 28	early feeding group

	Setting: n/a **Funding Sources**: Catholic Cancer Center, Seoul St. Mary's Hospital, The Catholic University of Korea. **Dropout rates**: n/a **Study limitations**: discharge criterion in this study might be somewhat subjective to evaluate the effect of early oral feeding	• Control group n= 26 **Inclusion criteria:** Gastric adenocarcinoma by endoscopic biopsy; 20 ≤ Age ≤75; Possible curative respectability; ASA < 3; Informed consent **Exclusion criteria:** Patients who simultaneously have another type of cancer, had undergone a prior gastric resection or cancer with bleeding, perforation, or obstruction, patients who were or were to become pregnant or were diabetic on insulin	-began a liquid diet on the second postoperative day, and then were fed a soft diet from the third day until the day they were discharged control group -began a liquid diet on the fourth day Type of Surgery: Curative surgery for gastric cancer
Notes	**Author's Conclusion:** Our study did not show significantly better results for early oral feeding compared with conventional feeding with regard to postoperative morbidity, pain, gastrointestinal symptoms, and hospital costs. As mentioned previously, multimodal critical regimens, including proper pain control and the supplementation of preoperative oral carbohydrates, may have provided positive results. In addition, our trial was conducted at a single center and was limited by the number of patients enrolled. Therefore, a multicenter RCT including multimodal care may provide more clinical evidence supporting early oral feeding after gastric cancer surgery.		
Outcome measures/results	**Primary outcome measures:** duration of hospital stay **Secondary outcome measures**: postoperative mortality and morbidity within 30 days, recovery of bowel function, postoperative symptoms, intensity of pain, overall cost of hospitalization, QOL		No significant differences were found in the clinico-operative characteristics between the 2 groups. The duration of hospitalization (P = .044) and time until flatus (P = .036) in the early group were decreased significantly. With regard to the rates of morbidity, cost of hospitalization, postoperative symptoms, and pain scales, no significant differences were found. The quality of life scores were decreased significantly at the fatigue (P = .007) and nausea and vomiting (P = .048) immediately after operation in the early feeding group.

53. Schwenk W, Bohm B, Haase O, Junghans T, Muller JM Laparoscopic versus conventional colorectal resection: a prospective randomised study of postoperative ileus and early postoperative feeding. Langenbecks Arch Surg 1998; 383:49-55.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1-	**Countries:** n/a **Centers:** n/a **Setting**: n/a **Funding Sources**: n/a	**Total no. patients**: n = 60 • Laparoscopic n = 30 • Conventional n = 30	We performed this trial to assess If a shorter duration of postoperative ileus and earlier oral alimentation of patients may be a clinically relevant benefit of laparoscopic compared with conventional

	Dropout rates: n/a **Study limitations**: n/a	**Inclusion criteria:** n/a **Exclusion criteria:** n/a	colorectal resection. Therefore, patients were randomized to either laparoscopic or conventional resection of colorectal tumors. Type of surgery: resection of colorectal tumors
Notes	**Author's Conclusion:** The shorter duration of postoperative ileus allows earlier restoration of oral feeding after laparoscopic compared with conventional colorectal resection and therefore increases quality of life immediately after resection of colorectal tumors.		
Outcome measures/results	**Primary outcome measures:** Postoperative time to the first bowel movement and the time until oral feeding without parenteral alimentation were tolerated **Secondary outcome measures:** postoperative interval to the first peristalsis and first passage of flatus, the distribution of radio-opaque markers in abdominal radiographs on day 3 and day 5		Age, gender, ASA-classification and type of resection were comparable in the two groups. Peristalsis was first noticed 26+/-9 h after laparoscopic and 38+/-17 h after conventional colorectal resection (P<0.01). First flatus occurred 50+/-19 h after laparoscopic and 79+/-21 h after conventional surgery (P<0.01). The incidence of postoperative vomiting was similar in both groups. Three days after surgery radio-opaque markers were found more often in the right colon (P<0.01) and less often in the small intestine (P<0.05) in laparoscopic compared with conventional patients. Five days after laparoscopic surgery, more markers had reached the left colon (P<0.05). The first bowel movement occurred 70+/-32 h after laparoscopic and 91+/-22 h after conventional resection (P<0.01). Oral feeding without additional parenteral alimentation was tolerated 3.3+/-0.7 days after laparoscopic and 5.0+/-1.5 days after conventional surgery (P<0.01).

54. Basse L, Jakobsen DH, Bardram L, Billesbolle P, Lund C, Mogensen T, Rosenberg J, Kehlet H Functional recovery after open versus laparoscopic colonic resection: a randomized, blinded study. Ann Surg 2005; 241:416-423.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries:** Denmark **Centers:** n/a **Setting**: n/a **Funding Sources**: n/a **Dropout rates**: 14 patients (19 %) **Study limitations**: due to its relatively small size (n = 60), our study will not allow conclusions on other clinical outcomes such as cardiopulmonary,	**Total no. patients**: n = 60 **Inclusion criteria:** all patients over 55 years scheduled for elective right hemicolectomy or sigmoid resection **Exclusion criteria:** patients not able to take care of themselves at home or living in a nursing home and patients operated during summer and other holiday periods when the research team was not present. Patients	Patients underwent elective laparoscopic or open colonic resection with multimodal fast-track rehabilitation and planned discharge after 48 hours. Functional recovery was assessed in detail during the first postoperative month.

	thromboembolic, wound or cerebral complication	were excluded after randomization if an epidural catheter could not be inserted, if an anastomosis was performed below 12 cm from the anus, or if a different operation than the scheduled was performed (stoma or no resection)	
Notes	Randomization is mentioned but not specified, therefore the study is downgraded **Author's Conclusion:** In conclusion, based on the current results and other literature concerning fast-track laparoscopic or open colonic resection there may not be important differences in functional recovery between the 2 surgical techniques. However, the laparoscopic approach and its advantageous physiologic effects may result in reduced morbidity in high-risk patients, which should be explored in future studies		
Outcome measures/results	Hospital stay, Morbidity and mortality, Pain, Fatigue and Sleep Quality, Motor Function, Gastrointestinal Function, Cardiopulmonary Function, Mental Function, P-CRP and S-Albumin, Convalescence and Patient/Relatives' Satisfaction	Median postoperative hospital stay was 2 days in both groups, with early and similar recovery to normal activities as assessed by hours of mobilization per day, computerized monitoring of motor activity assessed, pulmonary function, cardiovascular response to treadmill exercise, pain, sleep quality, fatigue, and return to normal gastrointestinal function. There were no significant differences in postoperative morbidity, mortality, or readmissions, although 3 patients died in the open versus nil in the laparoscopic group.	

55. Vlug MS, Wind J, Hollmann MW, et al. Laparoscopy in combination with fast track multimodal management is the best perioperative strategy in patients undergoing colonic surgery: a randomized clinical trial (LAFA-study). Ann Surg. 2011; 254:868-75.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
PRCT 1+	**Countries:** the Netherlands **Centers:** 9 **Setting**: n/a **Funding Sources**: n/a **Dropout rates**: n/a **Study limitations**: the blinding of the treatment, which was difficult to achieve as the majority of the patients could not resist looking under the abdominal	**Total no. patients**: n = 400 • Laparoscopy and Fast Track (n = 100) • Open and Fast Track (n =93) • Laparoscopy and Standard care (n = 109) • Open and Standard care (n = 98) **Inclusion criteria:** Patients treated in 9 Dutch hospitals (3 University hospitals	In a 9-center trial, patients eligible for segmental colectomy were randomized to laparoscopic or open colectomy, and to FT or standard care, resulting in 4 treatment groups.

	dressing. After randomization more, patients in the open groups (n = 20) than in the laparoscopic groups (n = 7) were excluded, nevertheless we can assume that this is coincidental. Thirdly, as patients have been enrolled for over 4 years, there might have been in drift in care, i.e., patients included in a later phase of the study, allocated to standard care, might have received more FT elements than patients included at the start of the study.	and 6 teaching hospitals) were eligible if they were between 40 and 80 years of age, had an American Society of Anesthesiologists (ASA) grade of I, II, or III, were to undergo elective segmental colectomy for histologically confirmed adenocarcinoma or adenoma, and without evidence of metastatic disease **Exclusion criteria:** Exclusion criteria were prior midline laparotomy, unavailability of a laparoscopic surgeon, emergency surgery, or a planned stoma.	
Notes	Optimal perioperative treatment for patients requiring segmental colectomy for colon cancer is laparoscopic resection embedded in a FT program. If open surgery is applied, it is preferentially done in FT care.		
Outcome measures/results	**Primary outcome measures:** Total postoperative hospital stay (THS), measured in days. THS was defined as postoperative hospital stay (PHS) plus the additional hospitalization period in case patients were readmitted within 30 days of surgery. **Secondary outcome measures:** PHS, overall morbidity, reoperation rate, readmission rate, in-hospital mortality, quality of life at 2 and 4 weeks, patient satisfaction 4 weeks postoperatively and in-hospital costs.	Median THS in the laparoscopic/FT group was 5 (interquartile range: 4-8) days; open/FT 7 (5-11) days; laparoscopic/standard 6 (4.5-9.5) days, and open/standard 7 (6-13) days ($P < 0.001$). Median PHS in the laparoscopic/FT group was 5 (4-7) days; open/FT 6 (4.5-10) days; laparoscopic/standard 6 (4-8.5) days and open/standard 7 (6-10.5) days ($P < 0.001$). Secondary outcomes did not differ significantly among the groups. Regression analysis showed that laparoscopy was the only independent predictive factor to reduce hospital stay and morbidity.	

56.	Nematihonar B, Salimi S, Noorian V et al. Early Versus Delayed (Traditional) Postoperative Oral Feeding in Patients Undergoing Colorectal Anastomosis. Adv Biomed Res 2018; 7: 30. doi:10.4103/abr.abr_290_16		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1- ROB 4/7	**Countries:** Iran **Centers:** single-center, Imam-Hossein General Hospital **Setting:** Departments of General Surgery and Anesthesiology **Funding Sources:** None **Dropout rates:** 0% **Study limitations:** Risk of Bias: moderate Inconsistency: n/a Indirectness: low Impreciseness: moderate Publication bias: n/a	**Total no. patients:** 60 **Inclusion criteria:** any history of surgery involving anastomosis in the colon or rectum **Exclusion criteria:** diabetic patients with fasting blood sugar >200 mg/dl, immunosuppressive patients taking corticosteroid, patients with untrustworthy psychiatric problems, hypothyroid patients, patients who had experienced anastomosis apart from those of the colon or rectum, patients who had undergone total colectomy, patients with a history of radiotherapy, colostomy, or protective ileostomy	Two groups: Early feeding (n=30): diet initiated by filtrate liquids within 24 h after surgery. Over the next 24 h, the liquid diet was replaced by a normal diet in case tolerance was desirable. The diet continued in this group if there was no vomiting Late feeding (n=30): received the routine diet (late feeding) including filtrate liquids was only after the resolution of ileus, while the patients remained not per oral (NPO) until the resolution of ileus.
Notes	**Author's Conclusion**: Early oral feeding after colorectal surgeries is safe and tolerated by the majority of patients.		
Outcome measures/results	postoperative complications, pain scores (Visual analogue scale), start of bowel sounds, ileus resolution, gas passing, and defecation, period of regular diet intake and hospital stay and satisfaction state (Visual analogue scale)		- average prolonged days until the incidence of complications such as intestinal sounds, ileus, liquid diet, regular diet, discharge, gas passing, and defecation was significantly greater in the late feeding group compared to the early feeding group - pain scores (Visual analogue scale) of patients in the late feeding group with an average of 7.1 ± 1.6 were significantly lower than those in the early feeding group with an average of 8.6 ± 1.2 ($P < 0.0001$) - other complications were not significantly different between the two groups - earlier start of bowel sounds, ileus resolution, gas passing, and defecation, and lower period of regular diet intake and hospital stay, and higher

		satisfaction state (Visual analogue scale) in patients; all the above findings reached significance level.

57.	**Wu JM, Kuo TC, Chen HA et al. Randomized trial of oral versus enteral feeding for patients with postoperative pancreatic fistula after pancreatoduodenectomy. Br J Surg 2019; 106: 190-198. doi:10.1002/bjs.11087**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+ ROB 3/7	**Countries:** Taiwan **Centers:** single-center, National Taiwan University Hospital **Setting:** n/a **Funding Sources:** National Taiwan University Hospital **Dropout rates:** 0% **Study limitations:** Risk of Bias: high Inconsistency: n/a Indirectness: low Impreciseness: moderate Publication bias: n/a Blinding not feasible; included only postoperative pancreatic fistula after pancreatoduodenectomy, data cannot be extrapolated to postoperative pancreatic fistula after other forms of pancreatic resection	**Total no. patients:** 120 **Inclusion criteria:** patients with pancreatoduodenectomy who developed postoperative pancreatic fistula, which was defined as a drain output of any measurable volume on and after postoperative day 3 with an amylase content exceeding three times the upper limit of normal serum level **Exclusion criteria:** aged less than 18 years; had current or a history of severe heart, lung, kidney or liver failure; had a Karnofsky performance status score of below 60	Two groups: Group 1 (n=57): assigned to oral feeding: oral intake was increased to the calorie target Group 2 (n=57): assigned to enteral feeding: received feed from the gastrojejunal tube and nothing but water by mouth until 3 days after fistula closure. The amount of enteral feed was increased to the calorie target, providing protein of 0·15 per g nitrogen per kg bodyweight and energy of 150 kcal per g nitrogen
Notes	**Author's Conclusion:** Oral feeding in patients with postoperative pancreatic fistula after pancreatoduodenectomy did not increase the duration or grade of postoperative pancreatic fistula, and was associated with reduced duration of stay and hospital costs		
Outcome measures/results	primary outcome: rate of postoperative pancreatic fistula closure within 30 days after fistula onset secondary outcomes: time from randomization to fistula closure, grade of postoperative pancreatic fistula, and duration of hospital stay and costs after randomization		- intention-to- treat analysis, the 30-day fistula closure rate was 88 per cent (50 of 57) in the oral feeding group and 89 per cent (51 of 57) in the enteral feeding group, with a difference of –1·8 per cent (lower limit of 95 per cent c. i. –14·4 per cent; P = 0·020 for non-inferiority)

		- The time to fistula closure was also comparable between the two groups (median 17 days in both; P = 0·617) - Compared with enteral feeding, oral feeding significantly reduced hospital costs and duration of stay. No significant differences were noted in the number of patients whose postoperative pancreatic fistula evolved into grade B/C, or other outcomes

58. Fujii T, Nakao A, Murotani K et al. Influence of Food Intake on the Healing Process of Postoperative Pancreatic Fistula After Pancreatoduodenectomy: A Multi-institutional Randomized Controlled Trial. Ann Surg Oncol 2015; 22: 3905-3912. doi:10.1245/s10434-015-4496-1			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1++	**Countries:** Japan **Centers:** multi-center, Nagoya University Hospital and 4 affiliated hospitals **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** 2% **Study limitations:** type II error may exist; the results of this study only deny the hypothesis that oral food intake prolongs the duration of drain placement; not adequate sample size, underpowered	**Total no. patients:** 60 **Inclusion criteria:** age of ≥20 years and a diagnosis of postoperative pancreatic fistula according to the ISGPF definition **Exclusion criteria:** regular use of medication that may affect the healing process (e.g., adrenal corticosteroids); current hemodialysis treatment; and past or current severe cardiovascular, pulmonary, renal, or liver dysfunction; Patients who underwent pancreaticogastrostomy	Two group: Dietary intake group (n=30): food intake was started on postoperative day 6. Rice porridge of 750 kcal (38 g protein, 30 g fat) was given for the first 3 days, soft rice of 1300 kcal (63 g protein, 40 g fat) was given for the next 4 days, and a solid diet of 1650 kcal (78 g protein, 45 g fat) was given thereafter. Actual oral caloric intake was measured at every meal. No dietary intake group (n=30): patients in the NDI group were fasted until drain removal. Parenteral nutrition was commenced after surgery via a central venous catheter. A 1600-kcal all-in-one admixture containing vitamins, electrolytes, and trace elements, was administered continuously for 24 h/day
Notes	**Author's Conclusion:** food intake did not aggravate postoperative pancreatic fistula and did not prolong the length of drain placement or hospital stay after pancreatoduodenectomy. Although not confirmative, the current study implies that there is no need to avoid dietary intake in patients with postoperative pancreatic fistula		
Outcome measures/results	**primary endpoint**: length of drain placement. **secondary endpoints**: incidence of clinically relevant postoperative pancreatic fistula (ISGPF grade B/C), incidence of postoperative pancreatic fistula-related intra-abdominal hemorrhage, postoperative mortality of any cause within 60 days after surgery, the length of the postoperative hospital stay, and the rates of	- No significant differences in the length of drain placement between the dietary intake and non-dietary intake groups [27 (7–80) vs. 26 (7–70) days, respectively; p = .8858] - postoperative pancreatic fistula progressed to a clinically relevant status (grade B/C) in 20 patients in the dietary intake group and 19 patients in the non-dietary intake group (p = .9257)	

	postoperative complications other than postoperative pancreatic fistula	- postoperative pancreatic fistula-related intra-abdominal hemorrhage was found in 2 patients in the non-dietary intake group, but in no patients in the dietary intake group (p = .1434) - no significant differences in postoperative pancreatic fistula-related intra-abdominal hemorrhage, the incidence of other complications, or the length of the postoperative hospital stay between the 2 groups

59.	**Zeng S, Xue Y, Zhao J et al. Total parenteral nutrition versus early enteral nutrition after cystectomy: a meta-analysis of postoperative outcomes. Int Urol Nephrol 2019; 51: 1-7. doi:10.1007/s11255-018-2031-6**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis 1++ AMSTAR II 11/16	**Countries:** Italy, Switzerland, Netherlands, USA, Belgium **Centers:** n/a **Setting:** n/a **Funding Sources:** Shanghai Sailing Program, Starting Foundation for Young Scientists of Second Military Medical University, National Natural Science Foundation of China, Natural Science Foundation of Shandong Province, Medical Science and Technology Development Project of Shandong Province **Dropout rates:** n/a **Study limitations:** Overall confidence in the results of the review: Low Risk of bias of single studies: low Inconsistency: low Indirectness: moderate	**Total no. Studies:** 5 **Inclusion criteria:** (a) studies comparing total parenteral nutrition and early enteral nutrition after cystectomy, (b) indications for cystectomy could be oncological or non-oncological diseases, (c) cystectomy with different types of urinary diversions (ileal conduit, Indiana pouch, orthotopic ileal neobladder, ureterocutaneostomy) were available, (d) at least one of the main outcomes mentioned previously **Exclusion criteria:** Case reports, reviews, and duplicate publications	Evaluation of the current evidence regarding the effect of total parenteral nutrition versus early enteral nutrition on postoperative outcomes of cystectomy.

	Impreciseness: moderate Publication bias: n/a Only small number of studies, sample size relatively small; significant heterogeneities existed among included studies; subgroup analysis of the effect of total parenteral nutrition and early enteral nutrition on different nutritional statuses was not possible due to lack of data		
Notes	**Author's Conclusion:** early enteral nutrition was found to have a significant effect on reducing infectious complications and costs compared with total parenteral nutrition treatment after cystectomy. Remarkably, early enteral nutrition had no significant impact on mortality incidence, postoperative ileus, length of hospital stay, or the time to resumption of full diet.		
Outcome measures/results	Primary outcomes: incidence of perioperative mortality, overall complications, infectious complications, and postoperative ileus Secondary outcomes: length of hospital stay after cystectomy, time needed to resume a full diet after cystectomy and economic cost		- early enteral nutrition was shown to have a significant effect on reducing the overall complications (odds ratio (OR) 0.52, 95% confidence interval (CI) 0.37–0.75, P < 0.01) and infectious complications (OR 0.32, 95% CI 0.21–0.49, P < 0.01) compared with total parenteral nutrition - early enteral nutrition saved €614–€3120 in costs compared to total parenteral nutrition - no significant differences between total parenteral nutrition and early enteral nutrition groups regarding mortality rate (OR 0.47, 95% CI 0.06–3.51, P = 0.46), the incidence of postoperative ileus (OR 0.90, 95% CI 0.55–1.47, P = 0.68), length of hospital stay (mean difference (MD) 2.12, 95% CI − 0.15 to 4.40, P = 0.07), or time to resume a full diet (MD 1.31, 95% CI − 1.15 to 3.77, P = 0.30).

60.	Ji HB, Zhu WT, Wei Q et al. Impact of enhanced recovery after surgery programs on pancreatic surgery: A meta-analysis. World J Gastroenterol 2018; 24: 1666-1678. doi:10.3748/wjg.v24.i15.1666		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis 1++ AMSTAR II 7/16	**Countries:** US, Italy, Britain, India, Holland, Japan, China, Switzerland, Sweden, Spain, Greece **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** Overall confidence in the results of the review: Critically Low Risk of bias of single studies: moderate Inconsistency: low Indirectness: moderate Impreciseness: moderate Publication bias: low diagnostic criteria of some postoperative complications were not uniformly defined, information bias possible; only retrospective case control studies; the degree of implementation of ERAS programs and the compliance of patients may be different between studies	**Total no. Studies:** 20 **Inclusion criteria:** studies concerning patients undergoing pancreatic surgery; the enhanced recovery after surgery group implemented enhanced recovery after surgery programs management, and the control group adopted traditional perioperative management; measures in perioperative management were described in both groups; studies reported at least the following outcome measures: POPF, DGE, abdominal infection, mortality and PLOS, and explained their diagnostic criteria for postoperative complications. **Exclusion criteria:** sample size of less than 10; comments, guidelines, reviews, case reports, abstracts, letters and non-comparative studies; repeated publication of the same study population; incomplete clinical data	Evaluation of the impact of enhanced recovery after surgery programs on postoperative complications of pancreatic surgery
Notes	**Author's Conclusion:** implementation of enhanced recovery after surgery programs could reduce overall complication rates, especially of mild complications, delayed gastric emptying, rates of abdominal infection, and postoperative length of hospital, while not affecting the rates of postoperative pancreatic fistula, reoperation, readmission, and mortality during the perioperative period for pancreatic surgery. The perioperative period for pancreatic		

	surgery is safe and effective to implement enhanced recovery after surgery programs that can decrease postoperative complication rates and promote recovery.	
Outcome measures/results	postoperative pancreatic fistula, delayed gastric emptying, postoperative length of hospital stay, abdominal infection, mortality, readmission, unintended reoperation and occurrence of any complication within a postoperative period of 30 d	- Compared to the control group, enhanced recovery after surgery group had lower delayed gastric emptying rates [odds ratio (OR) = 0.58, 95% confidence interval (CI): 0.48-0.72, P < 0.00001], lower postoperative complication rates (OR = 0.57, 95%CI: 0.45-0.72, P < 0.00001), particularly for the mild postoperative complications (Clavien-Dindo I-II) (OR = 0.71, 95%CI: 0.58-0.88, P = 0.002), lower abdominal infection rates (OR = 0.70, 95%CI: 0.54-0.90, P = 0.006), and shorter postoperative length of hospital stay (PLOS) (WMD = -4.45, 95%CI: -5.99 to -2.91, P < 0.00001) - no significant differences in complications, such as, postoperative pancreatic fistulas, moderate to severe complications (Clavien-Dindo III-V), mortality, readmission and unintended reoperation, in both groups.

61. Sun HB, Li Y, Liu XB et al. Impact of an Early Oral Feeding Protocol on Inflammatory Cytokine Changes After Esophagectomy. Ann Thorac Surg 2019; 107: 912-920. doi:10.1016/j.athoracsur.2018.09.048			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1++ ROB 5/7	**Countries:** China **Centers:** Cancer Hospital of Zhengzhou University **Setting:** Thoracic Surgery Unit **Funding Sources:** Science Foundation for Young Scholars of Henan Cancer Hospital and the Project of Science and Technology of Henan Province **Dropout rates:** 0% **Study limitations:** Risk of Bias: moderate Inconsistency: n/a Indirectness: low Impreciseness: moderate Publication bias: n/a	**Total no. patients:** 280 **Inclusion criteria:** patients aged ≥ 18 years undergoing McKeown minimally invasive esophagectomy with cervical hand- sewn anastomosis for esophageal cancer **Exclusion criteria:** (i) age ≥ 80 years; (ii) inability to perform McKeown minimally invasive esophagectomy due to tumor extension; (iii) severe preoperative comorbidities and inability to undergo minimally invasive esophagectomy (FEV1 < 50% predicted, EF < 50% and organ failure); (iv) obvious hepatocirrhosis; (v) diabetes with organ injury; and (vi) lack of written informed consent to participate.	Two groups: Early oral feeding group (n=140): patients were encouraged to consume food on the morning of the first post-operative day according to the following protocol, if no aspiration after drinking liquids was observed Late oral feeding group (n=140): nasogastric and nasoenteral feeding tubes were placed with the help of interventional radiology on postoperative day 1. The patients received nutrition via a nasoenteral feeding tube at 40 mL/h on postoperative day 1, and the rate was increased by 40 mL/h each day, if tolerated, up to 120 mL/h. On postoperative day 7, the nasogastric tube was removed, and the patients were allowed the same food as in the early oral feeding group according to the dieticians' guidance

	single-center study; only included patients with minimally invasive esophagectomy with hand-sewn cervical anastomosis; rate of postoperative complications was relatively low in both groups; patients in study relatively young	Postoperative exclusion criteria were (i) exploratory surgery; (ii) recovery in the intensive care unit (ICU) for more than 24 hours; and (iii) bilateral recurrent laryngeal nerve injury	
Notes	**Author's Conclusion:** In selected cases, early oral feeding after minimally invasive esophagectomy is a safe and feasible strategy. An early recovery of intestinal function and an improvement of quality of life are the main advantages of early oral feeding versus late oral feeding		
Outcome measures/results	**Primary endpoint**: postoperative cardiac, respiratory and gastrointestinal complications during hospital stay **secondary endpoints:** bowel function recovery, patients' short-term Quality of life, length of postoperative stay (days) and kilocalories intake.		- Early oral feeding was noninferior to late oral feeding for cardiac, respiratory and gastrointestinal complications (25.0% in the early oral feeding group versus 27.9% in the late oral feeding group; 95% confidence interval: −13.2% – 7.4%) - Compared with the late oral feeding group, the Early oral feeding group showed significantly shorter time to first flatus (median of 2 days versus 3 days, P = 0.001) and bowel movement (median of 3 days versus 4 days, P < 0.001) - Two weeks after the operation, patients in the early oral feeding group reported higher global quality of life and function scores and lower symptom scores than patients in the late oral feeding group

62. Berkelmans GHK, Fransen LFC, Dolmans-Zwartjes ACP et al. Direct Oral Feeding Following Minimally Invasive Esophagectomy (NUTRIENT II trial): An International, Multicenter, Open-label Randomized Controlled Trial. Ann Surg 2020; 271: 41-47. doi:10.1097/SLA.0000000000003278			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1++ ROB 4/7	**Countries:** Netherlands, Sweden **Centers:** multi-center, Catharina Hospital, Eindhoven, the Netherlands; Hospital Group Twente, Almelo, the Netherlands and the Karolinska University Hospital, Stockholm, Sweden	**Total no. patients:** 148 **Inclusion criteria:** patients aged 18 years or above scheduled to undergo a minimally invasive esophagectomy with intrathoracic Ivor Lewis anastomosis **Exclusion criteria:** inability to tolerate oral intake, inability to	Two groups: intervention group (direct oral feeding) (n= 65): started directly with a liquid oral diet slowly increasing calories each day. From postoperative day 15, patients could eat solid foods without restrictions control group (n=67): Patients in the control group (standard of care) had a delay in start of oral intake and were only allowed to drink clear liquids up to 250cc/day. They received tube feeding via the jejunostomy and started oral intake on postoperative

	Setting: n/a **Funding Sources:** KWF Kankerbestrijding (Dutch Cancer Society, project number 10495) and Covidien/Medtronic. **Dropout rates:** 11% **Study limitations:** Risk of Bias: moderate Inconsistency: n/a Indirectness: low Impreciseness: high Publication bias: n/a finding that median time to functional recovery was 7 days in the intervention group and 8 days in the control group was lower than expected before start of the study; complication rate may be a factor in the current results	receive a feeding jejunostomy, diagnosed with a preoperative swallowing disorder or achalasia, a Karnofsky Performance Status <80, or malnourishment (defined as >15% weight loss in the period before surgery); Patients with metastases found during surgery or patients who received a total gastrectomy were	day 5, expanding this diet exactly the same as in the oral group. Fourteen days after initiation of oral intake, all patients could start a solid oral diet.
Notes	**Author's Conclusion:** direct start of oral feeding after esophagectomy does not affect functional recovery compared with starting oral intake 5 days postoperatively. Importantly, direct start of oral intake did not increase incidence or severity of postoperative complications.		
Outcome measures/results	**Primary outcome:** the day of functional recovery **Secondary outcomes:** pulmonary complications; anastomotic leakage and nutritional status; pneumonia rate, and other surgical complications scored by predefined definitions.		- Functional recovery was 7 days for patients receiving direct oral feeding compared with 8 days in the control group (P = 0.436). - Anastomotic leakage rate did not differ in the intervention (18.5%) and control group (16.4%, P = 0.757) - Pneumonia rates were comparable between the intervention (24.6%) and control group (34.3%, P = 0.221) - Other morbidity rates were similar, except for chyle leakage, which was more prevalent in the standard of care group (P = 0.032).

63.	**Speicher JE, Gunn TM, Rossi NP et al. Delay in Oral Feeding is Associated With a Decrease in Anastomotic Leak Following Transhiatal Esophagectomy. Semin Thorac Cardiovasc Surg 2018; 30: 476-484. doi:10.1053/j.semtcvs.2018.08.004**

Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
Retrospective cohort study 2+ NOS 7/9	**Countries:** USA **Centers:** University of Iowa Hospitals and Clinics **Setting:** n/a **Funding Sources:** none **Dropout rates:** 0% **Study limitations:** Risk of Bias: moderate Inconsistency: n/a Indirectness: low Impreciseness: moderate Publication bias: n/a result for the Wilcoxon test is limited in that it is a less ideal test for determining significance of this data series; design in which the two study cohorts were obtained over different time periods; statement about direct causation between delay in feeding and decrease in leak rate not possible	**Total no. patients:** 203 **Inclusion criteria:** patients undergoing elective open transhiatal esophagectomy by a senior surgeon **Exclusion criteria:** underwent non-elective operations for esophageal perforations	- Patients with operations performed between February 2004 and March 2008 (n=83) had their oral intake resumed on postoperative day 3 - Patients undergoing operations between April 2008 and November 2013 (n=120) were kept as strict nil per os until postoperative day 15 - Patients in the delayed intake group began jejunal tube feedings on postoperative day 3 and patients in the early intake group were supplemented as necessary based upon routinely obtained nutrition labs
Notes	**Author's Conclusion:** increasing the time to oral feeding after transhiatal esophagectomy with cervical anastomosis is associated with a decrease in anastomotic leak rate. There is a trend towards decrease in anastomotic stricture as well, as expected with the known association between leak and stricture rate.		
Outcome measures/results	postoperative length of stay, rate of anastomotic leak, esophageal stricture rate, 30- and 90-day mortality		- Median postoperative length of stay was noted to be shorter in the delayed group compared with the early group - statistically significant decrease in the rate of anastomotic leak from 14.5% to 4.2% between the early and delayed intake groups, respectively (p=0.0089)

		- trend (p=0.05) towards a lower rate of anastomotic stricture in all patients in the delayed intake group (15.8%) compared with those in the early feeding group (27.7%) - Thirty- and 90-day mortality in the delayed intake group was two and five patients, respectively, and none of the deaths were in leak patients - in the early intake group, 30- and 90-day mortality was 3 and 7 patients, respectively, and one of the deaths was in a leak patient

64.	**Eberhard KE, Achiam MP, Rolff HC et al. Comparison of "Nil by Mouth" Versus Early Oral Intake in Three Different Diet Regimens Following Esophagectomy. World J Surg 2017; 41: 1575-1583. doi:10.1007/s00268-017-3870-5**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Retrospective Study 2+ NOS 7/9	**Countries:** Denmark **Centers:** single-center, Rigshospitalet, Denmark **Setting:** Department of surgical gastroenterology **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** Risk of Bias: moderate Inconsistency: high Indirectness: low Impreciseness: low Publication bias: n/a based on information extracted from clinical databases, reporting is not standardized; criteria for operation and selection of patients could have changed slightly during the 56-month period; maybe introduced bias	**Total no. patients:** 359 **Inclusion criteria:** histologically verified adenocarcinoma or high-grade dysplasia (Barrett's esophagus); preoperative CT scan of thorax/abdomen and laparoscopy without sign of dissemination; esophagectomy with Ivor Lewis or robot-assisted hybrid with open-thorax technique; age ≥ 18 years. **Exclusion criteria:** n/a	No intervention, just comparison of three different diet regimens after esophagectomy, focusing on the postoperative oral fluid intake and its influence on anastomotic leakage as well as complications in general Three oral intake protocols were evaluated: regimen 1, nil by mouth until postoperative day 7 followed by a normal diet; regimen 2, oral intake of clear fluids from postoperative day 1 followed by a normal diet; regimen 3, nil by mouth until postoperative day 7 followed by a slow increase to a blended diet
Notes	**Author's Conclusion:** postoperative oral intake affects morbidity—and that nil by mouth for the first seven postoperative days followed by a slow increase to a blended diet held until the 21st postoperative day, resulting in less severe complications; this regimen may decrease the numbers of anastomotic		

	leakages; comorbidity is one of the most important predictive factors of the postoperative course, both regarding anastomotic leakage and complications in general.	
Outcome measures/results	anastomotic leakage; complications [severity and number described using the Dindo–Clavien Classification and Comprehensive Complication Index]; length of stay	- incidence of anastomotic leakage was lower in regimen 3, 2%, compared with 7% and 9% in regimen 1 and 2 ($p = 0.115$; $p = 0.043$ for regimen 2 vs. 3). No significant differences in grade or in time to leakage were found - Patients in regimen 3 stayed significantly shorter at hospital compared to regimen 1 and 2, 4 and 3 days, respectively ($p < 0.001$) - Comprehensive complication index was significantly lower in regimen 3 (16 vs. 22 and 26 in regimen 1 and 2, $p = 0.027$) - significantly fewer patients in regimen 3 suffered from severe complications of Dindo–Clavien grade IIIb–IV ($p = 0.025$)

65. Jamel S, Tukanova K, Markar SR. The evolution of fast track protocols after oesophagectomy. J Thorac Dis 2019; 11: S675-S684. doi:10.21037/jtd.2018.11.63			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic review 1- AMSTAR II 1/16	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** National Institute of Health Research NIHR **Dropout rates:** n/a **Study limitations:** Overall confidence in the results of the review: Critically Low Risk of bias of single studies: n/a Inconsistency: n/a Indirectness: high Impreciseness: n/a Publication bias: n/a	**Total no. Studies:** 24 **Inclusion criteria:** Comparative and non-comparative Cohort studies and randomized trials investigating the effect of enhanced recovery after surgery with a clearly documented fast track pathway **Exclusion criteria:** Articles assessing the effect of one component of fast track	Assessment of the evolution of fast-track protocols following esophagectomy since its implementation and the resulting effect on postoperative outcomes
Notes	**Author's Conclusion:** Fast track protocols is esophagectomy shows variations in practice due to the complexity of the procedure. Fast track has been shown to reduce hospital stay and morbidity following esophagectomy. It has been advocated that early mobilization, early enteral feeding, early removal of chest tube, limiting the use of nasogastric decompression and optimizing the use of epidural anesthesia or analgesia facilitates early discharge of patients		

Outcome measures/results	**primary outcome**: length of hospital stay (defined at the time from surgery to discharge from hospital) **Secondary outcomes:** in-hospital mortality and postoperative complications, specifically anastomotic leak, and pulmonary complications (including pneumonia, persistent pneumothorax, and acute respiratory distress syndrome)	- fast track had positive effect on patient outcomes - Anastomotic leak rate persistently lower in the ERAS group in comparison to the non- enhanced recovery after surgery - Reduction in pulmonary complications and length of stay in the enhanced recovery after surgery group - rate of anastomotic leak and pneumonia varied across the years which may reflect variation in the criteria used to define those outcomes - Mean length of stay did not exceed 12 days in the fast-track groups, whilst this could extend up to a mean length of stay of 19 days in the conventional care groups - mortality rate followed the same pattern and fast track led to reduction in mortality rate in comparison to traditional care

66.	**Kalra R, Vohra R, Negi M et al. Feasibility of initiating early enteral nutrition after congenital heart surgery in neonates and infants. Clinical Nutrition ESPEN 2018; 25: 100-102. doi:10.1016/j.clnesp.2018.03.127**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Prospective randomized control single blind study 1- ROB 3/7	**Countries:** India **Centers:** single-center, tertiary care hospital, New Delhi **Setting:** Pediatric cardiac intensive care Unit **Funding Sources:** none **Dropout rates:** n/a **Study limitations:** Risk of Bias: high Inconsistency: n/a Indirectness: high Impreciseness: high Publication bias: n/a	**Total no. patients:** 30 **Inclusion criteria:** patients with the cyanotic congenital heart disease with increase pulmonary blood flow, weighing less than 5 kg and undergoing congenital heart repair during the study period **Exclusion criteria:** Patients with single ventricle status, those undergoing palliative procedures (PA band), open chest, requiring extracorporeal membrane oxygenation before leaving operating room, having any other contraindication for starting enteral feeding	Two groups: Patients randomized to the Feed group received trophic feeds (n=15) (@10-20 ml/kg/day) within 4-6 h after completion of surgery; feed were increased gradually with objective of achieving full feeds within 5-6 days. Feeds were withheld 6 h before and after extubation Patients in the control group (NPO group, n=15) received enteral feeds after extubation.
Notes	**Author's Conclusion:** Neonates and Infants tolerate trophic feeds immediately following congenital heart repairs. Moreover, trophic feeds appear to decrease the infection related morbidity following congenital heart repairs		

Outcome measures/results	**Primary outcome**: length of mechanical ventilation and length of intensive care unit stay **Secondary outcomes**: were variable like blood sugar levels, acute phase reactant protein (CRP, TNF alpha), total leucocyte count inotropes used and sepsis.	- Mean duration of mechanical ventilation in the feeds group was 58.2 ± 4.71 h, which was less then significantly less than those in the NPO group (P value 0.05). Similarly, duration of intensive care unit stay was only 179.04 ± 41.28 h in feeds group as compared to 228.72 ± 85.44 h in the NPO group - values of CRP and TNF alpha were found to be similar in both the groups as shown in figures - both mean blood sugar levels during first 72 h after surgery and blood sugars at 72 h post op period were found to be significantly higher in the NPO group when compared to the feed group

4. Indikation zur Ernährungstherapie

4.1 Wann ist eine Ernährungstherapie beim chirurgischen Patienten indiziert?

4.1.1 Wann ist eine kombiniert enterale/parenterale („duale“) Ernährung beim chirurgischen Patienten indiziert?

<u>Empfehlung 7b</u>

Die supplementierte parenterale Ernährung soll sobald wie möglich begonnen werden, wenn bei Indikation zur Ernährungstherapie eine Kontraindikation zur enteralen Ernährung besteht (z.B. intestinale Obstruktion). (BM)

Empfehlungsgrad A – Starker Konsens 100 % Zustimmung

<u>Empfehlung 7c</u>

Wenn die voraussichtliche Dauer der Supplementierung zwischen vier und sieben Tagen liegt, kann die Ernährung über einen peripheren Zugang parenteral zugeführt werden. (BM)

Empfehlungsgrad 0 – Starker Konsens 100 % Zustimmung

<u>Empfehlung 7d</u>

Wenn die Implantation eines zentralvenösen Katheters ausschließlich zur Durchführung einer parenteralen Ernährung erforderlich ist, soll diese Indikation kritisch in Bezug auf die voraussichtliche Ernährungsdauer gestellt werden. (BM)

Empfehlungsgrad A – Starker Konsens 100 % Zustimmung

1. Wu W, Zhong M, Zhu DM et al. Effect of Early Full-Calorie Nutrition Support Following Esophagectomy: A Randomized Controlled Trial. JPEN J Parenter Enteral Nutr 2017; 41: 1146-1154. doi:10.1177/0148607116651509			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+ ROB 5/7	**Countries:** China **Centers:** single-center, Zhongshan Hospital Affiliated to Shanghai Fudan University School of Medicine, Shanghai **Setting:** Department of Thoracic Surgery **Funding Sources:** none	**Total no. Patients:** 80 **Inclusion criteria:** patients underwent scheduled esophagectomy for esophageal cancer, including intended nasojejunal tube placement or jejunostomy for postoperative feeding	- Resting energy expenditure and body composition measurements were performed in all patients preoperatively and postoperatively - EN administered after surgery, followed by randomization to either EN+PN (n=40) or EN (n=40) alone - The amount of PN administered was calculated to meet the full calorie requirement, as measured by indirect calorimetry, and 1.5 g protein/kg fat-

	Dropout rates: 12% **Study limitations:** Risk of Bias: moderate Inconsistency: n/a Indirectness: low Impreciseness: high Publication bias: n/a Non-double-blinded design and the relatively small sample size; Patients were not followed up long enough after discharge, thus preventing long-term evaluation of physical functions or health-related quality-of-life	**Exclusion criteria:** contraindications for EN or PN, preoperative initiation of EN or PN, ongoing infections, preexisting organ failure, treatment with high doses of steroids, severe metabolic	free mass per day was added as determined by body composition measurement
Notes	**Author's Conclusion:** Addition of early parenteral nutrition to supplement standard enteral nutrition did not significantly change the perioperative outcomes of patients undergoing esophagectomy. However, for patients who received supplementary parenteral nutrition, increased calorie and protein intakes were associated with preservation of body weight, fat-free mass, and better health-related quality-of-life in short-term follow-up		
Outcome measures/results	**primary outcome**: preservation of fat-free mass **secondary outcomes**: effects of full-calorie nutrition on surgery-associated mortality and postoperative complications; length of hospital stay; blood biochemistry; health-related quality-of-life assessment on 90 days postoperative.		- Patients in the EN+PN group but not in the EN group preserved body weight (0.18 ± 3.38 kg vs −2.15 ± 3.19 kg, $P < .05$) and fat-free mass (1.46 ± 2.97 kg vs −2.08 ± 4.16 kg) relative to preoperative measurements - Length of hospital stay, postoperative morbidity rates, and standard blood biochemistry profiles were similar - scores for physical functioning (71.5 ± 24.3 vs 60.4 ± 27.4, $P < .05$) and energy/fatigue (62.9 ± 19.5 vs 54.2 ± 23.5, $P < .05$) were higher in the EN+PN group 90 days following surgery

2.	Gao X, Liu Y, Zhang L, Zhou D, Tian F, Gao T, et al. Effect of Early vs Late Supplemental Parenteral Nutrition in Patients Undergoing Abdominal Surgery: A Randomized Clinical Trial. JAMA Surg. 2022 1;157:384-393.		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+ ROB 13/14	**Countries:** China **Centers:** n/a **Setting:** multicenter **Funding Sources:** grant 201502022 from the Research Special Fund for Public Welfare Industry of Health and grant 81770531 from the National Natural Science Foundation of China **Dropout rates:** 0.4% **Study limitations:** Risk of Bias: low Inconsistency: n/a Indirectness: low Impreciseness: moderate Publication bias: n/a Indirect calorimetry was unavailable in some of our centers, and we used the recommended formula; select cohort of patients who had undergone major abdominal surgery and had a high nutritional risk and poor tolerance to EN, which may compromise the validity and applicability of our findings, no blinding possible	**Total no. Patients:** 230 **Inclusion criteria:** adult patients who underwent elective gastric, colorectal, hepatic, and pancreatic resections (both benign and malignant disease) without traumatic reasons; were at risk of malnutrition defined as a Nutritional Risk Screening 2002 (NRS-2002) score of 3 or higher; were expected to have a postoperative hospital stay longer than 7 days; and had received 30% or less of the energy target by EN on day 2 after surgery **Exclusion criteria:** n/a	After the randomization, both groups received nutrition support for a minimum of 5 days, until 80% of the energy target had been reached via EN, or until hospital discharge. Enteral nutrition was performed by tube feeding. Parenteral nutrition was administered via peripheral or central veins. Eligible patients were randomly assigned to the E-SPN (early supplemental parenteral nutrition) group or the L-SPN (late supplemental parenteral nutrition) group For patients in the E-SPN group, SPN was initiated on day 3 after surgery to reach the energy target, whereas SPN was initiated on day 8 after surgery for patients in the L-SPN group. The energy target of combined EN and SPN was 100% of the energy requirement. When enteral feeding comprised 80% of the energy goal, SPN was reduced and eventually discontinued.
Notes	**Author's Conclusion:** In this randomized clinical trial, E-SPN was associated with reduced nosocomial infections in patients undergoing abdominal surgery. Early SPN seems to be a favorable strategy for patients at high nutritional risk and with poor tolerance to EN after major abdominal surgery to reduce the number of nosocomial infections.		

Outcome measures/results	Energy delivery, nosocomial infections, noninfectious complications, total adverse events, mean number of therapeutic antibiotic days	- A total of 230 patients (mean [SD] age, 60.1 [11.2] years; 140 men [61.1%]; all patients were of Han race and Asian ethnicity) were randomized (115 to the E-SPN group and 115 to the L-SPN group). - The E-SPN group received more mean (SD) energy delivery between days 3 and 7 compared with the L-SPN group (26.5 [7.4] vs 15.1 [4.8] kcal/kg daily; P < .001). The E-SPN group had significantly fewer nosocomial infections compared with the L-SPN group (10/115 [8.7%] vs 21/114 [18.4%]; risk difference, 9.7%; 95% CI, 0.9%-18.5%; P = .04). - No significant differences were found between the E-SPN group and the L-SPN group in the mean (SD) number of noninfectious complications (31/115 [27.0%] vs 38/114 [33.3%]; risk difference, 6.4%; 95% CI, −5.5% to 18.2%; P = .32), total adverse events (75/115 [65.2%] vs 82/114 [71.9%]; risk difference, 6.7%; 95% CI, −5.3% to 18.7%; P = .32), and rates of other secondary outcomes. - A significant difference was found in the mean (SD) number of therapeutic antibiotic days between the E-SPN group and the L-SPN group (6.0 [0.8] vs 7.0 [1.1] days; mean difference, 1.0 days; 95% CI, 0.2-1.9 days; P = .01).

3. Sánchez-Guillén L, Soriano-Irigaray L, López-Rodríguez-Arias F, Barber X, Murcia A, Alcaide MJ, et al. A. Effect of Early Peripheral Parenteral Nutrition Support in an Enhanced Recovery Program for Colorectal Cancer Surgery: A Randomized Open Trial. J Clin Med. 2021;10:3647.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1- ROB 9/12	**Countries:** Spain **Centers:** n/a **Setting:** n/a **Funding Sources:** investigator-initiated grant from Baxter SL (Spain) to Antonio Arroyo via FISABIO (Foundation for the Promotion of Healthcare and Biomedical Research of the Autonomous Community of Valencia) in Hospital de Elche (Alicante)	**Total no. Patients:** 170 **Inclusion criteria:** patients with diagnosis of colorectal cancer; all patients diagnosed with a colorectal tumor scheduled for surgery with preoperative T1-T3NxM0 **Exclusion criteria:** patients at severe nutrition risk by one of the ESPEN guidelines criteria; emergency surgery, an American Society of Anaesthesiologists (ASA) physical status IV, renal failure defined as necessitating hemodialysis, hepatic failure, allergy or sensitivity to egg	Comparison of the influence of peripheral parenteral nutrition (PPN) (with Peri-Olimel N4-E) versus conventional fluid therapy (FT) on postoperative complications in colorectal surgery patients. All patients were admitted the day before surgery, and patients were preoperatively prepared with only a low fiber diet for three days before surgery. The ERAS bundles used were based on previously published protocols. Furthermore, it was required that the patients receive carbohydrate-rich beverages the day before and 2 h before surgery. The control group received conventional FT the day before surgery. The experimental group was treated with peripheral parenteral nutrition (PPN) Peri-Olimel N4E for 4 days (the day before the scheduled surgery and 3 days after surgery). Both groups received antithrombotic therapy and intravenous tobramycin 300 mg and metronidazole 1.5 g at the time of anesthetic induction. All patients underwent surgery by colorectal surgeons.

	Dropout rates: 7.1% **Study limitations:** Risk of Bias: moderate Inconsistency: n/a Indirectness: low Impreciseness: moderate Publication bias: n/a Some differences about the type of complications are lost	or soy protein, severe bleeding disorder, congenital abnormality of amino acid metabolism, hyperlipidemia, and inability to comply with the ERAS protocol	
Notes	**Author's Conclusion:** This randomized open trial demonstrates the benefits of proving early perioperative PPN in patients undergoing colorectal surgery. This is the first trial that shows that PPN supplementation and early compliance with ERAS programs can reduce postoperative morbidity. Patients receiving PPN had a lower risk of complications than those who received conventional FT, and PPN decreased the chance of worsening postoperative complications or developing major complications. It also revealed the importance of postoperative compliance with ERAS bundles during the first postoperative days. For patients who cannot truly fulfil ERAS protocols because of any deviation of the postoperative course, PPN has shown a protective effect on postoperative complications, defining a clear pathway that can help in these challenging patients.		
Outcome measures/results	90-day complication rate, complications		- The overall 90-day complication rate was 38.6% (61 patients), and 24 patients had major complications (Clavien–Dindo III–V) (15.2%). - In the multivariate analysis, the intervention (PPN vs. FC) showed a protective effect against postoperative complications (p = 0.0031, OR = 0.2 (CI: 0.08–0.87)). - Following ordinal regression, peripheral parenteral nutrition (PPN) and early oral tolerance showed a protective effect, being less likely to develop complications or to move from minor to major complications. - In patients with low compliance to ERAS during the first postoperative day, PPN showed a protective effect, preventing 28% of morbidity.

4.	**López-Rodríguez-Arias F, Sánchez-Guillén L, Lillo-García C, Aranaz-Ostáriz V, Alcaide MJ, Soler-Silva Á, et al. Assessment of Body Composition as an Indicator of Early Peripheral Parenteral Nutrition Therapy in Patients Undergoing Colorectal Cancer Surgery in an Enhanced Recovery Program. Nutrients. 2021;13:3245.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 2- ROB moderate	**Countries:** Spain **Centers:** n/a **Setting:** n/a **Funding Sources:**	**Total no. Patients:** 156 **Inclusion criteria:** individuals aged ≥18 years and a diagnosis of colorectal cancer with preoperative	Sub-analysis of procedure-target cohort of patients obtained from a randomized clinical trial that compares the influence of PPN with PeriOlimel N4-E vs. conventional FT depending on body composition according to the SMI on postoperative complications of colorectal surgery patients.

	investigator-initiated grant from Baxter SL (Spain) to Dr Antonio Arroyo via FISABIO (Foundation for the Promotion of Healthcare and Biomedical Research of the Autonomous Community of Valencia) in Hospital de Elche (Alicante) **Dropout rates:** n/a **Study limitations:** Risk of Bias: moderate Inconsistency: n/a Indirectness: moderate Impreciseness: moderate Publication bias: n/a	staging T1-T3NxM0 **Exclusion criteria:** patients at severe nutritional risk via one of the ESPEN guidelines criteria, intraoperative diagnosis of carcinomatosis, metastasis, and locally advanced (T4) or unresectable tumors, need for emergency surgery, an American Society of Anaesthesiologists (ASA) physical status IV, renal failure defined via hemodialysis, hepatic failure, allergy or sensitivity to egg or soy protein, severe bleeding disorder, congenital abnormality of amino acid metabolism hyperlipidemia, not accepting or not being able to comply with the ERAS protocol, or the absence of a CT scan one month prior to surgery	All patients underwent perioperative management following the current indications of the ERAS protocols. Patients were preoperatively prepared at home with a low-fiber diet three days before surgery and admitted to the hospital the day before the surgery. Antibiotic prophylaxis was administered following the policy of our center; in addition, patients received drinks rich in carbohydrates with dextromaltose a day before the surgery and on the morning of the surgery. In the intervention group, PPN with Peri-Olimel N4-E was started one day prior to colorectal resection and continued for 3 days postoperatively. In the control group, standard FT was administered postoperatively and removed when the patient began to tolerate oral feeds. All patients underwent surgery performed by surgeons from the coloproctology unit, giving priority to laparoscopic surgery.
Notes	**Author's Conclusion:** The analysis of the body composition of patients through the determination of SMI is a useful tool to identify patients at high surgical risk. In these patients, peripheral parenteral nutrition has been shown to be effective in improving the outcomes of surgery, and could contribute to reducing the length of hospital stay.		
Outcome measures/results	Body composition, postoperative complications		Of the 156 patients analyzed, 88 patients (56.4%) were classified as having high-risk body composition (BC) according to CT measurements. Peripheral parenteral nutrition led to a 15.4% reduction in postoperative complications in high-risk vs. 1.7% in low-risk BC patients. In the multivariate analysis, high-risk BC was related to an OR (95% CI) of 2 ($p = 0.044$) of presenting complications and of 1.9 ($p = 0.066$) for major complications and was associated with an increase in LOS of 3.6 days ($p = 0.039$).

Empfehlung 8

Bei der parenteralen Ernährung sollten Dreikammerbeutel (all-in-one) den Einzelkomponenten (Mehrflaschensysteme) vorgezogen werden. (BM, HE)

Empfehlungsgrad B – Starker Konsens 97 % Zustimmung

5. Menne R, Adolph M, Brock E et al. Cost analysis of parenteral nutrition regimens in the intensive care unit: three-compartment bag system vs multibottle system. JPEN J Parenter Enteral Nutr 2008; 32: 606-612. doi:10.1177/0148607108322404			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Cost-Analysis 2+	**Countries:** Germany **Centers:** n/a **Setting:** ICU **Funding Sources:** Baxter, Munich, Germany (in part) **Dropout rates:** n/a **Study limitations:** n/a	**Total no. Patients:** n/a **Inclusion criteria:** n/a **Exclusion criteria:** n/a	3-compartment bag vs. multibottle systems
Notes	**Author's Conclusion:** Verifying comparable results from other countries, this study demonstrated a clear overall cost advantage of 22% for the 3-compartment bag system in a German ICU. To the best of our knowledge, this is the first study performed to evaluate global cost of the administration of 3-compartment bags in a German hospital by applying a specially developed economic model based on primary data collected specifically for this purpose.		
Outcome measures/results	costs of the materials, costs of personnel, associated costs of the services following the actual treatment, e. g. waste disposal		The costs associated with feeding a patient using the multibottle system were €51.62 per day. In contrast, the costs associated with feeding a patient using the 3-compartment bag system amount to €42.26 per day. Assuming that a patient receives PN for 10 days, costs for the ICU were €423 for the 3-compartment bag system and €516. for the multibottle system. The 3-compartment bag system of PN was associated with cost savings for the ICU of €94 per patient per case compared with the multibottle system. The 3-compartment bag system's main cost advantage lies in its labor-saving aspects. However, the 3-compartment bag system also cost less for materials (€43) for 10 days of PN.

6. Pichard C, Schwarz G, Frei A et al. Economic investigation of the use of three-compartment total parenteral nutrition bag: prospective randomized unblinded controlled study. Clin Nutr 2000; 19: 245-251. doi:10.1054/clnu.2000.0106			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Prospective, randomized, unblinded, controlled economic study. 1+	**Countries:** **Centers:** n/ **Setting:** na **Funding Sources:** n/a **Dropout rates:** 0% **Study limitations:** Hospital-compounded bags and industrial three-compartment bags cannot be routinely used simultaneously in a given hospital. So it is not possible to obtain all necessary data in the same hospital. We decided therefore to base our analysis on mean Swiss data, except for time measurements on the ward which are not dependant on study location.	**Total no. Patients:** 60 **Inclusion criteria:** n/a **Exclusion criteria:** n/a	• Classic separate bottles system (SB) • Hospital-compouinded “All-in-one” system • Industrial three-compartment bags “All-in-one” system
Notes	**Author’s Conclusion:** The use of three-compartment TPN bags is less expensive in terms of application costs than separate bottles or hospital-compounded bag systems. TPN application costs are partly transfered from the pharmacy to the ward in the three-compartment bag system compared to hospital-compounded bags. Detailed manpower times measured in the present studies are published, allowing hospitals to calculate their own application costs using local salaries, product prices and production costs.		
Outcome measures/results	Physicians' and nurses' TPN activities for the first 24 hours of TPN, cost calculations (based on mean Swiss data)		SB system required more material and solution items ($p<0.01$) than hospital-compounded and three-compartment bags. SB system required more time ($p<0.01$) on the ward than the other two systems for all activities, except preparation which was as long as in the three-compartment bag system, because mean mixing time after breaking the connectors is long. The three- compartment bag system was signi®cantly ($p<0.01$) more time-consuming than hospital-compounded bag system for all activities except for bag installation, monitoring and disconnection, as these tasks are essentially similar for the two systems. Overall, manpower cost of SB

		system (22CHF) was about 25% higher than in hospital-compounded bag (14.50 CHF) and 2 times higher than in three-compart- ment bag systems (10CHF). Nurses' activities were responsible for a major part of manpower costs in SB and three-compartment bags systems, whereas pharmacy compounding activity resulted in the highest cost for hospital-compounded bags. A mathematical model was used to simulate the e□ects of either very short or long time (5 and 25 minutes) compounding times. The global cost varied costs between 141.60 and 154.45 CHF, and hospital-compounded bags remained signi®cantly (p<0.01) more expensive than SB and three-compartment bag systems. Medical material accounted for a more important portion of the application cost for SB system than for the other two systems, because more items were used. Net nutrient solutions cost was comparable between all three systems.

7. Turpin RS, Canada T, Rosenthal V et al. Bloodstream infections associated with parenteral nutrition preparation methods in the United States: a retrospective, large database analysis. JPEN J Parenter Enteral Nutr 2012; 36: 169-176. doi:10.1177/0148607111414714			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Retrospective database analysis 2+	**Countries:** USA **Centers:** Hospital network database **Setting:** parenteral nutrition **Funding Sources**: Baxter healthcare **Dropout rates:** n/a **Study limitations:** lack of randomization, type of catheters unclear, validity of ICD-9 codes to identify infection unclear	**Total no. Patients:** 68,984 **Inclusion criteria:** all hospitalized patients 18 years and older who received PN from January 1, 2005, to December 31, 2007 **Exclusion criteria:** patients with bacterial infection, hepatic dysfunction, hypoglycemia, acute cholecystitis, phlebitis, thrombophlebitis, and pulmonary embolism	Compounded PN (CPN) solution (n=64,315) vs. premixed multichamber bag (MCB) PN (n=4,669).
Notes	**Author's Conclusion:** Our analysis is one of the first reports describing PN patients and associated bloodstream infection rates in the real-world setting. The CPN group had a higher patient acuity, higher observed BSI rate, and longer length of stay than those who received MCB. Once illness severity and other baseline variables were accounted for, the adjusted probability of BSIs remained significantly lower for the MCB than the CPN group, particularly when compared to the HCPN group. These results were replicated in the sensitivity analyses. These findings are useful for generating hypotheses for a large-scale study and may provide impetus for individual hospital-focused quality improvement for patient safety, pharmacy compounding practices, and infection control initiatives.		

Outcome measures/results	bacterial infection, hepatic dysfunction, hypoglycemia, acute cholecystitis, phlebitis, thrombophlebitis, and pulmonary embolism	The observed bloodstream infection rate in the MCB group was 17.5%, significantly lower than that of the CPN group (26.6%; P < .001). After adjustment for various confounders, the bloodstream infection rate was still significantly different (19.6% vs 25.9%, P < .001; OR = 1.54; 95% CI, 1.39–1.69).

4.2 Gibt es eine Indikation zur Supplementierung mit Glutamin?

<u>Empfehlung 10a</u>

Eine parenterale Glutamin Supplementierung kann nicht bei Patienten empfohlen werden, die ausreichend enteral ernährt werden können. (BM, HE)

Empfehlungsgrad 0 – Starker Konsens 100 % Zustimmung

<u>Empfehlung 10b</u>

Patienten mit schwerem Leber-, Nieren- oder Multiorganversagen sollen keine zusätzliche Glutamin Supplementierung erhalten. (BM, HE)

Empfehlungsgrad A – Starker Konsens 100 % Zustimmung

<u>Empfehlung 10c</u>

Eine zusätzlich enterale Pharmakotherapie mit Glutamin sollte generell nicht durchgeführt werden. (BM, HE)
Empfehlungsgrad B - Starker Konsens 100 % Zustimmung

4.2.1 Gibt es eine Indikation für die orale Supplementierung mit Glutamin?

<u>Empfehlung 10d</u>

Für oder gegen die orale Supplementierung mit Glutamin kann keine generelle Empfehlung gegeben werden. (BM)

Empfehlungsgrad 0 – Starker Konsens 100 % Zustimmung

8. Kang K, Shu XL, Zhang YS, Liu XL, Zhao J Effect of glutamine enriched nutrition support on surgical patients with gastrointestinal tumor : A meta-analysis of randomized controlled trials. Chines Med J 2015; 128: 245-251.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-analysis 1+	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a	**Total no. Patients:** n= 1034 (13 trials) **Inclusion criteria:** RCTS with parallel controlled designs; surgical patients with GI	Six databases were systematically searched to find eligible randomized controlled trials (RCTs) from 1966 to May 2014. When estimated the analysis indexes, the relative risk (RR) was used as the effect size of the categorical variable, while the weighted mean difference (MD) was used as the effect size of a continuous variable.

	Study limitations: - a large proportion of included studies came from China, literatures of other areas were relatively few (may selection bias) - some trials' study-quality score are lower because blinding was not mentioned - the study-quality score of Gianotti *et al*. was three but the number of enrolled subjects was large, which will bring uncertainty biases to the final result of the meta-analysis - statistically significant results were not equal to the effective clinical significance, which provided clinical evidence for the effectiveness and the rational application of Gln to clinicians	tumor; supplementation of Gln was the only difference between the treatment group and the control group; reported specific outcomes: relevant biochemical indices (serum total protein, serum albumin, serum prealbumin and serum transferrin), immune indices (concentration of IgG, IgM, IgA, $CD3^+$, $CD4^+$, $CD8^+$, CD4/CD8 ratio and tumor necrosis factor alpha [TNF-α]) and clinical outcomes (infectious complication, noninfectious complication and length of hospital stay); data related to supplementation of were available **Exclusion criteria:** no randomized designs; no report of adequate statistical analysis; reviews or case reports	
Notes	**Author's Conclusion:** Glutamine enriched nutrition support was superior in improving immune function, reducing the incidence of infectious complications and shortening the length of hospital stay, playing an important role in the rehabilitation of surgical GI cancer patients.		
Outcome measures/results	the purpose of this meta-analysis was to assess the effect of Gln enriched nutrition support on surgical patients with GI tumor in term of relevant biochemical indices, immune indices, and clinical outcomes.		Thirteen RCTs, involving 1034 patients, were included in the meta-analysis. The analysis showed that Gln enriched nutrition support was more effective in increasing serum albumin (MD: 0.10; 95% confidence interval [CI]: 0.02–0.18; $P < 0.05$), serum prealbumin (MD: 1.98; 95% CI: 1.40–2.55; $P < 0.05$) and serum transferring (MD: 0.35; 95% CI: 0.12–0.57; $P < 0.05$), concentration of IgG (MD: 1.26; 95% CI: 0.90–1.63; $P < 0.05$), IgM (MD: 0.18; 95% CI: 0.11–0.25; $P < 0.05$), IgA (MD: 0.22; 95% CI: 0.10–0.33; $P < 0.05$), $CD3^+$ (MD: 3.71; 95% CI: 2.57–4.85; $P < 0.05$) and CD4/CD8 ratio (MD: 0.27; 95% CI: 0.12–0.42; $P < 0.05$). Meanwhile, it was more significant in decreasing the incidence of infectious complications (RR: 0.67; 95% CI:

		0.50–0.90; *P* < 0.05) and shortening the length of hospital stay (MD: −1.72; 95% CI: −3.31—−0.13; *P* < 0.05).

9. Bollhalder L, Pfeil AM, Tomonaga Y, Schwenkglenks M (2013) A systematic literature review and meta-analysis of randomized clinical trials of parenteral glutamine supplementation. Clin Nutr 2013; 32:213-223.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-analysis 1++	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** Fresenius Kabi (Schweiz) AG **Dropout rates:** n/a **Study limitations:** -inclusion of studies written in the English or German language -we could not rule out an element of publication bias, but had no means of locating and considering unpublished data - substantial between-trial and within-trial variety, e.g., in terms of patient types included, disease severity or surgeries performed - limited methodological quality of some trials	**Total no. Patients:** n=3107 (within 40 trials) **Inclusion criteria:** parallel-group RCTs of parenteral glutamine supplementation in populations of critically ill or major surgery patients who received parenteral nutrition, standard parenteral nutrition formulation and the glutamine supplemented formulation had to be isonitrogenous and isocaloric, standard additions of fluid, electrolytes, vitamins and minerals were allowed, irrespective glutamine dose, female or male patients, age >16 years, patients with: major surgery, surgical complication, trauma, burns, pancreatitis, or admission to an intensive care unit (ICU) for any reason. **Exclusion criteria:** enteral glutamine supplementation in any arm (Immediate use of enteral nutrition (tube feeding) in a proportion of study patients was allowable)*;* studies of patients after organ transplantation, receiving	Based on a systematic database search, RCTs published since 1990 were included if they evaluated the effect of parenteral glutamine supplementation against a background of parenteral nutrition. Enteral (tube) feeding in a proportion of patients was allowable.

		chemotherapy or with leukemia in order to reduce the risk of heterogeneity	
Notes	**Author's Conclusion:** Parenteral glutamine supplementation in severely ill patients may reduce infections, length of stay and mortality, but substantial uncertainty remains. Unlike previous meta-analyses, we could not demonstrate a significant reduction in mortality.		
Outcome measures/results	**Primary outcome measure:** mortality in the hospital or ICU **Secondary outcome measures:** mortality after 28 or 30 days, six months and/or one or three years, occurrence of infectious complications, and LOS in the hospital or ICU		Forty RCTs were eligible for meta-analysis. Parenteral glutamine supplementation was associated with a non-significant 11% reduction in short-term mortality (RR = 0.89; 95% CI, 0.77–1.04). Infections were significantly reduced (RR = 0.83; 95% CI, 0.72–0.95) and length of stay was 2.35 days shorter (95% CI, −3.68 to −1.02) in the glutamine arms. Meta-analysis results were strongly influenced by one recent trial. An element of publication bias could not be excluded.

10. Wang Y, Jiang ZM, Nolan MT, Jiang H, Han HR, Yu K, Li HL, Jie B, Liang XK The impact of glutamine dipeptide-supplemented parenteral nutrition on outcomes of surgical patients: a meta-analysis of randomized clinical trials. JPEN J Parenter Enteral Nutr 2010; 34:521-529.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-analysis 1++	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** *JP* Wu Medical Research Foundation **Dropout rates:** n/a **Study limitations:** -Although we limited the target population to surgical patients, clinical heterogeneity may still exist -variation of type of operation and the underlying diseases varied, led to variation in the surgical stress and baseline nutrition status	**Total no. Patients:** n=587 (14 randomized controlled trials) **Inclusion criteria:** randomized controlled trials with parallel control group, surgical patients, intervention: study group received GLN-PN (either GLY-GLN or ALA-GLN), whereas the control group received the isonitrogenic and isocaloric standard PN and the presence or the absence of GLN dipeptide is the only difference between the 2 groups, reported Clinical outcomes: infectious complications, length of hospital stay (LOS), mortality, cost **Exclusion criteria:**	The studies were included if they were randomized controlled trials that evaluated the effect of GLN-PN and standard PN on clinical outcomes of surgical patients. Clinical outcomes of interest were postoperative morbidity of infectious complication, mortality, length of hospital stay, and cost.

	-results should be interpreted with caution in view of the publication bias and the poor quality of the small studies	nonrandomized controlled trials with self-control, case-control design, study groups received other immunonutritional interventions (e.g., arginine, ω-3 fatty acids, recombinant human growth hormones) , patients were medical critical car, burn, trauma or organ transplantation, clinical outcomes were not of interest	
Notes	**Author's Conclusion:** GLN-PN was beneficial to postoperative patients by shortening the length of hospital stay and reducing the morbidity of postoperative infectious complications.		
Outcome measures/results	To evaluate the impact of glutamine dipeptide–supplemented parenteral nutrition (GLN-PN) on clinical outcomes (postoperative morbidity of infectious complication, mortality, length of hospital stay, and cost) in surgical patients		Fourteen randomized controlled trials (RCTs) (N = 587) were included in this meta-analysis. The results showed that glutamine dipeptide significantly reduced the length of hospital stay by around 4 days in the form of alanyl-glutamine (weighted mean difference [WMD] = −3.84; 95% confidence interval [CI] −5.40, −2.28; *z* = 4.82; *P* < .001) and about 5 days in the form of glycyl-glutamine (WMD = −5.40; 95% CI −8.46, −2.33; *z* = 3.45; *P* < .001). The overall effect indicated a significant decrease in the infectious complication rates of surgical patients receiving GLN-PN (risk ratio = 0.69; 95% CI 0.50, 0.95; *z* = 2.26; *P* = .02).

11. Novak F, Heyland DK, Avenell A, Drover JW, Su X Glutamine supplementation in serious illness: a systematic review of the evidence. Crit Care Med ; 30:2022-2029.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-analysis 1++	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** Review contains few studies with even fewer observed clinical end points, missing location or utilization of	**Total no. Patients:** n=737 of 14 trials **Inclusion criteria:** randomized control trials, elective surgical or critically ill human adult subjects, intervention with glutamine compared with placebo or standard care, reported	We reviewed 550 titles, abstracts, and articles. Primary studies were included if they were randomized trials of critically ill or surgical patients that evaluated the effect of glutamine vs. standard care on clinical outcomes

	some unpublished data, the attempt to obtain data on an intention-to-treat basis was not possible in the majority of the cases	outcome: complications, length of stay, mortality **Exclusion criteria:** studies in which glutamine was one of several nutrients given together (e.g., with arginine and omega-3 fatty acids), studies evaluating effects of glutamine keto-analogues or metabolites (namely, [alpha]-ketoglutarate, ornithine-[alpha]-ketoglutarate, or glutamate), studies that only evaluated the impact of glutamine on nutritional outcomes (i.e., nitrogen balance, amino acid profile, and others) or other biological or mechanistic endpoints (i.e., immune function, gastrointestinal permeability, and others)	
Notes	**Author's Conclusion:** In surgical patients, glutamine supplementation may be associated with a reduction in infectious complication rates and shorter hospital stay without any adverse effect on mortality. In critically ill patients, glutamine supplementation may be associated with a reduction in complication and mortality rates. The greatest benefit was observed in patients receiving high-dose, parenteral glutamine. The results of this meta-analysis have to be considered hypothesis generating. There is a signal that a benefit from glutamine may exist for surgical and critically ill patients. These two groups should be studied separately in studies powered large enough to detect clinically important differences using parenterally delivered glutamine at a dose of >0.20 $g \cdot kg^{-1} \cdot day^{-1}$. As there is no evidence of harm, further studies are warranted.		
Outcome measures/results	To examine the relationship between glutamine supplementation and hospital length of stay, complication rates, and mortality in patients undergoing surgery and experiencing critical illness.	When the results of these trials were aggregated, with respect to mortality, glutamine supplementation was associated with a risk ratio (RR) of 0.78 (95% confidence interval [CI], 0.58–1.04). Glutamine supplementation was also associated with a lower rate of infectious complications (RR, 0.81; 95% CI, 0.64–1.00) and a shorter hospital stay (-2.6 days; 95% CI, -4.5 to -0.7). We examined several a priori–specified subgroups. Although there were no statistically significant subgroup differences detected, there were some important trends. With respect to mortality,	

		the treatment benefit was observed in studies of parenteral glutamine (RR, 0.71; 95% CI, 0.51–0.99) and high-dose glutamine (RR, 0.73; 95% CI, 0.53–1.00) compared with studies of enteral glutamine (RR, 1.08; 95% CI, 0.57–2.01) and low-dose glutamine (RR, 1.02; 95% CI, 0.52–2.00). With respect to hospital length of stay, all of the treatment benefit was observed in surgical patients (-3.5 days; 95% CI, -5.3 to -1.7) compared with critically ill patients (0.9 days; 95% CI, -4.9 to 6.8).

12. Jiang ZM, Jiang H, Fürst P The impact of glutamine dipeptides on outcome of surgical patients: systematic review of randomized controlled trials from Europe and Asia: Clin Nutr Suppl 2004; 1: 17-23.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-analysis 1++	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** The Drug Evaluation Center of the Chinese State Food and Drug Administration **Dropout rates:** n/a **Study limitations:** n/a	**Total no. Patients:** n=443 of (13 RCTs) **Inclusion criteria:** Only RCTs set up with paralleled control groups (excluding self-control or cross-over trials), elective surgical patients, Studies published after 1996 **Exclusion criteria:** Critical illness, trauma, bone marrow transplantation and tumor chemotherapy, Unequal intake of calories and nitrogen between study and control, Studies not addressing any outcome mentioned above, Conference abstracts	We searched for European and Asian studies published in 1996 or later, that were RCTs for elective surgical patients. Parenteral nutrition, with or without l-alanyl-l-glutamine dipeptides (ala–gln), or in one study with or without glycyl-l-glutamine (gly–gln) dipeptides, was the only difference between intervention and control groups.
Notes	**Author's Conclusion:** The combined data demonstrate that surgical patients greatly benefit from supplementary glutamine dipeptides. The infectious complications were significantly reduced and the length of hospitalization was significantly shortened with glutamine dipeptides, and a clear trend to cost reduction was observed. The analysis of the dose–effect relation showed more benefit with high-dose glutamine dipeptide treatment.		
Outcome measures/results	The purpose of this study was to systematically review the effect of glutamine dipeptide (ala–gln and gly–gln) supplementation on		A total of 1335 titles were screened. Thirteen studies met our inclusion–exclusion criteria. Impact on infectious complication: 10 studies (pooled n = 355) were analyzed. Ala–gln significantly reduced infectious complications. Pooled relative risk

	clinical outcome in surgical patients from randomized controlled clinical trials (RCTs) carried out in Europe and Asia.	(RR) was 0.42 (95% CI 0.24–0.72; p = 0,002). Impact on the length of hospital stay (LOS): Five studies (pooled n = 179) met our criteria. Glutamine dipeptides significantly reduced LOS by a weighted mean difference of 3.86 days (95% CI −6.03 to −1.68d; P < 0,00001).

13. Jian ZM, Cao JD, Zhu XG, Zhao WX, Yu JC, Ma EL, Wang XR, Zhu MW, Shu H, Liu YW. The impact of alanyl-glutamine on clinical safety, nitrogen balance, intestinal permeability, and clinical outcome in postoperative patients: a randomized, double-blind, controlled study of 120 patients. JPEN J Parenter Enteral Nutr 1999; 23:S62-6.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Prospective, randomized, double-blind, multicenter clinical trial 1+	**Countries:** **Centers:** **Setting:** **Funding Sources:** Ministry of Public Health of China, Fresenius AG **Dropout rates:** **Study limitations: n/a**	**Total no. Patients:** n=120 • Intervention group n=60 • Control group n=60 **Inclusion criteria:** gastrointestinal surgery patients who needed PN for 6 days **Exclusion criteria:**	-Intervention group: parenteral nutrition (isonitrogenous and isocaloric) supplemented with alanyl-glutamine (Ala-GLN) (0,50 g/kg per day) -control group: isonitrogenous and isocaloric parenteral nutrition without supplementation
Notes	The clinical safety and outcome were observed for 60 patients in 2 centers (30 each). 60 patients from 2 additional centers (30 each) were observed for clinical safety, nitrogen balance, intestinal permeability and clinical outcome. **Author's Conclusion:** Ala-Gln-supplemented PN was clinically safe, had better nitrogen balance, and maintained intestinal permeability in postoperative patients. The clinical outcome of the patients in study group was better; it was significantly different from the control group.		
Outcome measures/results	Length of hospital stay (clinical outcome), infection rate ,nitrogen balance, lactulose/mannitol ratio (intestinal permeability), plasma amino acid profile		The patients in both groups were comparable prior to the operation. Vital signs and clinical chemical parameters were similar between groups. L/M ratio was 0.047+/-0.029 in control and 0.058+/-0.049 in study group before the operation (AOD-3). The L/M ratio was 0.132+/-0.081 in the control group, and 0.097+/-0.063 in study group on the seventh postoperative day. The difference of L/M ratio between groups was significant (p = .02). The cumulative nitrogen balance values were -5+/-162 mg/kg for 6 days in control and 144+/-145 mg/kg for 6 days in study group (p = .0004). All the patients recovered without incision infection. However, there were 3 cases that had infection-related complications in the control group; the difference was not significant between groups. The hospital stay in the study group was 12.5 days, which was 4 days less than that of the control group (p = .02).

14. Mertes N, Schulzki C, Goeters C, Winde G, Benzing S, Kuhn KS, Van Aken H, Stehle P, Furst P Cost containment through L-alanyl-L-glutamine supplemented total parenteral nutrition after major abdominal surgery: a prospective randomized double-blind controlled study. Clin Nutr 2000; 19:395-401.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
prospective randomized double-blind controlled study 1+	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** Fresenius Kabi **Dropout rates:** n=13 (26%) **Study limitations:** n/a	**Total no. Patients:** n=50 • Intervention group n=19 • Control group n=18 **Inclusion criteria:** patients with elective major abdominal and abdomino-thoracic surgery, adult patients aged 18±84 years and with BMI between 20 and 30 kg/m2. **Exclusion criteria:** instability of vital functions, chronic endocrine disease (diabetes mellitus, thyroid dysfunction, etc.), acute or chronic liver disorders (Quick < 45%, Bilirubin >5 mg/dl or threefold transaminase levels), renal insufficiency (creatinine clearance < 25 ml/min), congestive heart failure > NY-HA III, organ transplantation, glucocorticoid and/or catecholamine therapy, alcohol or drug abuse and psychiatric disorders, child-bearing potential, inborn errors of amino acid metabolism , severe drug hypersensitivity or other allergic diathesis, Continuous bleeding over several days with a postoperative transfusion need >2 erythrocyte concentrates/d and/or >4 units of fresh frozen plasma/d for 2	thirty-seven patients following major abdominal surgery received an isonitrogenous isoenergetic parenteral nutrition with or without alanyl-glutamine supplementation (0.5 g/kg BW/day) over a 5day period.

		consecutive days, Serious adverse drug reactions, violation of the study protocol (e.g. less than 85% of the planned parenteral nutrition), the development of severe organ failure (MOF45) or the need for major unplanned surgical interventions	
Notes	Randomization is mentioned, but method not specified **Author's Conclusion:** The results of the study confirm that supplementation with synthetic alanyl-glutamine dipeptide is associated with cost containment due to shortened hospitalization and improved nitrogen economy.		
Outcome measures/results	To assess the effects of supplemental L-alanyl-L-glutamine (Ala-Gln) TPN treatment on nitrogen balance, plasma amino acids, selected mediators and protein concentrations, the length of hospital stay in unselected patients after major abdominal surgery		Supplemental alanyl-glutamine improved the overall mean (−3.5±1.6 vs. −5.5±1.4 g N;*P*<0.05) and cumulative nitrogen balance (−14.1±9.1 vs. −21.7±11.4 g N;*P*<0.05) compared with the isonitrogenous, isoenergetic standard regimen. Alanyl-glutamine normalized plasma glutamine concentration and reduced the length of hospital stay (12.8±2.6 vs. 17.5±6.4 days; *P*<0.05).

15. Morlion BJ, Stehle P, Wachtler P, Siedhoff HP, Koller M, Konig W, Furst P, Puchstein C Total parenteral nutrition with glutamine dipeptide after major abdominal surgery: a randomized, double-blind, controlled study. Ann Surg 1998; 227:302-308.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** n/a	**Total no. Patients:** n=28 • Intervention group: n=15 • Control group: n=13 **Inclusion criteria:** patients admitted for elective resection of carcinoma of the colon or rectum **Exclusion criteria:** manifest metabolic diseases (e.g., diabetes mellitus,	All patients received isonitrogenous (0.24 g nitrogen $kg^{(-1)}$ $day^{(-1)}$) and isoenergetic (29 kcal/122 kJ $kg^{(-1)}$ $day^{(-1)}$) TPN over 5 days (24hours a day). intervention group -1.2 g of amino acids and 0.3 g of L-alanyl-L-glutamine (Ala-Gln) $kg^{(-1)}$ $day^{(-1)}$ control group -1.5 g of amino acids $kg^{(-1)}$ $day^{(-1)}$

		hyperthyroidism), chronic renal or liver disease	
Notes	Randomization is mentioned, but method not specified **Author's Conclusion:** We confirm the beneficial effects of Gln dipeptide-supplemented TPN on nitrogen economy, maintenance of plasma Gln concentration, lymphocyte recovery, cysteinyl-leukotriene generation, and shortened hospital stay in surgical patients.		
Outcome measures/results	To assess the efficacy of glutamine (Gln) dipeptide-enriched total parenteral nutrition (TPN) on selected metabolic, immunologic, and clinical variables in surgical patients. *Outcome measures:* Length of stay in hospital, nitrogen balance on days 2–5 after the operation, and immune status (lymphocyte count) on days 1, 3, and 6 after the operation.	No side effects or complaints were noted. Patients receiving Gln dipeptide revealed improved nitrogen balances (cumulative balance over 5 days: -7.9 +/- 3.6 vs. -23.0 +/- 2.6 g nitrogen), improved lymphocyte recovery on day 6 (2.41 +/- 0.27 vs. 1.52 +/- 0.17 lymphocytes/nL) and improved generation of cysteinyl-leukotrienes from polymorphonuclear neutrophil granulocytes (25.7 +/- 4.89 vs. 5.03 +/- 3.11 ng/mL). Postoperative hospital stay was 6.2 days shorter in the dipeptide-supplemented group.	

16. Neri A, Mariani F, Piccolomini A, Testa M, Vuolo G, Di Cosmo L (2001) Glutamine-supplemented total parenteral nutrition in major abdominal surgery. Nutrition 2001; 17:968-969.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** n/a	**Total no. Patients:** n=33 • Intervention group: n=16 • Control group: n=17 **Inclusion criteria:** patients undergoing major abdominal surgery for cancer, where total parenteral nutrition (TPN) was part of standard postoperative treatment **Exclusion criteria:** distant metastases, high-risk patients according to Seltzer's Nutritional Prognostic index, diabetes, hyper or hypothyroidism, liver and kidney disfunctions, American Society of	All patients received an isocaloric (30 kcal/kg of body weight per day), isonitrogenous (0.2 g/kg of body weight per day) TPN, 65% of non-protein energy came from glucose and 35% from a medium-chain fat emulsion. TPN began the day after surgery and continued for at least 7 d. Intervention group -1.2 g of amino acids per kilogram of body weight per day supplemented with Gln, given as dipeptide alanyl-Gln control group -1.5 g of amino acids per kilogram of body weight per day

		Anaesthesiologists (ASA) score above 3	
Notes	Randomization is mentioned, but method not specified. **Author's Conclusion:** These data, in our opinion, support supplementation of Gln to standard TPN in patients undergoing major abdominal surgery and substantially confirm the results of other studies finding positive effects on postoperative or posttrauma recovery**.**		
Outcome measures/results	Investigation of the effects of Glutamine (Gln) supplementation to TPN on postoperative outcome of patients after major abdominal surgery. **Primary outcome measure:** nitrogen balance and lymphocyte count in the early postoperative period, from 1 to 6 d after surgery, incidences of surgical infections, hospital mortality **Secondary outcome measures:** length of hospital stay	TPN was well tolerated in all patients and administered for a median of 8 d after surgery in the control group (range = 7–13 d) and the study group (range = 7–11 d). Lymphocyte counts were comparable in the two groups, except for a modest, non-significant difference on postoperative day 6 in favor of the study group. Patients receiving Gln-supplemented TPN had significantly better daily nitrogen balances on days 2 to 4 and better cumulative nitrogen balance on days 2 to 5. One wound infection and three infection-related complications (two pulmonary and one urinary tract) were recorded in the control group, whereas only one infectious complication (pulmonary) occurred in the study group, but this difference did not reach statistical significance. Postoperative mortality was absent. Hospital stay was significantly shorter in the Gln-supplemented group (11.5±2.5 versus 15±3 d; $P < 0.05$).	

17. Fuentes-Orozco C, Anaya-Prado R, Gonzalez-Ojeda A, Arenas-Marquez H, Cabrera-Pivaral C, Cervantes-Guevara G, Barrera-Zepeda LM L-alanyl-L-glutamine-supplemented parenteral nutrition improves infectious morbidity in secondary peritonitis. Clin Nutr 2004; 23:13-21.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** Mexican Institute of Social Securit, Fresenius Kabi **Dropout rates:** n/a **Study limitations:** n/a	**Total no. Patients:** n=33 • Intervention group n=17 • Control group n=16 **Inclusion criteria:** Patients with diagnosis of secondary peritonitis who required TPN **Exclusion criteria:** renal failure (creatinine >180 µmol/l) or hepatic failure (bilirubin >40 µmol/l, alanine	Intervention group -TPN supplemented with l-alanyl-l-glutamine, 0.40 g/kg/d plus 8.5% standard amino acids (1.1 g/kg/d) control group - standard TPN with protein given as 8.5% amino acids (1.5 g/kg/d) TPN formulae were isonitrogenous and Isocaloric, which commenced the morning after surgery and ran continuously for 10 consecutive days.

		aminotransferase >100 U/l and aspartate aminotransferase >100 U/l), patients with severe neutropenia (<500 cells/mm^3), patients receiving cytotoxic, radiation and/or steroid therapy, patients with hemodynamic instability or resistant to aggressive fluid resuscitation	
Notes	**Author's Conclusion:** l-alanyl-l-glutamine-supplemented TPN improved the infectious morbidity of patients with secondary peritonitis. Gln supplementation to parenteral nutrition may be an alternative for enhancing host defenses and improving infectious morbidity.		
Outcome measures/results	the aim of this study was to investigate whether the provision of Gln-enriched TPN after surgical and medical treatment of secondary peritonitis improves infectious morbidity **Primary outcome measure:** Infectious morbidity, nitrogen balance, leukocytes, lymphocytes, subpopulations CD_4 and CD_8, Immunoglobulin A (IgA), total proteins, albumin **Secondary outcome measures:** hospital and intensive care unit (ICU) stays, and mortality	Patients in both groups were comparable prior to the operation. Nitrogen balance and the levels of albumin and IgA were significantly better than those in the control group. Also, a significant reduction in the infectious morbidity was found in the Gln-treated group. Lymphocyte counts as well as subpopulations CD_4 and CD_8, and proteins showed a propensity to improvement and a tendency to reduced rates of mortality were observed when comparing the groups. Hospital and ICU stays were similar.	

18. Exner R, Tamandl D, Goetzinger P, Mittlboeck M, Fuegger R, Sautner T, Spittler A, Roth E Perioperative GLY-GLN infusion diminishes the surgery-induced period of immunosuppression: accelerated restoration of the lipopolysaccharide-stimulated tumor necrosis factor-alpha response. Ann Surg 2003; 237:110-115.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** n/a	**Total no. Patients:** n=45 • GLY-GLN group: n=15 • ALA-GLN group: n=15 • Control group: n=15 **Inclusion criteria:** patients undergoing major abdominal surgery **Exclusion criteria:**	GLY-GLN (glycyl-l-glutamine) group - 0.5 g/kg/24 h GLN as dipeptides administered as GLY-GLN starting 24 hours before surgery until 48 hours postoperatively ALA-GLN (l-alanyl-l-glutamine) group -0.5 g/kg/24 h GLN as dipeptides administered as ALA-GLN starting 24 hours before surgery until 48 hours postoperatively Control group - glutamine-free amino acid solution

		acute liver failure (Normotest < 15%, signs of encephalopathy), liver cirrhosis, Child B or C type 1 diabetes, HIV infection, thyroid disorder, platelets less than 50,000/µL, leukocytes less than 2,500/µL, renal insufficiency (creatinine clearance < 25 mL/d), need for transfusion of more than two units of packed red cells/d or more than four units of fresh-frozen plasma/d, inclusion in other studies, pregnancy, and mental disorders	
Notes	**Author's Conclusion:** In this study perioperative infusion of GLY-GLN reduced immunosuppression. The effect of GLN-containing dipeptides seems to be different when administered in glycine or alanine form.		
Outcome measures/results	To investigate whether the administration of different glutamine-containing dipeptides, glycyl-L-glutamine (GLY-GLN) and L-alanyl-L-glutamine, has a differing impact on perioperative immunomodulation.	The groups were comparable in age, gender distribution, and length of operative time. At the end of surgery, a significant reduction in ex vivo LPS-stimulated TNF-α production was observed in all groups. In patients who received GLY-GLN, the induced TNF-α production was restored after 48 hours.	

19. Jiang-Xiang S, Xiao-Huang T, Lie W, Chen-Jing L Glutamine dipeptide-supplemented parental nutrition in patients with colorectal cancer. Clin Nutr Suppl 2004; 1:49-53.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** n/a	**Total no. Patients:** n=40 • Ala-gln group n=20 • TPN group n=20 **Inclusion criteria:** adult patients with colorectal cancer **Exclusion criteria:**	Ala-gln group - ala-gln supplemented (0.3–0.4 g/ kg^{-1} d^{-1}) parenteral nutrition (25–30 kcal kg^{-1} d^{-1} energy; lipids 35–50% of nonprotein energy; 0.15–0.20 kg^{-1} d^{-1} nitrogen) starting on postoperative day 2 for 7 days TPN group - isocaloric and iso-nitrogenous standard parenteral nutrition (25–30 kcal kg^{-1} d^{-1} energy; lipids 35–50% of nonprotein energy; 0.15–0.20 kg^{-1} d^{-1} nitrogen) starting on postoperative day 2 for 7 days

Notes	-The patients' immune parameters were compared with those of a matched group of 20 patients with gastrointestinal benign diseases preoperatively (control group) -Randomization is mentioned, but method not specified **Author's Conclusion:** Glutamine dipeptide supplementation improved immune-function and nitrogen balance in patients with colorectal cancer postoperatively.	
Outcome measures/results	Plasma/serum/blood IgA; IgG; IgM, C3, C4, CH50 (50% complement hemolysis unit),CD3, CD4, CD8, CD25, NK, IL-2R expression, nitrogen balance (blood samples were collected on the preoperative day as well as on the postoperative day 1, 4, 7)	Compared to a matched group of patients with gastrointestinal benign diseases (control group) colorectal cancer patients showed immune suppression preoperatively. Postoperatively, from the fourth day onwards CD4, NK cell counts, CD4/CD8 ratio and IL-2R expression were higher (Po0.05) in the ala-gln group as compared with the TPN group. Nitrogen balance became positive from postoperative day 4 onwards in the ala-gln group, whereas it remained negative in the TPN group for the study period.

20. Lin MT, Kung SP, Yeh SL, Liaw KY, Wang MY, Kuo ML, Lee PH, Chen WJ Glutamine-supplemented total parenteral nutrition attenuates plasma interleukin-6 in surgical patients with lower disease severity. World J Gastroenterol 2005; 11:6197-6201.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
randomized, double-blind, parallel multicenter clinical trial 1+	**Countries:** Taiwan **Centers:** National Taiwan University Hospital, Veterans General Hospital **Setting:** n/a **Funding Sources:** Frensenius AG **Dropout rates:** n/a **Study limitations:** n/a	**Total no. Patients:** n=48 • Intervention group: n=25 (APACHE II≤ 6: n=10, APACHE II≤ 6: n=15) • Control group: n=23 (APACHE II≤ 6: n=11, APACHE II≤ 6: n=12= **Inclusion criteria:** major gastrointestinal surgery patients who needed TPN for nutritional support, APACHE II between 2-10 **Exclusion criteria:** major metabolic, circulatory and renal diseases	intervention group -0.972 g amino acids/kg per day and 0.417 g L-alanyl-L-glutamine (Ala-Gln)/kg per day for 6 days postoperatively Control group (Conv) -conventional TPN solution received 1.5 g amino acids/kg per day for 6 days postoperatively Both TPN were isonitrogenous (0.228 g nitrogen/kg per d) and isocaloric (30 kcal/kg per d)
Notes	**Author's Conclusion:**		

	TPN supplemented with Gln dipeptide had no effect on plasma IL-8 levels after surgery. However, Gln supplementation had a beneficial effect on decreasing systemic IL-6 production after surgery in patients with low admission illness severity, and lower plasma IL-6 may improve nitrogen balance in patients with abdominal surgery when Gln was administered.	
Outcome measures/results	To evaluate whether the effect of Gln dipeptide-enriched total parenteral nutrition (TPN) on postoperative cytokine alteration depended on the disease severity of surgical patients. Therefore, blood samples were collected on d 1 and d 6 postoperatively for plasma interleukin (IL)-2, IL-6, IL-8, and interferon (IFN)-g analysis.	Plasma IL-2 and IFN-g were not detectable. IL-6 concentrations were significantly lower on the 6th postoperative day in the Ala-Gln group than those in the Conv group in patients with APACHE II≤6, whereas no difference was noted in patients with APACHE II>6. There was no difference in IL-8 levels between the two groups. No difference in cumulative nitrogen balance was observed on d 2-5 after the operation between the two groups (Ala-Gln -3.2±1.6 g *vs* Conv -6.5±2.7 g). A significant inverse correlation was noted between plasma IL-6 levels and cumulative nitrogen balance postoperatively in the Ala-Gln group, whereas no such correlation was observed in the Conv group.

21. Yao GX, Xue XB, Jiang ZM, Yang NF, Wilmore DW Effects of perioperative parenteral glutamine-dipeptide supplementation on plasma endotoxin level, plasma endotoxin inactivation capacity and clinical outcome. Clin Nutr 2005; 24:510-515.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** n/a	**Total no. Patients:** n=40 • Intervention group n=20 • Control group n=20 **Inclusion criteria:** men and non-pregnant women 35–75 years of age who required gastrointestinal surgery and were considered appropriate candidates to receive perioperative parenteral nutrition from 1 day before operation to 3 days after operation **Exclusion criteria:** Immunosuppressive drug therapy within the previous 6 months; an immunosuppressive condition, including acquired immunodeficiency syndrome,	Intervention group - standard parenteral nutrition ((60% calories as carbohydrate and 40% as fat, isocaloric (25 kcal/kg/day), isonitrogenous) supplemented with the dipeptide alanyl-glutamine (0.5 g/kg/day) ,1 day before operation to the 3rd day after operation for 5 days Control group -standard parenteral nutrition ((60% calories as carbohydrate and 40% as fat, isocaloric (25 kcal/kg/day), isonitrogenous), 1 day before operation to the 3rd day after operation for 5 days

		autoimmune disorders, organ transplantation, radiation therapy or chemotherapy within the previous 6 months; insulin-dependent diabetes mellitus (type 1); chronic obstructive pulmonary disease with a PCO_2 >45 mmH_2O (6 kPa) on admission, cardiac function class 3 or 4, renal disease requiring peritoneal or hemodialysis or with an admission serum creatine concentration of >2.5 mg/dL (221 µmol/L) and hepatic dysfunction, with biopsy-proven cirrhosis or a serum total bilirubin of >3.0 mg/dL (51.3 µmol/L) on admission	
Notes	**Author's Conclusion:** Perioperative parenteral nutrition supplemented with dipeptide alanyl-glutamine ameliorated postoperative immunodepression without direct effect on endotoxemia.		
Outcome measures/results	Blood samples were collected on the morning of 1 day before operation, 3 h after operation, and on the morning of 1, 4 and 7 days after operation and analyzed for plasma endotoxin level, plasma sCD14 level and plasma endotoxin inactivation capacity (EIC)		There were no differences between the two groups on plasma endotoxin level. After surgery a rapid reduction in plasma EIC was observed in both groups, a significant restoration of the plasma EIC was observed on the morning of 1 and 4 days after surgery in the study group (0.12±0.02 and 0.078±0.022 EU/mL, respectively, P<0.01P<0.01). A significant rise in plasma sCD14 level was found in the study group on the morning of 1 and 4 days after surgery (14.32±1.69 and 10.34±1.14 µg/mL, respectively, P<0.01P<0.01). Shortened hospital stay was observed in the study group (11.7±2.0 days in the control group and 10.6±1.2 days on the study group respectively, P=0.03P=0.03).

22. Heyland D, Muscedere J, Wischmeyer PE, Cook D, Jones G, Albert M, Elke G, Berger MM, Day AG, Canadian Critical Care Trials Group. A randomized trial of glutamine and antioxidants in critically ill patients. N Engl J Med 2013; 368: 1489-1497.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT	**Countries:** n/a	**Total no. Patients:** n=1223	The administration of all study

1+	**Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n=5 (0,4%) **Study limitations:** n/a	• Glutamine group n=301 • Placebo group n=300 • Antioxidant group n=307 • Glutamine+antioxidant group n=310 **Inclusion criteria:** Mechanically ventilated adult patients (>18 years old) admitted to ICU if they had 2 or more of the following organ failures related to their acute illness: A PaO2/FiO2 ratio of <300, Clinical evidence of hypoperfusion defined as the need for vasopressor agents (norepinephrine, epinephrine, vasopressin, >5 μg/kg/min of dopamine, or >50 μg/min phenylephrine) for greater than or equal to 2 hours, In patients without known renal disease, renal dysfunction defined as a serum creatinine >171 μmol/L or a urine output of less than 500 ml/last 24 hours (or 80 ml/last 4 hours if a 24-hour period of observation not available); In patients with acute on chronic renal failure (pre-dialysis), an absolute increase of >80 μ mol/L from baseline or pre-admission creatinine or a urine output of <500 ml/l last 24 hours (or 80 ml/last 4 hours) will be required; A platelet count of <50 x109/L **Exclusion criteria:**	solutions was initiated as soon as possible after randomization and were administered for a maximum of 28 days, until discharge from the ICU or death. Glutamine group - glutamine supplementation: 0.35 g per kilogram of body weight per day intravenously according to ideal body weight, provided as 0.50 g of the dipeptide alanyl-glutamine per kilogram per day given intravenously and 42.5 g of alanyl-glutamine and glycine-glutamine dipeptides, which provide 30 g of glutamine, per day given enterally Placebo group -matching placebo solutions intravenously and enterally Antioxidant group - 500 μg of selenium intravenously, vitamins and minerals enterally: 300 μg of selenium, 20 mg of zinc, 10 mg of beta carotene, 500 mg of vitamin E, and 1500 mg of vitamin C Glutamine+antioxidant group -glutamine and antioxidant supplementation (see above)

		>24 hours from admission to the intensive care unit (ICU); Patients who are moribund (not expected to be in ICU for more than 48 hours due to imminent death); lack of commitment to full aggressive care (anticipated withholding or withdrawing treatments in the first week) ; absolute contraindication to enteral nutrients (e.g., gastrointestinal [GI] perforation, obstruction or no GI tract access for any reason): patients with severe acquired brain injury: a) Significant head trauma (defined as an injury, in the opinion of the investigator, that represents a severe, disabling, or fatal brain injury) b) Grade 4 or 5 subarachnoid hemorrhage c) Stroke resulting in coma and intubation d) Post-cardiac arrest with suspected significant anoxic brain injury Seizure disorder requiring anticonvulsant medication; Cirrhosis - Child's class C liver disease; Metastatic cancer or Stage IV Lymphoma with life expectancy <6 months; Routine elective cardiac surgery (patients with complicated peri-operative course requiring pressors, intra-aortic balloon pump, ventricular assist devices can be included); Patients with primary admission diagnosis of burns (>30% body surface area); Weight less than 50	

		kg or greater than 200 kg; pregnancy or lactating; Previous randomization in this study; Enrollment in a related ICU interventional study	
Notes	**Author's Conclusion:** this trial showed that the early administration of glutamine in critically ill patients with multiorgan failure was harmful. The observation that the majority of these patients did not have glutamine deficiency early in the course of their critical illness challenges the prevailing concept that glutamine is an essential nutrient that is deficient in critically ill patients and requires immediate supplementation. We also conclude that antioxidant supplementation as provided in this trial conferred no therapeutic benefit.		
Outcome measures/results	**Primary outcome measure:** 28-day mortality **Secondary outcome measures:** length of ICU stay, development of infectious complications, multiple organ dysfunction using sequential organ failure assessment scores 3, duration of mechanical ventilation, hospital length of stay, antibiotic use, survival up to 6 months	There was a trend toward increased mortality at 28 days among patients who received glutamine as compared with those who did not receive glutamine (32.4% vs. 27.2%; adjusted odds ratio, 1.28; 95% confidence interval [CI], 1.00 to 1.64; P=0.05). In-hospital mortality and mortality at 6 months were significantly higher among those who received glutamine than among those who did not. Glutamine had no effect on rates of organ failure or infectious complications. Antioxidants had no effect on 28-day mortality (30.8%, vs. 28.8% with no antioxidants; adjusted odds ratio, 1.09; 95% CI, 0.86 to 1.40; P=0.48) or any other secondary end point. There were no differences among the groups with respect to serious adverse events (P=0.83).	

23. Cui Y, Hu L, Liu Y, Wu Y, Jing L Intravenous alanyl-L-glutamine balances glucose-insulin homeostasis and facilitates recovery in patients undergoing colonic resection - a randomised trial. Eur J Anaestesiol 2014; 31: 212-218.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries:** n/a **Centers:** n/a **Setting:** Southeast University Affiliated Zhongda Hospital, China **Funding Sources:** Department of Anesthesiology, Southeast University Affiliated	**Total no. Patients:** n=60 • Glutamine group n=20 • Dilution vehicle group n=20 • Control group n=20 **Inclusion criteria:** patients of either sex; aged from 35 to 75 years; BMI between 18.5 and 25 kg m^{-2}; ASA physical status I–II;	Glutamine group - intravenous infusion of 0.5 g kg^{-1} of glutamine (22.4 ml kg^{-1} of 3.4% Ala-glutamine) administered 24 h before and 1 h after the start of surgery dilution vehicle group - intravenous infusion of 8.5% 18AA-II (an 8.5% compound amino acid injection containing 18 amino acids with a total of amino acids 85 g) administered 24 h before and 1 h after the start of surgery Control group - intravenous infusion of physiological saline administered 24 h before and 1 h after the start of surgery

	Zhognda Hospital, Nanjing, China **Dropout rates:** n/a **Study limitations:** n/a -no measurement of plasma glutamine levels after the different interventions -no assessment of pain (no exclusion of influence of postoperative pain on patients' outcomes)	diagnosed with colon cancer; and listed for elective cancer resection **Exclusion criteria:** diabetes mellitus, preoperative jaundice, or immunologic, metabolic disease, cardiovascular or cerebrovascular disease; if they were obese, infection or critical illness; unable to take oral fluids or malabsorption of the gut; Intake of thyroid medication, corticosteroids or diuretic medication; pregnancy; surgeries which lasted more than 5 h or the transfusion volume was more than 1500 ml before T3 or blood loss more than 500 ml or there was a need of blood transfusion	
Notes	**Author's Conclusion:** Intravenous supplementation with glutamine balances glucose–insulin homeostasis and facilitates recovery in patients undergoing colon cancer resection.		
Outcome measures/results	**Primary outcome measure:** Insulin resistance index and insulin sensitivity check index **Secondary outcomes measures:** blood glucose, insulin, tumor necrosis factor-alpha (TNF-[alpha]) , free fatty acid measured at 24 h before surgery (T1), 30 min before anesthesia (T2), 2.5 h after the beginning of surgery (T3), and 1 h (T4) and 24 h (T5) after the end of surgery, first passage of wind, length of hospital stay were recorded	Intraoperative and postoperative insulin resistance or calculated insulin sensitivity were worse in the physiological saline and 18AA-II treated patients compared with those treated with glutamine ($P < 0.05$). Blood glucose increased intraoperatively and postoperatively in all three groups compared with baselines ($P < 0.05$), but glutamine attenuated the peak level of blood glucose ($P < 0.05$). Glutamine reduced the intraoperative and postoperative concentrations of TNF-[alpha] and free fatty acid, ($P < 0.05$), and shortened the time to the first passage of wind after surgery and the length of hospital stay ($P < 0.05$).	

24. Gianotti L, Braga M, Biffi R, Bozzetti F, Mariani L, GlutamItaly Research Group of the Italian Society of Parenteral, and Enteral Nutrition Perioperative intravenous glutamine supplementation in major abdominal surgery for cancer: a randomized multicenter trial. Ann Surg 2009; 250:684-690.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
prospective, randomized,	**Countries:** n/a **Centers:** n/a	**Total no. Patients:** n=555	Intervention group (Ala-Glu group)

multicenter clinical trial 1+	**Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n=127 (22,88%) **Study limitations:** n/a	• Intervention group n=212 • Control group n=216 **Inclusion criteria:** adult, well-nourished (preoperative weight loss <10% with respect to usual body weight), with documented cancer of the gastrointestinal tract (GI), and candidate to elective major surgery **Exclusion criteria:** denied written informed consent, Child-Pugh class C, New York Heart Association class (NYHA) >3, renal insufficiency (hemodialysis, plasma creatinine >3 mg/dL, or both), respiratory insufficiency (arterial blood PaO_2 <70 mm Hg), Karnofsky performance status <80, American Society of Anesthesiology score (ASA) >3, ongoing infection, immunosuppressive diseases (including steroid use), emergency operation, or pregnancy	- intravenous infusion of l-alanine-L-glutamine dipeptide (0.40 g/kg/d, equal to 0.25 g of free glutamine) in 500 mL 5% glucose vehicle (Ala-Glu group) , treatment started the day before operation and continued postoperatively for at least 5 days. Control group: -500 mL 5% glucose vehicle No postoperative artificial nutrition was allowed unless patients could not adequately eat by day 7.
Notes	The paper is a much-discussed topic (see discussion by other experts at the end of the paper) **Author's Conclusion:** Perioperative glutamine does not affect outcome in well-nourished gastrointestinal cancer patients.		
Outcome measures/results	**Primary outcome measure:** postoperative complication rate **Secondary outcome measures:** reduction of length hospitalization, need of postoperative artificial nutritional support		Patients were homogenous for baseline and surgical characteristics. Mean percent of weight loss was 1.4 (2.7) in controls and 1.4 (2.4) in Ala-Glu group. Overall postoperative complication rate was 34.9% (74/212) in Ala-Glu and 32.9% (71/216) in control group (P = 0.65). Infectious morbidity was 19.3% (41/212) in Ala-Glu group and 17.1% (37/216) in controls (P = 0.55). The rate of major complications was 7.5% (16/212) in Ala-Glu group and 7.9% (17/216) in controls (P = 0.90). Mean length of hospitalization was 10.2 days (4.8) in Ala-Glu group versus 9.9 days (3.9) in controls (P = 0.90). The rate of patients requiring postoperative artificial nutrition was 13.2% (28/212) in Ala-Glu group and 12.0% (26/216) in controls (P = 0.71).

25. Ziegler TR, May Ak, Hebbar G, Easley KA, Griffith DP, Dave N, Collier BR, Cotsonis GA, Hao L, Leong T; Manatunga AK, Rosenberg ES, Jones DP, Martin GS, Jensen GL, Sax HC, Kudsk KA, Galloway JR, Blumberg HM, Evans ME, Wischmeyer PE Efficacy and safety of glutamine-supplemented parenteral nutrition in surgical ICU patients: an American multicenter randomized controlled trial. Ann Surg 2016; 263: 646-655.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+ ROB 14/14	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** National Institutes of Health grants, Fresenius Kabi **Dropout rates:** n/a **Study limitations:** n/a	**Total no. Patients:** n=150 • Intervention (GLN_PN) group n=75 • Control group n=75 **Inclusion criteria:** patient required admission to the surgical intensive care unit (SICU) following cardiac, non-neurologic vascular, or complete or partial esophageal, gastric, or intestinal surgery or after exploratory laparotomy to identify a source of peritonitis when evidence of a bowel perforation was present; patient deemed by the investigator team (each led by an expert in SICU nutrition support) and attending physician to likely require parenteral nutrition (PN) for ≥ 7 subsequent days; age 18–90 years; body mass index (BMI) < 40 kg/m^2 prior to surgery; requires current SICU care and is ≤ 14 days postoperative from the following open (non- laparoscopic) surgical procedures: CABG, cardiac valve, vascular (non-neurological), complete or partial esophageal, gastric, small bowel, colon and/or rectal resection or exploratory laparotomy to identify a source of	GLN-PN (glutamine group) -parenteral nutrition containing alanyl-GLN dipeptide (0.5 g/kg/d), proportionally replacing amino acids in PN ; PN was isonitrogenous, isocaloric PN [1.5 g/kg/d amino acids (AAs) and energy at 1.3× estimated basal energy expenditure]; PN was given for a maximal time of 28 days after entry STD-PN (control group) -standard glutamine-free parenteral nutrition (isonitrogenous, isocaloric PN (1.5 g/kg/d amino acids ,energy at 1.3× estimated basal energy expenditure)); PN was given for a maximal time of 28 days after entry both groups: dextrose initially comprised 70% of study PN non-amino acid kcal and a standard soybean oil-based fat emulsion initially comprised 30% of study PN non-amino acid kcal daily; Conventional formulations of vitamins and trace elements were added daily

		peritonitis when evidence of a bowel perforation was present; deemed to require central venous PN for ≥ 7 subsequent days after entry; central venous access for administration of the study PN in place by entry; patient's primary physician(s) will allow the investigative team to manage the study PN and enteral feedings during the current hospitalization **Exclusion criteria:** pregnancy; current clinical sepsis, defined as an unstable blood pressure despite vasopressor agent support AND mean arterial pressure (MAP) < 60 mm Hg on at least 3 consecutive readings within a 3-hour period during the 24 hours prior to study entry; current malignancy requiring surgery as the study qualifying operation or receiving an active regimen of chemotherapy and/or radiotherapy to treat a previously diagnosed malignancy; history of seizures or pre-existing seizure disorder; current encephalopathy; known history of cirrhosis or a serum total bilirubin level ≥ 10.0 mg/dL); history of chronic renal failure requiring dialysis, or significant renal dysfunction (defined as serum creatinine > 2.5 mg/dL and not receiving continuous renal replacement therapy (CRRT) or the patient requires acute hemodialysis	

		postoperatively; concomitant burn or trauma injury; previously organ transplant; history of HIV/AIDS; administration of any investigational drug within 60 days prior to study entry; administration of enteral or parenteral enteral feedings enriched in arginine and/or glutamine within 30 days prior to study entry; subject unable or unwilling to participate in study procedures such as longitudinal blood draws and outpatient follow-up visits	
Notes	Subjects were followed for a total of 6 months after entry. **Author's Conclusion:** PN supplemented with GLN dipeptide was safe, but did not alter clinical outcomes among surgical intensive care unit patients.		
Outcome measures/results	**Primary outcome measure:** hospital mortality , incident total hospital-acquired infections **Secondary outcome measures:** ventilator-free days, ICU and hospital LOS after entry		Baseline characteristics, days on study PN and daily macronutrient intakes via PN and EN, were similar between groups. There were 11 hospital deaths (14.7%) in the GLN-PN group and 13 deaths in the STD-PN group (17.3%; difference, -2.6%; 95% confidence interval, -14.6% to 9.3%; P = 0.66). The 6-month cumulative mortality was 31.4% in the GLN-PN group and 29.7% in the STD-PN group (P = 0.88). Incident bloodstream infection rate was 9.6 and 8.4 per 1000 hospital days in the GLN-PN and STD-PN groups, respectively (P = 0.73). Other clinical outcomes and adverse events were similar.

26. Tan HB, Danilla S, Murray A et al. Immunonutrition as an adjuvant therapy for burns. Cochrane Database Syst Rev 2014. doi:10.1002/14651858.CD007174.pub2: CD007174. doi:10.1002/14651858.CD007174.pub2			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic Review 1++	**Countries:** Italy, Chile, France, Canada, China, USA **Centers:** n/a **Setting:** hospital **Funding Sources:** n/a	**Total no. Studies:** 16 **Inclusion criteria:** studies with at least one of the following immunonutrients: glutamine, BCAAs, n-3 fatty acids (fish oil),	Assessment of the effects of a diet with added immunonutrients (glutamine, arginine, BCAAs, n-3 fatty acids, combined immunonutrients or precursors to known immunonutrients) versus an isonitrogenous diet (a diet wherein the overall protein

	Dropout rates: n/a **Study limitations:** n/a	combined immunonutrients or immunonutrient precursors; studies that employed standard immunonutrient therapy as the comparator, but administered by a different route or dosage, and those that compared immunonutrients versus no treatment or placebo; Immunonutrient interventions were provided by an enteral or parenteral route. **Exclusion criteria:** not randomized controlled trial, no report on primary or secondary outcomes of this review, animal studies	content is held constant, but individual constituents may be changed) on clinical outcomes in patients with severe burn injury.
Notes	**Author's Conclusion:** evidence of an effect of glutamine on mortality reduction, finding should be taken with care. The number of study participants analyzed in this systematic review was not sufficient to permit conclusions that recommend or refute the use of glutamine.		
Outcome measures/results	**Primary outcome**: All-cause mortality **Secondary outcomes**: Length of hospital stay; Burn wound infection; non-wound infection		All-cause mortality: The pooled RR of death was 0.25 (95% CI 0.08 to 0.78; P value 0.02). Length of hospital stay: pooled RR was -5.65 (95% CI -8.09 to -3.22; P value < 0.0001). Burn wound infection: pooled RR was 0.42 (95% CI 0.16 to 1.06; P value 0.07). Non-wound infection: pooled RR was 0.73 (95% CI 0.27 to 1.95; P value 0.53)

4.4 Gibt es eine Indikation für eine parenterale Supplementierung mit Omega-3-Fettsäuren?

Empfehlung 11

Eine postoperative parenterale Ernährung mit Supplementierung von Omega-3-Fettsäuren sollte bei Patienten eingesetzt werden, die enteral nicht ausreichend ernährt werden können und daher eine überwiegend parenteral oder kombiniert enteral/parenterale Ernährung benötigen. (BM, HE)

Empfehlungsgrad B – Starker Konsens 100 % Zustimmung

27. Li NN, Zhou Y, Quin XP, Chen Y, He D, Feng JY, Wu XT Does intravenous fish oil benefit patients post-surgery? A meta-analysis of randomised controlled trials. Clin Nutr 2014; 33: 226–239.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-analysis 1++	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** n/a	**Total no. Patients:** n=1487 (21 RCTs) **Inclusion criteria:** Adult undergoing major surgery, Randomized controlled trials, intervention: FO/n-3/EPA/DHA enriched lipid emulsion vs. standard (SO/ML) lipid emulsion administered postoperatively TPN, At least one of the following outcomes: Mortality, Length of hospital stay, Postoperative infection rate, Hepatic function, Immune status, Costs of postoperative period **Exclusion criteria:** Children, Animal data, Healthy volunteers, Severe infection or trauma, Reviews/editorials/case reports, Cohort/cross-over/non-randomized studies, Published as an abstract, Intervention with Arginine, Glutamine, RNA, Peri/pre-operatively, TPN + EN/EN/oral feeding	We searched for RCTs to access the clinical efficacy of fish oil-enriched total parenteral nutrition in post-surgery patients.

Notes	**Author's Conclusion:** FO-enriched lipid emulsions are likely to reduce infections, the length of hospital stay and liver dysfunction without influencing mortality and may be a safe and preferable choice in post-surgery patients. Further well-designed trials should be performed to determine whether FO lipid emulsions reduce mortality in patients undergoing hepatic surgery, especially liver transplantation, and the cost effectiveness of such treatment.	
Outcome measures/results	Mortality, Length of hospital stay, Postoperative infection rate, Hepatic function, Immune status Costs of postoperative period	Twenty-one RCTs were enrolled for meta-analysis. FO was associated with a significant reduction in the length of hospital stay (mean = −2.14 d, 95% CI = −3.02 to −1.27), infections (OR = 0.53, 95% CI = 0.35–0.81), ALT (mean = −6.35 U/L, 95% CI = −11.75 to −0.94), GGT (mean = −11.01 U/L, 95% CI = −20.77 to −1.25) and total bilirubin (mean = −2.06 μmol/L, 95% CI = −3.6 to −0.52), as well as a non-significant change in mortality and postoperative medical cost. The quality of evidence of each clinical outcome was accessed as high.

28. Tian H, Yao X, Zeng R, Sun R, Tian H, Shi C, Li L, Tian J, Yang K Safety and efficacy of a new parenteral lipid emulsion (SMOF) for surgical patients: a systematic review and meta-analysis of randomized controlled trials. Nutr.Rev.2013; 71: 815–821.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-analysis 1+	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** -small number of included studies and some of them could include reporting bias - missing data in some trials - insufficient description of methodology (occurrence of methodology bias) - duration of the trials did not exceed 7 days, clinical data on the long-term safety and efficacy of these lipid emulsions in adults are still needed	**Total no. Patients:** n=306 (6 RCTs) **Inclusion criteria:** report on randomized controlled trials comparing SMOFlipid20% with other lipid emulsions administered as total parenteral nutrition (TPN) in the immediate postoperative period after elective abdominal or thoracic surgery **Exclusion criteria:** lack of trial approval by local ethics committees, duplicate publications, unbalanced matching of patient populations	The aim of the present systematic literature review was to evaluate the safety and efficacy of SMOFlipid20% (lipid emulsion containing a physical mixture of soybean oil, medium-chain triglycerides (MCT), olive oil, and fish oil) versus other parenteral lipid emulsions in postoperative patients via a meta-analysis of randomized controlled trials

Notes	**Author's Conclusion:** The results of the present meta-analysis indicate that for postoperative patients receiving parenteral nutrition SMOFlipid20% may be less toxic to the liver than either Lipoven20% or ClinOleic20% and there are no significant differences between SMOFlipid20% and MCT/LCT20%. However, the data available are so limited that some of the reported findings could not be confirmed. Based on the GRADE approach, the quality of evidence for almost all of the outcomes investigated was moderate for the trials of Lipoven20% and low for the trials investigating ClinOleic20% and MCT/LCT20%. Larger, longer-term, and better-designed RCTs should be carried out to provide more reliable evidence on the safety and efficacy of various parenteral lipid emulsions in the postsurgical setting.	
Outcome measures/results	Aspartate aminotransferase, Alanine aminotransferase, Gamma-glutamyl transferase, Alkaline phosphatase, C-reactive protein, Low-density lipoprotein triglycerides, Length of hospital stay, Adverse events	Compared with a soybean-based (Lipoven20%) and a soybean- and olive oil-based (ClinOleic20%) lipid emulsion, SMOFlipid20% was associated with lower levels of hepatic enzymes, suggesting less toxicity. Changes in low-density lipoprotein triglyceride and C-reactive protein levels were also lower with SMOFlipid20% compared with Lipoven20%. Differences between SMOFlipid20% and a lipid emulsion containing medium- and long-chain triglycerides (MCT/LCT20%) were not statistically significant. For all trials, there were no significant differences in adverse events and length of hospital stay. The quality of evidence from the RCTs evaluating SMOF20% versus Lipoven20% was moderate, while most of the evidence from RCTs of SMOF20% versus ClinOleic20% and MCT/LCT20% lipid emulsions was low.

29. Pradelli L, Mayer K, Muscaritoli M, Heller AR n-3 fatty acid-enriched parenteral nutrition regimens in elective surgical and ICU patients: a meta-analysis. Crit.Care 2012; 16): R184.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-analysis 1++	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** n/a	**Total no. Patients:** n=1502 (23 RCTs) **Inclusion criteria:** randomized clinical trials (RCTs) comparing n-3 PUFA-enriched lipid emulsions with standard non-enriched lipid emulsions (that is, soybean oil, MCT/LCT or olive/soybean oil emulsions) in adult ICU patients and/or in elective surgery patients, in terms of clinical outcomes, markers of inflammation and antioxidant status, fatty acid composition of plasma	Medline was searched for randomized controlled trials comparing n-3 PUFA-enriched lipid emulsions with standard non-enriched lipid emulsions (i.e. soybean oil, MCT/LCT or olive/soybean oil emulsions) in surgical and ICU patients receiving parenteral nutrition. Extracted data were pooled by means of both random and fixed effects models, and subgroup analyses were carried forward to compare findings in ICU versus non-ICU patients.

		phospholipids, and/or routine laboratory parameters **Exclusion criteria:** n/a	
Notes	**Author's Conclusion:** In conclusion, these results confirm previous findings in surgical patients and extend them to the ICU population: the body of available evidence indicates that the use of n-3 PUFA-enriched parenteral nutrition is safe and effective in reducing the infection rate and hospital/ICU stay in surgical patients, and that these benefits also apply to ICU patients. Other beneficial effects included reduced markers of inflammation, improved lung gas exchange, liver function, antioxidant status and fatty acid composition of plasma phospholipids, and a trend towards less impairment of kidney function.		
Outcome measures/results	Mortality, Infection rate, Hospital length of stay (LOS), ICU LOS, Transfused blood units, Oxygenation index *Serum parameters:* Alpha-tocopherol, Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Bilirubin, C-reactive protein (CRP), Creatinine, Interleukin (IL)-6 change, Lactate, Triglycerides, Urea *Other laboratory parameters:* Leukotriene B5 (LTB5), Leukotriene B4 (LTB4), LTB5/LTB4 ratio, Eicosapentaenoic acid (EPA), Docosahexaenoic acid (DHA), Arachidonic acid (AA), Prothrombin time, PT (Quick), Partial thromboplastin time (PTT), Platelets	A total of 23 studies (n = 1502 patients: n = 762 admitted to the ICU) were included. No statistically significant difference in mortality rate was found between patients receiving n-3 PUFA-enriched lipid emulsions and those receiving standard lipid emulsions (RR= 0.89; 0.59, 1.33), possibly reflecting a relatively low underlying mortality risk. However, n-3 PUFA-enriched emulsions are associated with a statistically and clinically significant reduction in the infection rate (RR =0.61; 0.45, 0.84) and the lengths of stay, both in the ICU (-1.92; -3.27, -0.58) and in hospital overall (-3.29; -5.13, -1.45). Other beneficial effects included reduced markers of inflammation, improved lung gas exchange, liver function, antioxidant status and fatty acid composition of plasma phospholipids, and a trend towards less impairment of kidney function.	

30. Chen B, Zhou Y, Yang P, Wan HW, Wu XT Safety and efficacy of fish oil-enriched parenteral nutrition regimen on postoperative patients undergoing major abdominal surgery: a meta-analysis of randomized controlled trials. JPEN J Parenter Enteral Nutr 2010; 34:387-394.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-analysis 1++	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** -Because of the incomplete data, no discussion of other clinical laboratory tests (e.g., cholesterol, serum glucose)	**Total no. Patients:** n=892 (13 RCTs) **Inclusion criteria:** Clinical RCTs of patients undergoing major abdominal surgery, the trials compared standard PN with PN supplemented with FO (fish oil) **Exclusion criteria:** lack of approval of local ethics committees; duplicate	we performed a systematic review and meta-analysis of published randomized controlled trials (RCTs) to evaluate the safety and efficacy of FO-enriched PN in patients undergoing major abdominal surgery

	- some bias (e. g., measurement, publication) might distort the results - Given the sample size limitation and chance differences, some results should be interpreted with caution -no search for unpublished studies related to the safety and efficacy of FO emulsions – no definitively determination of the optimal start time for the treatment to be enriched with FO emulsions in all RCTs	publications; incomplete data; unbalanced matching in patient populations. We did not consider unpublished reports or abstracts.	
Notes	**Author's Conclusion:** In conclusion, our study indicated that FO emulsions were safe and effective in reducing length of hospital and ICU stay, improving the risk of postoperative infection, modulating plasma levels of PUFAs and α-tocopherol, and regulating the LT synthetic capacity in patients undergoing major abdominal surgery. However, analysis of these trials failed to show improvement in postoperative mortality rate and some laboratory test results in these patients. Further large-scale, high-quality RCTs are required. Hospital cost and more laboratory parameters should be considered in future meta-analyses.		
Outcome measures/results	clinical safety: incidence rate of cardiac complications (e.g., myocardial ischemia/infarction, arrhythmia, atrial fibrillation, brachycardia, or tachycardia) and serum levels of liver enzymes, bilirubin, and triglycerides on postoperative day (POD) 6. Efficacy: mortality, postoperative infection rate, length of hospital and intensive care unit (ICU) stays, PUFA levels in plasma phospholipids, ex vivo stimulated release of LTs, plasma α-tocopherol level on POD 6 (All available laboratory test results were collected on POD 6)	The combined analysis showed that a fish oil–enriched parenteral nutrition regimen had a positive treatment effect on length of hospital stay (weighed mean difference = −2.98, $P < .001$), length of intensive care unit stay, postoperative infection rate (odds ratio = 0.56, $P = .04$), and serum levels of aspartate aminotransferase, alanine aminotransferase, and α-tocopherol on postoperative day 6 in these patients. The regimen increased the plasma levels of eicosapentaenoic acid (standardized mean difference = 3.11, $P < .001$) and docosahexaenoic acid and upregulated the leukotriene B_5 production in leukocytes on postoperative day 6. No significant differences were found between the 2 groups in postoperative mortality; incidence of postoperative cardiac complications; serum levels of bilirubin, triglyceride, or arachidonic acid; or the liberation of leukotriene B_4. No serious adverse events related to fish oil treatment were reported.	

31. de Miranda Torrinhas RS, Santana R, Garcia T, Cury-Boaventura MF, Sales MM, Curi R, Waitzberg DL (2013) Parenteral fish oil as a pharmacological agent to modulate post-operative immune response: a randomized, double-blind, and controlled clinical trial in patients with gastrointestinal cancer. Clin Nutr 2013, 32:503-510.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
prospective, randomized, double-blind, parallel, and controlled clinical trial 1+	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** FAPESP, CNPq, Fresenius-Kabi, Farmoterápica-Brazil **Dropout rates:** n=21 (25%) **Study limitations:** - Inclusion of adult surgical patients with gastrointestinal cancer, similar results may therefore not be achieved in other surgical groups -Inclusion of patients without consideration of their nutritional status or alimentary habits and Treatment evaluation was assessed only in patients who completed the protocol of LE infusion (no intention to treat analysis) → it is not possible to attribute the immunological benefits observed after pre-operative infusion of fish oil LE only to their omega-3 fatty acids contend, as long as this LE emulsion also have large amounts of the	**Total no. Patients:** n= 63 • Intervention group n=31 • Control group n=32 • **Inclusion criteria:** adult patients (18-75 years) admitted for elective surgery for resection of gastric or colon cancer, Karnofsky performance status score ≥60 and peripheral venous access suitable for continuous access during parenteral therapy and blood collection **Exclusion criteria:** intolerance or allergy to any ingredient of LE, infection (i.e., acquired immune deficiency syndrome), inflammatory disease (i.e., arthritis), immunologic disease (i.e., lupus), metabolic disease (i.e., insulin-dependent diabetes), dementia or other cognitive and behavioral problems, ingestion of drugs that significantly modulate intermediary metabolism, implanted electromagnetic instruments, refusal to sign the inform consent	Intervention group: -pre-operative peripheral infusion of a Fish oil-based lipid emulsion (0.2 g fat/kg body weight/d)for 3 days control group - pre-operative peripheral infusion of a lipid emulsion (rich in medium-chain triglycerides, 0.2 g fat/kg body weight/d) for 3 days

	antioxidant alpha-tocopherol		
Notes	**Author's Conclusion:** Short-term pre-operative infusion of FOLE (Fish oil-based lipid emulsions) alone improves the post-operative immune response of gastrointestinal cancer patients without significantly changing post-operative infections or length of ICU and hospital stay.		
Outcome measures/results	Post-operative concentrations of inflammatory mediators, leukocyte functions, surface molecules, infections, length of intensive care unit (ICU) and hospital stay	FOLE patients had a significant increase of IL-10 levels on day 3, decrease of IL-6 and IL-10 levels on day 6, lower decrease in leukocyte oxidative burst, maintenance of monocyte percentage expressing HLA-DR and CD32, and increase of CD32 neutrophil expression compared to MCT/LCT patients. No changes were observed in the frequency of post-operative infections or length of ICU and hospital stay.	

32. Pradelli L, Mayer K, Klek S et al. omega-3 Fatty-Acid Enriched Parenteral Nutrition in Hospitalized Patients: Systematic Review With Meta-Analysis and Trial Sequential Analysis. JPEN J Parenter Enteral Nutr 2020; 44: 44-57. doi:10.1002/jpen.1672			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic Review and Meta-Analysis 1++ AMSTAR II 12/16	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** Fresenius Kabi GmbH. **Dropout rates:** n/a **Study limitations:** Overall confidence in the results of the review: Critically Low Risk of bias of single studies: moderate Inconsistency: low Indirectness: high Impreciseness: moderate Publication bias: n/a	**Total no. Studies:** 49 (3641 patients) **Inclusion criteria:** human studies of adult hospitalized patients who were eligible to receive PN covering at least 70% of their total energy provision; Intervention with omega-3 enriched PN, RCT containing at least 1 predefined outcome **Exclusion criteria:** enteral nutrition, "off-label" interventions, studies where EN provided >30% of daily calories	Investigation of ω-3 fatty-acid enriched parenteral nutrition (PN) vs standard (non-ω-3 fatty- acid enriched) PN in adult hospitalized patients
Notes	**Author's Conclusion:** Study provides clear evidence that omega-3 fatty-acid enriched PN provides significant clinical and nonclinical benefits over standard non-ω-3 fatty-acid enriched PN in adult hospitalized patients		
Outcome measures/results	**Primary outcome**: Infection rate **Co-primary outcomes**: mortality rate length of hospital stay, length of intensive care unit stay, sepsis rate, hospital readmissions,	- relative risk of infection was 40% lower with ω-3 fatty- acid enriched PN than standard PN (RR 0.60, 95% confidence interval [CI] 0.49-0.72; $P < 0.00001$)	

	intensive care unit-free days until day 30 or day 60, and ventilation-free days until day 30	- Patients given ω-3 fatty-acid enriched PN had reduced mean length of intensive care unit stay (10 RCTs; 1.95 days, 95% CI 0.42-3.49; *P* = 0.01) and reduced length of hospital stay (26 RCTs; 2.14 days, 95% CI 1.36-2.93; *P* < 0.00001) - Risk of sepsis (9 RCTs) was reduced by 56% in those given ω-3 fatty-acid enriched PN (RR 0.44, 95% CI 0.28-0.70; *P* = 0.0004) - Mortality rate (co-primary outcome; 20 RCTs) showed a nonsignificant 16% reduction (RR 0.84, 95% CI 0.65-1.07; *P* = 0.15) for the ω-3 fatty-acid enriched group

33. Mocellin MC, Fernandes R, Chagas TR et al. A meta-analysis of n-3 polyunsaturated fatty acids effects on circulating acute-phase protein and cytokines in gastric cancer. Clin Nutr 2018; 37: 840-850. doi:10.1016/j.clnu.2017.05.008			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis 1++ AMSTAR II 9/16	**Countries:** China, Spain, Turkey, Poland, Japan, Italy, Iran **Centers:** n/a **Setting:** n/a **Funding Sources:** Graduate Program of Nutrition at Federal University of Santa Catarina and Coordination for the Improvement of Higher Education Personnel **Dropout rates:** n/a **Study limitations:** Overall confidence in the results of the review: Critically Low Risk of bias of single studies: moderate Inconsistency: moderate Indirectness: low Impreciseness: moderate	**Total no. Studies:** 9 **Inclusion criteria:** controlled or randomized clinical trial carried out in humans; study sample composed only by patients diagnosed with gastric cancer by a histological technique; n-3 PUFAs offered in capsules or liquid diet enriched with these fatty acids (cocktails with n-3 PUFA plus antioxidants, glutamine, arginine or nucleic acids were not excluded); control group with standard diet/ supplement, or none; assessment the effect of n-3 PUFAs on any 66 biomarkers of our interest **Exclusion criteria:** n/a	Evaluation of the evidence of n-3 PUFA supplementation on inflammatory markers in gastric cancer patients

	Publication bias: n/a Use combined of n-3 PUFAs with arginine, glutamine 127 and antioxidants in most of included RCTs, use of control rich in omega-6 in many studies; use of antibiotic in study period; low number of studies assessing the effects on n-3 PUFAs on cytokines and CRP; all studies presented risk of bias; the publication bias was not assessed due the low number of included studies.		
Notes	**Author's Conclusion:** supplementation of n-3 PUFAs in gastric cancer has a potential effect on increasing the levels of albumin and prealbumin, and decreasing the pro-inflammatory cytokines IL-6 and TNF-a.		
Outcome measures/results	Inflammatory status		- few RCTs did show significant benefits from n-3 PUFAs supplementation on inflammatory status - meta-analysis demonstrated a favorable effect of treatment with n-3 PUFAs in increase albumin (SMD 0.28; CI 0.07, 0.48) and prealbumin (SMD 0.56; CI 0.12, 1.00) concentrations, and decreased IL-6 (SMD 0.71; CI 1.15, 0.27) and TNF-a (SMD 0.92; CI 1.58, 0.26) concentrations.

34. Lu S, Yang Z, Tang H, Sun X, Wang B, Qu J, et al. Associations between omega-3 polyunsaturated fatty acids supplementation and surgical prognosis in patients with gastrointestinal cancer: A systematic review and meta-analysis. Food Chem (Oxf). 2022;4:100099.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic review and Meta-Analysis 1++ AMSTAR II 12/16	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** National Natural Science Foundations	**Total no. Studies:** 10 **Inclusion criteria:** research design: randomized controlled trials; participants: the patients with gastrointestinal cancer; intervention	This meta-analysis aims to explore the efficacy of n-3 PUFAs on GI cancer patients undergoing surgery.

	of China (Grant No. 81660484), Major special projects of the ministry of science and technology of China (Grant No.2017YFC309200),Project of Beijing Key Laboratory (Grant No. 2020KF01) **Dropout rates:** n/a **Study limitations:** Overall confidence in the results of the review: Low Risk of bias of single studies: moderate Inconsistency: moderate Indirectness: low Impreciseness: moderate Publication bias: low Most of included studies were single-center trials with small sample sizes; moderate heterogeneity in the pooled outcome of the level of pre-albumin and significant heterogeneity in the pooled outcome of the level of retinol-binding protein; limitation of the number of existing studies	measures: n-3 fatty acid supplementation during perioperative period; outcomes: postoperative infectious complications, length of hospital stay, immune indicators: CD4(%), CD8(%), CD4/CD8; Inflammation indicators: Interleukin-6 (IL-6), Tumor Necrosis Factor-α (TNF-α), C-reactive protein (CRP); nutritional indicators: Prealbumin (PAB), Albumin (ALB),Retinol-binding protein (RBP) **Exclusion criteria:** animal studies, in vitro studies, review, case report, conference summary and other non-clinical research literature; incorrect or incomplete data could not be extracted; The intervention group contains other immunonutrition such as glutamine or arginine	
Notes	**Author's Conclusion:** As a basic nutritional supplement, n-3 PUFAs can effectively enhance the immune function of patients with gastrointestinal cancer and reduce the level of inflammatory cytokines, and shortening the length of hospital stay, but it has no significant impact on the incidence of infectious-related complications and the level of nutrient protein. The results of this study can provide a basis for the clinical application of n-3 PUFAs. However, due to the limitations of the included studies and the potential risk of bias, it is necessary to conduct a large-scale, randomized, prospective trial to further evaluate the impact of n-3 PUFAs supplementation on patients with gastrointestinal tumors after surgery.		

Outcome measures/results	interleukin-6 (IL-6), C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), CD4+T cells, CD8+T cells, CD4+/CD8+, infection complications rate, level of pre- albumin, albumin, retinol-binding protein, length of hospital stay	- The analysis demonstrated that the n-3 PUFAs group significantly reduced levels of interleukin-6 (IL-6) ($P = 0.001$), C-reactive protein (CRP) ($P < 0.00001$), tumor necrosis factor-α (TNF-α) ($P = 0.0003$) compared with the control group. - higher levels of CD4+T cells ($P = 0.03$), CD8+T cells ($P = 0.02$) and CD4+/CD8+ratio ($P = 0.03$) compared with the control group. - no significant difference in infection complications rate ($P = 0.50$) and the level of pre- albumin ($P = 0.80$), albumin ($P = 0.21$), retinol-binding protein ($P = 0.80$) between the two groups. - n-3 PUFAs group significantly reduced the length of hospital stay ($P = 0.007$).

4.5 Gibt es eine Indikation für eine bestimmte orale / enterale Formel, die mit unterschiedlichen, immunologisch wirksamen Nährstoffkombinationen (Immunonutrition) angereichert ist?

Empfehlung 12

Patienten, die sich einer größeren Tumoroperation unterziehen, kann präoperativ oder perioperativ eine Immunonutrition (angereichert mit Arginin, Omega-3-Fettsäuren, Ribonukleotiden) angeboten werden. (BM, HE)

Empfehlungsgrad 0 – Konsens 91 % Zustimmung

35. Hegazi RA, Hustead DS, Evans DC Preoperative standard oral nutrition supplements vs immunonutrition: Results of a systematic review and meta-analysis. J Am Coll Surg; 2016; 219:1078-1087.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic Review and Meta-Analysis 1++	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** - variation of used standard ONS (different ingredients) - missing record on patients' compliance with supplements or total protein intake (both from supplements and regular diets) - slight variation of length supplementation - patients receiving preoperative supplementation might have received more monitoring in a nutrition support program resulting in improved outcomes	**Total no. Patients:** n=1456 (15RCTs) • 8 RCTs of preoperative IN vs ONS n=561 • RCTs of IN vs no supplements n=895 **Inclusion criteria:** randomized controlled trials (RCTs) with primary comparisons between the nutrition interventions, report on clinically relevant outcomes pertaining to the postoperative period, namely wound infections, infectious and noninfectious complications, and length of hospital stay **Exclusion criteria:** Retrospective studies and those using perioperative immunonutrition (IN) or parenteral nutrition	We performed a systematic literature review to identify all relevant RCTs that used IN preoperatively. Meta-analysis was performed for reported outcomes including wound infection, infectious and non-infectious complications, and length of stay (LOS).

	- most standard ONS also contain arginine, fish oil, and antioxidants in a lower concentration - ideal dose of these immunonutrients has not been defined (standard ONS might contain therapeutic concentrations)		
Notes	**Author's Conclusion:** Given the lack of a significant difference between IN and standard ONS in the preoperative setting, and the fact that standard ONS are less expensive and widely available, we recommend use of standard ONS for nutritional optimization of the surgical patient. Cost and accessibility are key factors to patient compliance. As with smoking cessation or exercise, achieving patient buy-in is crucial to any successful preoperative optimization regimen.		
Outcome measures/results	This study aims to compare outcomes after preoperative nutritional supplementation with IN vs. standard oral nutritional supplements (ONS) or a regular diet without supplement. **Primary outcome measure:** wound infection, infectious and non-infectious complications, and length of stay (LOS)		We identified 561 patients in 8 RCTs of preoperative IN vs. ONS. 895 patients were identified in 9 RCTs of IN vs. no supplements. When compared to ONS, preoperative IN was not associated with reduced wound infection (OR 0.97, 95% Confidence Interval (CI) 0.45 to 2.11), all infectious complications (OR 0.71, 95% CI 0.30 to 1.68), non-infectious complications (OR 1.25, 95% CI 0.64 to 2.43), or LOS (mean difference 0.07 days, 95% CI −2.29 to 2.43). In RCTs controlled with non-supplemented standard diets, preoperative IN was associated with decreased infectious complications (OR 0.49, 95% CI 0.30 to 0.83, p≤0.01) and LOS (mean difference −2.22 days, 95% CI −2.99 to −1.45, p≤0.01).

36. Wong CS, Aly EH The effects of enteral immunonutrition in upper gastrointestinal surgery: a systematic review and meta-analysis. Int J Surg 2016; 29: 137-150.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meat-analysis and systematic review 1++	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** - low methodological quality of some included studies	**Total no. Patients:** n=2016 (19RCTs) • enteral immunonutrition n=1017 • standard enteral nutrition n=999 **Inclusion criteria:** patients undergoing upper gastrointestinal surgery, reported	We searched for studies reported clinical outcomes comparing standard enteral nutrition (SEN) and immunonutrition (IEN).

	- between-study heterogeneity among the included studies on the length of hospital stay - external validity is limited to only adult patients who underwent elective upper GI surgery	outcomes comparing enteral immunonutrition (excluded parenteral) and standard nutritional supplementation, randomized controlled trials **Exclusion criteria:** non-RCT (case-series, case-control study and cohort studies), narrative or expert reviews and animal studies or trials	
Notes	**Author's Conclusion:** Overall, our analysis found that IEN decreases wound infection rates and reduces length of stay. It should be recommended as routine nutritional support as part of the Enhanced Recovery after Surgery (ERAS) programs for upper GI Surgery.		
Outcome measures/ results	We undertook a systematic review to evaluate the effects of immune-enhancing enteral nutrition (IEN) in upper gastrointestinal (GI) surgery. *Outcome measures:* postoperative wound infection, length of hospital stay, mortality, post-operative morbidities		The ratio of patients underwent esophagectomy:gastrectomy:pancreatectomy was 2.2:1.2:1.0. IEN, when administered post-operatively, was associated with a significantly lower risk of wound infection (risk ratio (RR) 0.59, 95% confidence interval (CI) 0.40 to 0.88; p = 0.009) and shorter length of hospital stay (MD –2.92 days, 95% CI –3.89 to −1.95; p < 0.00001). No significant differences in other post-operative morbidities of interest (e.g. anastomotic leak and pulmonary infection) and mortality between the two groups were identified.

37. Song GM, Tan X, Liang H, Yi LJ, Zhou JG. Zeng Z, Shuai T, Ou YX, Zhang L, Wang Y. Role of Enteral Immunonutrition in Patients Undergoing Surgery for Gastric Cancer: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Medicine (Baltimore) 2015; 94: e1311			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-analysis and systematic review 1++	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** - power of all meta-analyses which were performed based on the end-point value were impaired due to	**Total no. Patients:** n=785 (9RCTs) **Inclusion criteria:** patients diagnosed with GC with histological techniques scheduled for gastrectomy, Intervention with Enteral immunonutrition in comparison to standard enteral nutrition, outcome measures: clinical outcomes including infectious complications	We searched for randomized controlled trials to identify any latent studies which investigated the effects of EIN (enteral immunonutrition) compared with standard EN (enteral nutrition) on GC (gastric cancer) patients who underwent surgery

	the durations of interventions are different across studies - inclusion of only a small number of studies reduced the power of these pooled results - no inclusion of studies in other languages (except English and Chinese) - missing electronic search of other databases (e.g. ISI WEB of Science) - significant statistical heterogeneity was detected for meta-analyses in terms of certain outcome measures -missing test on publication bias for studies due to the small number of eligible studies -unpublished and missing data - some descriptive analysis associated results which were different from estimated effects generated from synthesis analysis	categorized into surgical site infection (SSI) and other infectious complications (e.g., respiratory infection, urinary tract infection, abdominal abscess, etc.) defined according to the criteria issued by the American College of Chest Physician, Centers for Diseases Control guidelines, or others established by authors and length of hospitalization; immune indices which consisted of immunoglobulin (including IgA, IgG, and IgM), T cell subsets (included $CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$ ratio), cytokines (interlukin-2 [IL-6], IL-6, tumor necrosis factor-alpha [TNF-α]), and natural killer cell (NK cell); and biochemical indices (refers to total protein, albumin, proalbumin, transferrin), only RCTs **Exclusion criteria:** patients with unresectable neoplasm, underlying cardiovascular pathology, previous abdominal radiotherapy, active preoperative infection, administration of corticosteroids or immunosuppressive agents, and renal or hepatic function impairment; experimental data; lack of essential information and cannot acquire primary data from authors; we only incorporate one with the most strict methodology and most complete data of articles, in which the same data were	

		reported by 1 author or a medical center, into our study; nonoriginal research, such as review, letter and specialist comments and non-RCTs	
Notes	**Author's Conclusion:** EIN is effective for improving the nutritional and immunological status of GC patients undergoing gastrectomy because it can effectively enhance the host immunity and relieve the inflammatory response through significantly increasing the level of IgG, relevant T cell subsets and NK cell, and obviously decreasing the concentration of cytokines such as IL-6 and TNF-α. However, more well-designed and large-scale RCTs are urgently warranted to further establish the effects because of insufficient evidences in present study and the differences in incidence postoperative complications, length of hospitalization, level of biochemical indices (refer to total protein, albumin, proalbumin, transferring), and CD8+ compared with standard EN were not identified. One point should be noted is that various compositions and timing of administration of EIN regime were included in individual studies. We conducted separate sensitive analyses with subgroup analysis to reassess the estimated effects of EIN relative to standard EN, but not enough sample size and number of eligible studies impaired these pooled results generated from different subgroups. Consequently, more RCTs concerning comparative effects of EIN regime with similar compositions and timing of administration compared to standard EN were needed. Moreover, it is necessary to develop more RCTs with high-quality to verify the comparative effects of preoperative with postoperative EIN in the treatment of GC patients undergoing gastrectomy.		
Outcome measures/results	clinical outcomes including infectious complications, length of hospitalization, immune indices (immunoglobulin, T cell subsets, cytokines, natural killer cells), biochemical indices (total protein, albumin, proalbumin, transferrin)	The meta-analysis results shown that EIN increased level of IgA (MD, 0.31; 95% CI, 0.12–0.51), IgG (MD, 1.5; 95% CI, 0.73–2.28), IgM (MD, 0.22; 95% CI, 0.06–0.39), CD4+ (SMD, 0.81; 95% CI, 0.53–1.09), CD3+ (SMD, 0.68; 95% CI, 0.21–1.15), CD4+/CD8+ ratio (MD, 0.56; 95% CI, 0.12–1.01), and NK cell (MD, 2.35; 95% CI, 0.66–4.05); decreased IL-6 (MD, −98.22; 95% CI, −156.16 to −40.28) and TNF-α (MD, −118.29; 95% CI, −162.00 to −74.58), but not improve remained outcomes of interest involving postoperative complications, length of hospitalization, serum total protein, and CD8+. Descriptive analysis suggested that EIN also increased the concentration of IL-2 but not CRP. Impact on lymphocytes remains inconsistent.	

38. Song GM, Tian X, Zhang L, Ou YX, Yi LJ, Shuai T, Zhou JG, Zeng Z, Yang HL Immunonutrition Support for Patients Undergoing Surgery for Gastrointestinal Malignancy: Preoperative, Postoperative, or Perioperative? A Bayesian Network Meta-Analysis of Randomized Controlled Trials. Medicine (Baltimore) 94(29): e1225			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-analysis 1++	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a	**Total no. Patients:** n=2538 (27RCTs) **Inclusion criteria:** patients scheduled to selective surgery for gastric cancer, trials	Beside a databases search for RCTs we manually checked reference lists of eligible trials and review and retrieval unpublished literature. RCTs which investigated the comparative effects of EIN versus standard enteral nutrition (EN) or different EIN regimes were included if the clinical outcomes information can be extracted from it. Furthermore, we undertook a Bayesian NMA of RCTs regarding different deliver

	Study limitations: - nutrition status of participants varies across studies - conference abstract was ineligible for selection criteria of this study, and it may cause incomplete retrieval of literature - comparison-adjusted funnel plots were drawn and these graphs indicated small study effects - most of the results generated from NMA (network meta-analysis)are in accordance with that of traditional pair-wise meta-analyses, but there were significant inconsistency existed in the loop which was consisted of standard EN, postoperative EIN, and preoperative EIN for postoperative infectious complications and one which was made of standard EN, preoperative EIN, and postoperative EIN	evaluated the comparative effects of EIN (Enteral immunonutrition) diet which enriched at least 2 of arginine, glutamine, omega-3 fatty acids and RNA versus standard EN, EN administration was performed at preoperation, postoperation or perioperation period, outcome measures: postoperative infectious or noninfectious complications, length of postoperative hospitalization, only RCTs with or without blind method **Exclusion criteria:** patients with unresectable GI malignancy, underlying cardiovascular pathology, active preoperative infection, administration of corticosteroids or immunosuppressive agents, and renal or hepatic function impairment; experimental data; lack of essential information and cannot acquire primary data from authors; the article with the most strict methodology and most complete data was chosen to be analyzed in terms of duplicate literature; and nonoriginal research such as review, letter and specialist comments, and non-RCTs	routes of EIN compared with standard EN in order to establish the optimum immunonutrition support regime.
Notes	Bayesian NMA is a generalization of pair-wise meta-analysis. It is an alternative to pool direct and indirect or different indirect evidences simultaneously. **Author's Conclusion:** Our results suggest EIN support is promising alternative for operation management in comparison with standard EN, and perioperative EIN regime is the optimum option for managing clinical status of patients who underwent selective surgery for GI cancer.		

Outcome measures/results	postoperative infectious or noninfectious complications, length of postoperative hospitalization	Pair-wise meta-analyses suggested that preoperative (relative risk [RR], 0.58; 95% confidence interval [CI], 0.43–0.78), postoperative (RR, 0.63; 95% CI, 0.52–0.76), and perioperative EIN methods (RR, 0.46; 95% CI, 0.34–0.62) reduced incidence of postoperative infectious complications compared with standard EN. Moreover, perioperative EIN (RR, 0.65; 95% CI, 0.44–0.95) reduced the incidence of postoperative noninfectious complications, and the postoperative (mean difference [MD], −2.38; 95% CI, −3.4 to −1.31) and perioperative EIN (MD, −2.64; 95% CI, −3.28 to −1.99) also shortened the length of postoperative hospitalization compared with standard EN. NMA found that EIN support effectively improved the clinical outcomes of patients who underwent selective surgery for GI cancer compared with standard EN.

39. Marimuthu K, Varadhan KK, Ljungqvist O, Lobo DN A meta-analysis of the effect of combinations of immune modulating nutrients on outcome in patients undergoing major open gastrointestinal surgery. Ann Surg 2012; 255:1060-1068.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-analysis 1++	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** -Most of the included RCTs studied both malnourished and well-nourished patients, but some studies have included only malnourished patients or excluded obese patients -assessment of outcome variables using varying definition criteria between the RCTs -Nonavailability of the 30-day follow-up data could have significant impact on	**Total no. Patients:** n=2496 (26 RCTs) • Immune modulating nutrition (IMN) group n=1252 • Control group n=1244 **Inclusion criteria:** RCTs comparing enteral nutrition containing at least 2 IMN (Immune modulating nutrition) components with standard isocaloric and isonitrogenous diet with similar timing of initiation, dose, and duration in both the experimental and control groups provided for minimum of 5 days (pre-, post-, or perioperatively), adult patients undergoing major elective open abdominal surgery **Exclusion criteria:**	Randomized controlled trials published between January 1980 and February 2011 comparing isocaloric and isonitrogenous enteral IMN (L-arginine, L-glutamine, [omega]-3 fatty acids, and nucleotides) combinations with standard diet in patients undergoing major open gastrointestinal surgery were included

	the overall study outcome (missing incidence of delayed infectious and noninfectious complications and postoperative mortality)	single IMN in the study group, no supplementation in the control group, missing measuring of desired outcome, non-randomized designs, case-controlled trials, retrospective studies, RCT comparing pre- or postoperative IMN supplementation with perioperative IMN supplementation or in any combinations	
Notes	**Author's Conclusion:** In summary, this meta-analysis of RCTs supplementing IMN(Immune modulating nutrition) in patients undergoing major elective abdominal surgery suggests significant reduction in postoperative complications and length of hospital stay when compared with standard enteral nutrition. This relative improvement in the postoperative clinical outcome was more pronounced when IMN was given peri- or postoperatively. This analysis, using GRADEpro approach, has also provided a summary of the issues relating to methodology and quality of studies evaluating IMN supplementation in surgical patients. Robustly designed RCTs are still needed to evaluate the benefits of preoperative over postoperative supplementation and well-nourished over malnourished patients. It also became evident that methodological differences among clinical trials hamper comparisons of study outcomes. There are also some specific areas such as molecular signaling pathways where gaps in the knowledge still exist. Future research could take a more focused approach to identify specific mechanisms by which IMN improves the host defense in humans and to determine the optimal dose of IMN to promote these mechanisms.		
Outcome measures/results	postoperative infectious complications, postoperative noninfectious complications, length of hospital stay, and mortality		Twenty-six randomized controlled trials enrolling 2496 patients (1252 IMN and 1244 control) were included. The meta-analysis suggests strong evidence in support of decrease in the incidence of postoperative infectious [risk ratio (RR) (95% confidence interval [CI]): 0.64 (0.55, 0.74)] and length of hospital stay [mean difference (95% CI): -1.88 (-2.91, -0.84 days)] in those receiving IMN. Even though significant benefit was observed for noninfectious complications [RR (95% CI): 0.82 (0.71, 0.95)], the quality of evidence was low. There was no statistically significant benefit on mortality [RR (95% CI): 0.83 (0.49, 1.41)].

40. Osland E, Hossain MB, Khan S, Memon MA Effect of Timing of Pharmaconutrition (Immunonutrition) Administration on Outcomes of Elective Surgery for Gastrointestinal Malignancies: A Systematic Review and Meta-Analysis. JPEN J Parenter Enteral Nutr 38: 53-69.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**

Meta-analysis 1++	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** - variations in the composition of included pharmaconutrition Products -missing data about the real amount of nutrition the patients received - most studied have been funded at least in part by the companies that manufacture the products being investigated	**Total no. Patients:** n=2005 (20RCTs) • pharmaconutrition = 1010 • control n = 995 **Inclusion criteria:** studies comparing the provision of arginine-dominant (>9 g arginine/L) pharmaconutrition formulations with or without other immune-modulating nutrients with those of standard nutrition composition; RCTs with primary comparisons between the different nutrition formulations; adult (>18 years) elective GI surgical patients; report in 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 **Exclusion criteria:** Investigation of the effect of parenteral provision supplemented with pharmaconutrients and duplicate publications.	Randomized controlled trials comparing the use of pharmaconutrition with standard nutrition in elective adult surgical patients between 1980 and 2011 were identified.
Notes	Studies were categorized according to the timing of pharmaconutrition provision: -4 studies, yielding 5 sets of data, provided preoperative interventions (pharmaconutrition provided 5–7 days preoperatively as an oral supplement; (intervention-group n=107 control-group n=102) - 14 studies described postoperative interventions (pharmaconutrition product commenced via jejunal feeding tube on postoperative day [POD] 1 or 2, used to meet a defined nutrition goal until POD7 or when oral intake was established; intervention group n=732 control group n=734) - 2 studies provided perioperative interventions (providing both pre- and postoperative provision of pharmaconutrition; intervention-group n=163 control group n=162) **Author's Conclusion:** 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 where further research is required	
Outcome measures/results	in-hospital mortality, infective complications, anastomotic dehiscence, noninfectious complications, LOS, and GI tolerance.	Twenty studies yielding 21 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 length of stay were found with perioperative and postoperative administration. Perioperative administration was also associated with a statistically significant reduction in anastomotic dehiscence, whereas a reduction in noninfective complications was demonstrated with postoperative administration. Preoperative pharmaconutrition demonstrated no notable advantage over standard nutrition provision in any of the clinical outcomes assessed

41. Zhang Y, Gu Y, Guo T, Li Y, Ca H Perioperative immunonutrition for gastrointestinal cancer: A systematic review of randomized controlled trials. Surg Oncol 2012; 21: e87-e95			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-analysis 1++	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** n/a	**Total no. Patients:** n=2331 (19RCTs) **Inclusion criteria:** randomized controlled trials (RCTs) with or without blinding method, patients with digestive system malignancy and undergoing elective surgery; trials compared perioperative IN diet with standard diet, IN diet included at least two of following nutrients: arginine, glutamine, ω-3 PUFA or RNA; IN administration was performed at three periods, including pre-operation period, both pre- and post-operation period, or post-operation period; Outcome measurements: Postoperative	Randomized controlled trials (RCTs) published between 1995 and 2011 were identified and extracted to assess the effects of IN (immunonutrition) on postoperative complications and length of hospital stay.

		complications (including infectious and non-infectious complications) and length of hospital stay **Exclusion criteria:** no adequate controls, no randomization, patients with benign tumor, studies without full-text	
Notes	Nine trials were done to compare postoperative IN with standard diet, 2 trials were for comparing perioperative IN with standard diet, one trial was for comparing postoperative and perioperative IN with standard diet, 3 trials were for comparing perioperative and preoperative IN with standard diet, 4 trials were for comparing preoperative IN with standard diet. **Author's Conclusion:** Perioperative IN is effective and safe to reduce postoperative infection, non-infection complication and length of hospital stay.		
Outcome measures/results	Postoperative complications (including infectious and non-infectious complications) and length of hospital stay		Nineteen RCTs involving a total of 2331 patients were included in our meta-analysis. The results showed perioperative IN significantly reduced length of hospital stay (WMD, −2.62; 95% CI, −3.26 to −1.97; $P < 0.01$) and morbidity of postoperative infectious complication (RR, 0.44; 95% CI, 0.32 to 0.60; $P < 0.01$) compared with standard diet. Moreover, perioperative IN also significantly decreased morbidity of postoperative non-infectious complication in comparison with standard diet (RR, 0.72; 95% CI, 0.54 to 0.97; $P = 0.03$).

42. Cerantola Y, Hubner M, Grass F, Demartines N, Schafer M Immunonutrition in gastrointestinal surgery. Br J Surg 2011; 98:37-48.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-analysis 1++	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** only 12 of 21 included RCTs were considered as high quality, where significant heterogeneity of available trials was demonstrated	**Total no. Patients:** n=2730 (21RCTs) **Inclusion criteria:** RCTs considering patients undergoing elective major gastrointestinal surgery **Exclusion criteria:** trauma-related abdominal surgery, transplantation surgery and	Randomized controlled trials (RCTs) published between January 1985 and September 2009 that assessed the clinical impact of perioperative enteral IN in major gastrointestinal elective surgery were included and analyzed in a meta-analysis.

	cautious interpretation of results is needed	conservative treatment of critically ill patients, Studies comparing two different regimens of IN (different IN formulas, timings and duration) but with no actual control group, comparing IN with parenteral nutrition	
Notes	**Author's Conclusion:** Perioperative enteral IN decreases morbidity and hospital stay but not mortality after major gastrointestinal surgery; its routine use can be recommended		
Outcome measures/results	The aim of this systematic review and meta-analysis was to assess the impact of IN (immunonutrition) on postoperative complications, in particular infectious complications, length of hospital stay and mortality in patients undergoing major gastrointestinal surgery. Tolerance of IN diets and costs were also evaluated.	Twenty-one RCTs enrolling a total of 2730 patients were included in the meta-analysis. Twelve were considered as high-quality studies. The included studies showed significant heterogeneity with respect to patients, control groups, timing and duration of IN, which limited group analysis. IN significantly reduced overall complications when used before surgery (odds ratio (OR) 0·48, 95 per cent confidence interval (c.i.) 0·34 to 0·69), both before and after operation (OR 0·39, 0·28 to 0·54) or after surgery (OR 0·46, 0·25 to 0·84). For these three timings of IN administration, ORs of postoperative infection were 0·36 (0·24 to 0·56), 0·41 (0·28 to 0·58) and 0·53 (0·40 to 0·71) respectively. Use of IN led to a shorter hospital stay: mean difference − 2·12 (95 per cent c.i. − 2·97 to − 1·26) days. Beneficial effects of IN were confirmed when low-quality trials were excluded. Perioperative IN had no influence on mortality (OR 0·90, 0·46 to 1·76).	

43. Drover JW, Dhaliwal R, Weitzel L, Wischmeyer PE, Ochoa JB, Heyland DK Perioperative use of arginine-supplemented diets: a systematic review of the evidence. J Am Coll Surg 2011; 212:385-99, 399.e1.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-analysis 1++	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** -some included studies had small sample sizes	**Total no. Patients:** 35RCTs **Inclusion criteria:** randomized clinical trials (RCTs); studied elective surgical in adults; comparison of enteral nutrition supplemented with arginine with or without other immune-modulating agents with standard enteral nutrition; inclusion of	We have systematically reviewed all RCTs evaluating the effect of perioperative administration of arginine-supplemented diets in elective surgical patients.

	-different study designs (with more than 1 intervention and/or control group; same intervention was used in varying settings, i.e., pre-, post-,and/or perioperatively) -missing clear description of some data related to infections (these studies were related)	clinically important outcomes such as mortality, infectious complications, and hospital length of stay **Exclusion criteria:** Studies reporting only nutritional or immunological outcomes; critically ill patients who underwent urgent or emergent operations (i.e., trauma, ruptured aneurysms, etc.)	
Notes	**Author's Conclusion:** In conclusion, in this review we have demonstrated some clinical evidence that use of nutrition therapy containing arginine and omega-3 fatty acids used both pre- and postoperatively in high-risk elective surgical patients is associated with a substantial reduction in infection and shorter length of hospital stay. Efforts to implement the use of these diets in the perioperative setting are worthwhile. These efforts will result in considerable reduction in morbidity for our patients and substantial reductions in costs for the health care system.		
Outcome measures/results	**Primary outcome measure:** number of patients with new infectious complications **Secondary outcome measures:** hospital length of stay, mortality		Twenty-eight studies reported infectious complications on a per-patient basis. When they were combined statistically, the results showed that arginine-supplemented diets were associated with considerably reduced overall infectious complications when compared with standard formulas in surgical patients (RR = 0.59; 95% CI, 0.50-0.70;p < 0.00001;). The test for heterogeneity was not significant (p = 0.11, I^2 = 26%). When the analysis was repeated removing the 2 studies that used substantial amounts of glycine in the control group the observations were similar (RR = 0.56; 95% CI, 0.47-0.67; p <0.00001; test for heterogeneity p = 0.14, I2 = 24%). Overall hospital length of stay, aggregated across 29 studies, was reduced in surgical patients receiving arginine supplemented diets when compared with patients receiving standard formulas (WMD=- 2.38; 95% CI, -3.39 to -1.36; p < 0.00001;). The test for heterogeneity was significant, with an I^2 test indicating the presence of a large amount of heterogeneity (p <0.00001, I^2 = 87%). When the analysis was repeated, removing the one study with glycine in the control group that reported on this variable, the observations were similar (WMD=- 2.38; 95% CI, -3.42 to -1.34; p < 0.00001, with significant heterogeneity present (p <0.00001, I^2 = 88%). Twenty-one studies reported mortality as one of the outcomes. When their results were statistically aggregated, arginine-supplemented diets did not have a significant effect on mortality (RR = 1.08; 95% CI, 0.65-1.80; p =0.76). The test for

		heterogeneity was not significant (p = 0.99, I^2 = 0%). When the analysis was repeated, removing the one study with glycine in the control group that reported on this variable, the observations were similar, as this study reported no deaths (RR=1.08; 95% CI, 0.65-1.80; p = 0.76; test for heterogeneity was not significant (p = 0.99, I^2 = 0%).

44. Montejo JC, Zarazaga A, Lopez-Martinez J, Urrutia G, Roque M, Blesa AL, Celaya S, Conejero R, Galban C, Garcia de Lorenzo A, Grau T, Mesejo A, Ortiz-Leyba C, Planas M, Ordonez J, Jimenez FJ, Spanish Society of Intensive Care Medicine and Coronary Units Immunonutrition in the intensive care unit. A systematic review and consensus statement. Clin Nutr 2003; 22:221-233.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
A systematic review and consensus statement 1++	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** Novartis Consumer Health (Barcelona, Spain) **Dropout rates:** n/a **Study limitations:** - trials used any type of pharmaconutrients-enriched diet, so it is impossible to know what is the best combination of pharmaconutrients - heterogeneity of some results - no data to assess the cost/benefit of these diets	**Total no. Patients:** n=2383 (26RCTs) **Inclusion criteria:** RCTs, critically ill patients (defined as such in the study); randomly allocation of patients to receive enteral nutrition with an immune-enhancing diet or a standard diet; Inclusion of significant clinical outcomes: mortality or infectious complications, no surrogate endpoints like nutritional outcomes **Exclusion criteria:** comparison of immune-enhancing diets with nil by mouth or with parenteral nutrition	In order to develop a process with clinical-practice implications we decided to use a combined methodology. A methodological group performed a systematic review. After this, a group of clinicians with experience in the field of nutritional support in critically ill patients discussed the appreciated results in order to obtain a consensus about the relevance of the result for the clinical practice and, finally, establish clinical recommendations about the use of pharmaconutrition in critically ill patients.
Notes	-For the systematic review Randomized clinical trials of critically ill patients treated with enteral nutrition comparing diets enriched with pharmaconutrients vs not enriched diets were included. Infectious complications and outcome variables (days on mechanical ventilation, ICU and hospital length of stay and mortality) were evaluated. Studies were classified in four subgroups according to the patient's primary diagnosis: surgical, trauma, burned or medical. - None of the 26 trials obtain the maximum score (5 points) in the Jadad scale. According to this, the consensus group considered that existing data about the use of enteral nutrition with modified formulas in critically ill patients should be classed with a level II of evidence. **Author's Conclusion:**		

	Considering the beneficial effects and the absence of detrimental ones, the use of diets enriched with pharmaconutrients could be recommended in ICU patients requiring enteral feeding. Nevertheless, more investigation is needed in this field in order to find the more appropriate population of patients that can be beneficed with this nutritional therapy.	
Outcome measures/results	Nosocomial infection rate, Adult respiratory distress syndrome (ARDS) incidence, Multiple organ dysfunction syndrome (MODS) incidence, Hospital length of stay, Duration of mechanical ventilation, In-hospital mortality, Cost	Independent review of 267 articles identified 26 relevant primary studies. Global results indicate that there was a reduction in infection rate in the pharmaconutrition group, considering the appreciated lower incidence in abdominal abscesses (OR: 0.26, CI: 0.12–0.55) (*P*=0.005), nosocomial pneumonia (OR: 0.54, CI: 0.35–0.84) (*P*=0.007) and bacteremia (OR: 0.45, CI: 0.35–0.84) (*P*=0.0002). Also, patients treated with pharmaconutrition diets have a reduction in time on mechanical ventilation (mean 2.25 days, CI: 0.5–3.9) (*P*=0.009), ICU length of stay (mean reduction of 1.6 days, CI: 1.9–1.2) (*P*<0.0001) and hospital length of stay (mean reduction of 3.4 days, CI: 4.0–2.7) (*P*<0.0001). No effects were appreciated on mortality (OR: 1.10, CI: 0.85–1.42) (*P*=0.5). Nevertheless, the separate analysis for each subgroup showed that the reported beneficial effects were not the same for each patient population. Also, the clinician panel of experts identifies several problems in the published data about enteral pharmaconutrition in critically ill patients. In spite of the subgroup differences and of the problems detected, the clinician group considered that the appreciated results could support a Grade B recommendation for the use of these formulas in ICU patients. In the following there is a set of questions with interest in the decision-making process of nutritional support in critically ill patients (Answer to each question was obtained by consensus after considering results about the topic obtained in the systematic review; Answers applied only to the group of patients for which results were obtained and not for the whole critically ill patients' population; Letters in parentheses refers to the grade of recommendation in each case) *Question 1: Is there any evidence that specialized diets, enriched with immunonutrients, can decrease the incidence of nosocomial infections in critically ill patients when compared to standard diets?* Looking at the global infections rate, there is no evidence to support the hypothesis that immunonutrition can decrease the number of infected patients during ICU stay. The use of these diets in these patients should be recommended using other criteria (Recommendation grade C). Nevertheless, modified diets can decrease the incidence of some infections in different subgroups of patients: The use of these diets in trauma patients has a

		positive effect considering the lower incidence of bacteremia and intraabdominal infections (B) but the incidence of nosocomial pneumonia, wound infection, urinary tract infection or sepsis remain unchanged (C). The use of modified diets can be recommended in surgical patients considering the reduction in wound infections and urinary tract infections (Grade B) but other types of infection remain unchanged and could change the recommendation (C). In burn patients the reduction in nosocomial pneumonia obtained with the immunonutrition recommends the use of these diets (Grade B) but recommendation is of a lesser degree if the effect on other infectious complications is considered (C). Patients in the mixed group can benefit from modified diets considering the reduction in bacteremia (B) but there is no other effect on infectious complications (C). *Question 2: Is there any evidence that pharmaconutrients-enriched diets can decrease the incidence of ARDS or MODS in critically ill patients when compared to standard diets?* Data available in trauma patients do not support this hypothesis (C). Enteral nutrition with pharmaconutrients can be recommended in the mixed group of patients if we consider the appreciated reduction in the incidence of MODS (Grade B). There is no data to answer this question in surgical or burned patients. *Question 3: Is there any evidence that pharmaconutrition can shorten the duration of the mechanical ventilation, ICU length of stay or hospital length of stay in critically ill patients when compared to standard diets?* Time on mechanical ventilation is shortened in trauma patients that receive modified diets. Considering this effect, the use of these diets can be recommended (Grade B). There is no effect in burned patients or in the mixed group. ICU length of stay is diminished in trauma and surgical patients treated with immunonutrition; this permits the recommendation for its use (Grade B). This effect is not appreciated in patients in the mixed group. The recommendation for administering immunonutrition to surgical patients can be based also in the appreciated reduction in hospital length of stay (Grade B). Nevertheless, this is not applicable to trauma patients or to the mixed group.

		Question 4: Is there any evidence that diets enriched with immunonutrients can decrease in-hospital mortality in critically ill patients when compared to standard diets? There is no evidence that immune-enhancing diets have any effect on the in-hospital mortality of critically ill patients. The use of these modified diets with the purpose of diminish the mortality in critically ill patients cannot be recommended (Grade C). *Question 5: Is there any evidence that specialized diets, enriched with immunonutrients, can decrease the cost in critically ill patients when compared to standard diets?* There are not enough data available to answer this question. The expert panel believes that this question needs further research.

45. Wilhelm SM, Kale-Pradhan PB Combination of arginine and omega-3 fatty acids enteral nutrition in critically ill and surgical patients: a meta-analysis. Expert Rev Clin Pharmacol 2010; 3:459-469.			
Study Type/ Evidence Level	**Study details /limitations**	**Patient characteristics**	**Interventions**
Meta-analysis 1++	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** - included studies vary in sample sizes (20–390 subjects), different treatment exposure, patient population, study outcomes, total volume of formula administered, timing and duration of therapy also differ between the studies	**Total no. Patients:** n=2508 (23 trials) **Inclusion criteria:** studies that randomized patients to arginine and omega-3 fatty acids or a control enteral formula that did not contain any immunonutrient, such as glutamine; published in English in full; controlled trials; treatment group utilized arginine and omega-3 fatty acids in combination with nucleic acids (Impact); adult critically ill or surgical patients were dosed pre- or post-operatively; trial results included at least one of the following end	We performed a systematic literature search of RCTs to determine if the combination of arginine and omega-3 fatty acids impacts infection rate, hospital length of stay and mortality in critically ill or surgical patients.

	-Definitions of outcomes vary between studies (this may explanations may explain some of the differences in results observed in each study) -included studies were conducted in in various countries (medical treatments available and approaches to therapy in each country differ and may affect outcomes) -inclusion of patients with benign and malignant diseases - possible affection of results because of many advances in the care of the critically ill and surgical patients in the last two decades	points : infectious complications, LOS and mortality; trial results reported in a usable format for analysis **Exclusion criteria:** trials assessing arginine or omega-3 fatty acids as monotherapy or assessed these agents against another active immunonutrient therapy; trials which did not meet all of the inclusion criteria	
Notes	**Key issues:** • Immune-enhancing enteral preparations enriched with arginine, glutamine, omega-3 fatty acids, nucleotides and other immunonutrients are designed to help improve immune function. • This meta-analysis determined whether arginine and omega-3 fatty acids impact infection rate, hospital length of stay (LOS) and mortality in critically ill or surgical patients. Immunonutrition administered pre- and post-operatively showed a significant reduction in infection rate, but not in the critically ill population. • Overall, immunonutrition administered to surgical populations (pre- and post-operatively) showed significant reduction in LOS. However, this was not seen in the critically ill patients. • Overall mortality was not significantly different in any of the surgical or critically ill populations. • Immunonutrition significantly decreases infection rates and LOS in surgical populations. • The effect of immunonutrition is unclear in critically ill patients.		
Outcome measures/results	**Primary outcome measure:** Infection rate, Length of hospital stay, mortality		In total, 23 studies met all of the criteria. Immunonutrition with arginine and omega-3 fatty acids was administered either pre- or post-operatively or during intensive care unit stay in seven, ten and six studies, respectively. Infection rate and

		length of stay were significantly lower in patients receiving immunonutrition compared with the control group. In a subgroup analysis, these differences were maintained in the pre- and post-operative populations, but were not significant in the critically ill population. Mortality was not significantly different between the immunonutrition and control groups.

46. Marik PE, Zaloga GP Immunonutrition in high-risk surgical patients: a systematic review and analysis of the literature. JPEN J Parenter Enteral Nutr 2010; 34:378-386.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic Review and meta-analysis 1++	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** small number of studies in certain subgroups according to type of IMD used	**Total no. Patients:** n=1918 (21 RCTs) **Inclusion criteria:** report of 1 or more of the clinical outcomes: number of patients with new infections, wound complications (fistula, anastomosis, or incision dehiscence),hospital LOS, and Mortality; studies that randomized patients to an IMD or a control enteral formula that was similar in composition to the IMD except for the specific immunonutrients that were being tested **Exclusion criteria:** intervention/control group received parenteral nutrition, no inclusion of a group that received a control diet	Our aim was to identify all relevant randomized controlled clinical trials that investigated the clinical outcomes of IMDs (Immunomodulating diets) containing arginine and FO (fish oil) either alone or in combination in patients undergoing major elective surgery.
Notes	Studies were stratified according to the type of IMD (arginine supplementation alone, FO supplementation alone, or both) and the timing of the initiation (preoperatively only, postoperatively only, and perioperatively) of the IMD. **Author's Conclusion:** An immunomodulating enteral diet containing increased amounts of both arginine and fish oil should be considered in all high-risk patients undergoing major surgery. Although the optimal timing cannot be determined from this study, it is suggested that immunonutrition be initiated preoperatively when feasible.		

Outcome measures/results	To investigate the benefit of an IMD supplemented with arginine and FO either alone or in combination in patients undergoing major surgery. *Outcome measures:* new infections, wound complications, length of hospital stay (LOS), and mortality	Twenty-one relevant studies were identified, which included a total of 1918 patients. Immunonutrition significantly reduced the risk of acquired infections, wound complications, and LOS. The mortality rate was 1% in both groups. The treatment effect was similar regardless of the timing of the commencement of the IMD. The benefits of immunonutrition required both arginine and fish oil.

47. Stableforth WD, Thomas S, Lewis SJ A systematic review of the role of immunonutrition in patients undergoing surgery for head and neck cancer. Int J Oral Maxillofac Surg 2009; 38:103-110.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic review 1++	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** Major limitations relate to the limitations of the literature: - The diversity of the interventions and the type and stage of cancers studied meant that deciding when it was appropriate to use meta-analysis to combine results was difficult -Different dietary interventions may not have an equal effect, or even the same direction of effect, for	**Total no. Patients:** n=605 (10RCTs) **Inclusion criteria:** randomized controlled trials in which patients undergoing head and neck surgery for cancer had been randomly allocated to be in a control group receiving either traditional care (i.v. fluids) or polymeric nutritional supplements and an interventional group receiving polymeric nutritional supplements with immunonutritional additives **Exclusion criteria:**	This study reviews randomized trials comparing perioperative standard polymeric nutrition or no nutritional supplementation with immunonutrition in the treatment of head and neck cancer.

	different cancer sites and stages -Cancer stage, timing of the intervention in relation to treatment and the duration of the intervention varied between trials		
Notes	Arginine and omega-3 fatty acids are the investigated immunonutrition nutrients. **Author's Conclusion:** There is a discrepancy between the use of dietary interventions and the strength of evidence for their benefit. The large expenditure on immuno-feeding and other dietary supplements in people with head and neck cancer demonstrates an urgent need to understand the effect on cancer outcomes. A suitable powered clinical trial is required before firm recommendations can be made on the use of immunonutrition in head and neck cancer patients postoperatively.		
Outcome measures/results	The authors carried out a systematic review of randomized control trials to determine whether perioperative immunonutrition has a role in the treatment of head and neck cancer Wound infection, fistula formation, length of hospital stay, mortality	10 trials of polymeric nutritional supplementation with immunonutrition were identified; one compared two types of immunonutrition. There was little evidence of heterogeneity. Pooled estimates showed a reduction in length of hospital stay by 3.5 days (95% CI 0.7 to 6.3-day, P < 0.01). No reductions in clinical complications were seen. Perioperative immunonutrition is associated with reduced length of hospital stay; the mechanism is unclear as other outcomes were not improved. Trials were small with incomplete reporting of outcomes. An adequately powered trial is required to substantiate benefit.	

48. Waitzberg DL, Saito H, Plank LD, Jamison GG, Jagannath P, Hwang TL, Mijares JM, Bihari D Postsurgical infections are reduced with specialized nutritional support. World J Surg; 2006; 30: 1592-1604.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-analysis 1++	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** n/a	**Total no. Patients:** n=2305 (17 RCTs) • n=1392 (10 RCTs): examined the efficacy of pre- or perioperative IMPACT supplementation in patients undergoing elective surgery	All randomized clinical trials in which patients were supplemented by the IMPACT formula before and/or after elective surgery and the clinical outcomes reported were included in the meta-analysis.

		• n= 913 (7 RCTs): assessed postoperative efficacy of IMPACT • n=2083(14RCTs): involved gastrointestinal (GI) surgical patients. **Inclusion criteria:** randomized clinical trial, surgical patients undergoing major elective operations, type of intervention:enteral nutrition and/or oral supplementation with IMPACT before and/or after surgery, outcome measures: defined postoperative infectious complications, mortality, length of hospital stay, and cost of in-hospital care, Publication languages: English, German, French, Spanish, Portuguese, Japanese, and Chinese **Exclusion criteria:** Studies reporting only nutritional or immunological outcomes, no randomization	
Notes	**Author's Conclusion:** This study identifies a dosage (0.5–1 l/day) and duration (supplementation for 5–7 days before surgery) of IMPACT that contributes to improved outcomes of morbidity in elective surgery patients, particularly those undergoing GI surgical procedures. The cost effectiveness of such practice is supported by recent health economic analysis. Findings suggest preoperative IMPACT use for the prophylaxis of postoperative complications in elective surgical patients.		
Outcome measures/results	The objective was to examine the relationship between pre-, peri-, and postoperative specialized nutritional support with immune-modulating nutrients and postoperative morbidity in patients undergoing elective surgery. **Primary outcome measure:**		IMPACT supplementation, in general, was associated with significant (39%–61%) reductions in postoperative infectious complications and a significant decrease in LOS in hospital by an average of 2 days. The greatest improvement in postoperative outcomes was observed in patients receiving specialized nutrition support as part of their preoperative treatment. In GI surgical patients, anastomotic leaks were 46%

	number of patients with one or more postoperative-acquired infection(s), the LOS in hospital, and hospital mortality **Secondary outcome measures:** Infection rates and the frequently encountered noninfectious surgical complication, anastomotic leak	less prevalent when IMPACT supplementation was part of the preoperative treatment.

49. 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; 286:944-953.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic review 1++	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** -we excluded studies of single immune-enhancing agents, the results of our meta-analysis are not applicable to single interventions -method of scoring the quality of each trial did not allow us to determine which component of quality was most important -we did not apply meta-regression techniques to determine if there are confounding effects between different variables explaining the heterogeneity	**Total no. Patients:** n=2419 (22RCTs) **Inclusion criteria:** randomized clinical trials; critically ill or surgical patients; comparison of enteral nutrition supplemented with any combination of arginine, glutamine, omega-3 fatty acids, or nucleotides compared with standard enteral nutrition; inclusion of clinically important outcomes, such as mortality, infectious complications, and length of hospital stay **Exclusion criteria:** studies reporting only nutritional or immunological outcomes	The purpose of this article is to systematically review, critically appraise, and synthesize randomized clinical trial data evaluating the effect of enteral immunonutrients in critically ill patients.

Notes	We defined critically ill patients as being routinely cared for in a critical care environment. Although patients after major surgery are not necessarily cared for in a critical care environment, we included studies of elective surgical patients because their response to illness resembles the hypercatabolic state in critical illness. **Author's Conclusion:** Immunonutrition may decrease infectious complication rates but it is not associated with an overall mortality advantage. However, the treatment effect varies depending on the intervention, the patient population, and the methodological quality of the study.	
Outcome measures/results	**Primary outcome measure:** mortality (ICU and hospital) and number of patients with new infectious complications **Secondary outcome measures:** length of hospital and ICU stay and duration of mechanical ventilation	Twenty-two randomized trials with a total of 2419 patients compared the use of immunonutrition with standard enteral nutrition in surgical and critically ill patients. With respect to mortality, immunonutrition was associated with a pooled risk ratio (RR) of 1.10 (95% confidence interval [CI], 0.93-1.31). Immunonutrition was associated with lower infectious complications (RR, 0.66; 95% CI, 0.54-0.80). Since there was significant heterogeneity across studies, we examined several a priori subgroup analyses. We found that studies using commercial formulas with high arginine content were associated with a significant reduction in infectious complications and a trend toward a lower mortality rate compared with other immune-enhancing diets. Studies of surgical patients were associated with a significant reduction in infectious complication rates compared with studies of critically ill patients. In studies of critically ill patients, studies with a high-quality score were associated with increased mortality and a significant reduction in infectious complication rates compared with studies with a low-quality score.

50. Beale RJ, Bryg DJ, Bihari DJ Immunonutrition in the critically ill: a systematic review of clinical outcome. Crit Care Med1999; 27:2799-2805.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-analysis 1++	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** -variation of enteral formulas - widely variations in sample sizes -severity of illness and expected outcomes of	**Total no. Patients:** n= 1557 within 12RCTs (n= 1482 included in intention to treat analysis) **Inclusion criteria:** critically ill patients requiring enteral nutrition via a tube (nasoenteric or jejunostomy), Only trials with institutional review board approval and appropriate informed consent; randomized trials that compared critically ill patients who received enteral	we searched for randomized controlled trials comparing patients receiving standard enteral nutrition with patients receiving a commercially available immune-enhancing feed with arginine with or without glutamine, nucleotides, and omega-3 fatty acids.

	patients having major (usually upper gastrointestinal) planned surgery, victims of trauma, and emergency ICU admissions vary considerably	nutrition with a feed enriched with arginine with or without glutamine, nucleotides, and omega-3 fatty acids with patients receiving a standard enteral feed preparation; Outcome measures: mortality, infection rate, days of mechanical ventilation, intensive care unit (ICU) length of stay (LOS), hospital LOS, days with diarrhea **Exclusion criteria:** n/a	
Notes	**Author's Conclusion:** The benefits of enteral immunonutrition were most pronounced in surgical patients, although they were present in all groups. The reduction in hospital length of stay and infections has resource implications		
Outcome measures/results	mortality, infection rate, days of mechanical ventilation, intensive care unit (ICU) length of stay (LOS), hospital LOS, days with diarrhea, calorie intake, nitrogen intake	There was no effect of immunonutrition on mortality (relative risk = 1.05, confidence interval [CI] = 0.78, 1.41; p = .76). There were significant reductions in infection rate (relative risk = 0.67, CI = 0.50, 0.89; p = .006), ventilator days (2.6 days, CI = 0.1, 5.1; p = .04), and hospital length of stay (2.9 days, CI = 1.4, 4.4; p = .0002) in the immunonutrition group.	

51. 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; 229:467-477.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-analysis 1++	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** n/a	**Total no. Patients:** n=1009 (11 prospective RCTs) **Inclusion criteria:** n/a **Exclusion criteria:** n/a	To analyze the results of randomized, controlled studies comparing enteral nutrition support supplemented with combinations of key nutrients versus standard enteral nutrition support to determine effects on morbidity rates and hospital stay.
Notes	-the nutritional regimens varied among the different studies. However, the key nutrients used in the various combinations were L-arginine, L-glutamine, branched-chain amino acids, EFAs and RNA -Missing explanation of inclusion and exclusion criteria -because six of the studies had studied only patients undergoing surgery for GI cancer, a further analysis of these six studies was also undertaken separately		

	Author's Conclusion: This meta-analysis has demonstrated that nutritional support supplemented with key nutrients results in a significant reduction in the risk of developing infectious complications and reduces the overall hospital stay in patients with critical illness and in patients with gastrointestinal cancer. However, there is no effect on death. These data have important implications for the management of such patients.	
Outcome measures/results	incidences of pneumonia, infectious complications, and death, and length of hospital stay	The provision of nutritional support supplemented with key nutrients to patients with critical illness resulted in a decrease in infectious complications when compared with patients receiving standard nutritional support and a significant reduction in overall hospital stay. Similar results were documented in patients with gastrointestinal cancer. However, there were no differences between patient groups for either pneumonia or death.

52. Mabvuure NT, Roman I, Khan OA Enteral immunonutrition versus standard enteral nutrition for patients undergoing oesophagogastric resection for cancer. Int J Surg 2013; 11:122-127.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Review 1+	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** -variations in types of the undertaken operations -included studies used different formulas of the enteral nutrition -lack on reported outcomes - quality of the reporting of the RCTs was variable	**Total no. Patients:** n=556 (6RCTs) • enteral immunonutrition group n=287 • standard enteral diet n=269 **Inclusion criteria:** n/a **Exclusion criteria:** n/a	A best evidence topic in surgery was written according to a structured protocol. The question addressed was "In cancer patients undergoing esophageal or gastric resection for cancer and requiring postoperative nutritional support, does enteral immunonutrition confer additional clinical benefits as compared to standard enteral nutrition?
Notes	**Author's Conclusion:** Although postoperative enteral immunonutrition seems to improve humoral immunity in patients undergoing esophagogastric resection, this improvement does not lead to a reduced hospital stay, nor does it reduce the rate of infections. There is no convincing evidence in support of routine immunonutrition in patients undergoing esophageal or gastric resection for cancer.		
Outcome measures/results	postoperative clinical course, complications, length of hospital stay, inflammatory and immunological marker levels		All six of these randomized controlled trials compared the clinical benefits of standard enteral nutrition with those of enteral nutrition supplemented with a variety of immune-modulating substances. The studies failed to demonstrate

		consistent differences in patients' postoperative clinical course, complications, length of hospital stay and inflammatory marker levels. Hence although there is reasonable evidence to suggest that immunonutrition improves humoral immunity as opposed to cellular immunity, this improvement does not result in reductions in infection rates or reduced hospital stay. There is currently not enough evidence to recommend routine immunonutrition in all patients undergoing esophageal or gastric resection for cancer.

53. Gianotti L, Braga M, Nespoli L, Radaelli G, Beneduce A, Di Carlo V. A randomized controlled trial of preoperative oral supplementation with a specialized diet in patients with gastrointestinal cancer. Gastroenterology 2002; 122:1763-1770.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
prospective randomized clinical trial 1-	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** Novartis Consumer Health (Bern, Switzerland*)* **Dropout rates:** n/a **Study limitations:** n/a	**Total no. Patients:** n=305 • Preoperative group n=102 • Perioperative group n=101 • Conventional group n=102 **Inclusion criteria:** histologically documented neoplasm of the gastrointestinal tract, planned major elective surgery **Exclusion criteria:** weight loss ≥10% (with respect to usual body weight) in the past 6 months, age younger than 18 years, hepatic dysfunction (Child–Pugh class >B), respiratory dysfunction (arterial Pao_2 <70 torr), renal dysfunction (serum creatinine level >3 mg/dL, hemodialysis), cardiac dysfunction (New York Heart Class >3), Karnofsky score <60, pregnancy, ongoing infections, and immune disorder (neoadjuvant	-preoperative group: oral supplementation for 5 days before surgery with 1 L/day of a formula enriched with 2.5 g/L arginine, 3.3g/L ω-3 fatty acids, and 1.2g/L RNA, with no nutritional support given after surgery -perioperative group: oral supplementation for 5 days before surgery with 1 L/day of a formula enriched with2.5 g/L arginine, 3.3g/L ω-3 fatty acids, and 1.2g/L RNA, postoperative jejunal infusion with the same enriched formula - conventional group: no artificial nutrition before and after surgery

		radiochemotherapy, circulating neutrophils <2.0 × 10^9/L)	
Notes	**Author's Conclusion:** In conclusion, in our population, the administration of a supplemented diet significantly improved outcome compared with a conventional treatment. The simple preoperative supplementation was as effective as the perioperative approach. Additionally, it could reduce gastrointestinal side effects. Furthermore, we suggest in the analysis of future nutritional trials that surgical patients be stratified per BMI. This will enable a better evaluation of the risk of postoperative complications and the impact of different treatments.		
Outcome measures/results	**Primary outcome measure:** reduction of postoperative infection rate and length of postoperative stay **Secondary outcome measures:** nutritional parameters, gut function, and patient compliance	The 3 groups were comparable for all baseline and surgical characteristics. Intention-to-treat analysis showed a 13.7% incidence of postoperative infections in the preoperative group, 15.8% in the perioperative group, and 30.4% in the conventional group (P = 0.006 vs. preoperative; P = 0.02 vs. perioperative). Length of hospital stay was 11.6 ± 4.7 days in the preoperative group, 12.2 ± 4.1 days in the perioperative group, and 14.0 ± 7.7 days in the conventional group (P = 0.008 vs. preoperative and P = 0.03 vs. perioperative).	

54. Giger-Pabst U, Lange J, Maurer C, Bucher C, Schreiber V, Schlumpf R, Kocher T, Schweizer W, Krähenbühl S, Krähenbühl L. Short-term preoperative supplementation of an immuneenriched diet does not improve clinical outcome in well-nourished patients undergoing abdominal cancer surgery. Nutrition 2013; 29: 724-729.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries:** Switzerland **Centers:** Hospitals in Fribourg, St. Gallen, Aarau, Liestal, Baden, and Schaffhausen **Setting:** n/a **Funding Sources:** Novartis Consumer Health SA, Nyon, Switzerland **Dropout rates:** n/a **Study limitations:** n/a	**Total no. Patients:** n=108 • IEF group n=55 • Con group n=53 **Inclusion criteria:** Well-nourished patients (defined by a total score <3 on the nutritional risk screening tool (NRS 2002)) with histologically documented adenocarcinoma of the upper or lower gastrointestinal tract who were candidates for elective surgery **Exclusion criteria:** clinically relevant pulmonary (FEV1 <0.8 L/s), cardiovascular (Goldmann classification class >3),	IEF (immunoenriched formula): -750 mL of an immunoenriched formula (750ml contains 16.72 g of arginine, 3.3 g of omega-3 fatty acids, and 1.32 g of RNA) for 3 consecutive days preoperatively Con (placebo): -750 mL of an isocaloric, isonitrogenous placebo diet for 3 consecutive days preoperatively

		renal (serum creatinine level >165 µmol/L), hematological (Hb level <80 g/L; circulating neutrophils <2.0 × 109/L), or hepatic (Child-Pugh Class B or C) alterations. Further, patients were also excluded for pregnancy, severe mental disorders, age younger than 18 y, uncontrolled ongoing infection, intestinal obstruction, any concomitant dietary supplements containing omega 3-fatty acids, any immunomodulating therapy, other oral supplements, and/or an Eastern Cooperative Oncology Group (ECOG) performance status >2	
Notes	IEF group: n=49 received allocated intervention, lost to follow up n=2 Con group: n=49 received allocated intervention. Lost to follow up n=3 **Author's Conclusion:** Preoperative oral supplementation with an immunoenriched diet for 3 d preoperatively did not improve postoperative outcome compared with the placebo in well-nourished patients with elective gastrointestinal cancer surgery.		
Outcome measures/results	trial in well-nourished visceral cancer patients to find out whether preoperative supplementation with an immunoenriched diet for 3 d is superior to placebo concerning postoperative outcome. **Primary outcome measure:** rate of postoperative complications **Secondary outcome measures:** postoperative infectious complications, incidence of noninfectious complications, length of intensive and/or intermediate care unit (ICU/ICU), length of hospital stay (LOS), and postoperative antibiotic use	A total of 108 patients (IEF group: n = 55; Con group: n = 53) were randomized. The two groups were comparable for all baseline and surgical characteristics. The overall mortality was 2.8% and not significantly different between the two groups (IEF group: 3.6% vs. Con group: 1.9%, P = 1.00). Intention-to-treat analysis showed no difference for the incidence of postoperative overall (IEF group: 29% vs. Con group: 30%; P = 1.00) and infectious (IEF group: 15% vs. Con group: 17%; P = 0.79) complications. Length of hospital stay was 12 ± 4.9 d in the IEF group and 11.6 ± 5.3 d in the Con group (P = 0.68).	

55. Kinross JM, Markar S, Karthikesalingam A, Chow A, Penney N, Silk D, Darzi A (2013) A meta-analysis of probiotic and synbiotic use in elective surgery: does nutrition modulation of the gut microbiome improve clinical outcome?. JPEN J Parenter Enteral Nutr 2013; 37:243-253.			
Study Type/	**Study details/limitations**	**Patient characteristics**	**Interventions**

Evidence Level			
Meta-analysis 1++	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** - lack of standardization in the methodology of the clinical analysis of surgery of the gut ecosystem (e.g. no consistency across route of feeding, dosing strategy, type of probiotic or prebiotic used, dose of probiotic or synbiotic used) -variability in surgical techniques (may have an inadvertently influence the gut microbiome) - absence of standardized reporting of surgical methodology across the studies -poor reporting of confounding variables that may influence the gut microbiome during the perioperative course (e.g. nutrition status)	**Total no. Patients:** n=962 (13RCTs) **Inclusion criteria:** randomized controlled trials in which patients underwent abdominal surgery with the use of a prebiotic, probiotic, or a synbiotic agent, studies had to use a control group (placebo or no therapy), prebiotic must be selective for a particular species and have a health benefit to the host (following fibers were not considered functional prebiotics: plant non-starch polysaccharides (e.g., cellulose, pectin, gums, hemicelluloses, β-glucans, and fiber contained in oat and wheat bran) and lignin.) synbiotic was defined as a product that contains both pro- and prebiotics **Exclusion criteria:** n/a	We searched for Randomized controlled trials that compared perioperative dosing of probiotics and synbiotics in patients undergoing elective general surgical procedures
Notes	Subgroup analysis was performed to determine if there were specific benefits in rates of postoperative pneumonia, wound infection, or urinary tract infection requiring antibiotic treatment **Author's Conclusion:** Probiotic and synbiotic nutrition strategies reduce the incidence of postoperative sepsis in the elective general surgery setting. These effects appear more pronounced with the use of synbiotics. High-powered, mechanistic studies are now required for the optimization of pro- and prebiotic regimens to further improve their efficacy.		

Outcome measures/results	**Primary outcome measure:** development of postoperative sepsis (within 1 month of surgery) **Secondary outcome measures:** mortality, length of hospital stay, length of antibiotic treatment	Thirteen randomized controlled trials totaling 962 patients were included in this analysis (304 received synbiotics and 182 received probiotics). The incidence of postoperative sepsis was reduced in the probiotic group vs the control (pooled odds ratio [OR] = 0.42; 95% confidence interval [CI], 0.23–0.75; *P* = .003) and in the synbiotic group vs the control (pooled OR = 0.25; 95% CI, 0.1–0.6; *P* = .002). However, subgroup analysis failed to identify a significant reduction in the incidence of pneumonia, urinary tract infections, or wound infections in the postoperative phase for either treatment group. Synbiotics reduced the length of postoperative antibiotic use (weighted mean differences = −1.71; 95% CI, –3.2 to –0.21; *P* = .03).

56. Gu WJ, Deng T, Gong YZ, Jing R, Liu JC (2013) The effects of probiotics in early enteral nutrition on the outcomes of trauma: a meta-analysis of randomized controlled trials. JPEN J Parenter Enteral Nutr 37:310-317. [349]			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-analysis 1+	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** - the characteristics of populations, the probiotic regimen (species, dosage, route, timing, and duration of administration), and the study designs vary considerably among the reviewed studies - difficulty of addressing the isolated effects of probiotics (control groups may or may not have included glutamine and other substances that were not presented in the experiment group)	**Total no. Patients:** n= 281 (5RCTs) **Inclusion criteria:** patients with trauma, including injury to organs or physical damage to the body caused by violence, accident, or fracture and burns; only RCTs; comparison of an enteral pre-, pro-, or synbiotic with a control; 1 or more of the following clinical outcomes reported: nosocomial infections, length of ICU stay, VAP, and mortality **Exclusion criteria:** abstracts, letters, or meeting proceedings; repeated data or no report outcomes of interest; enrolled patients with drug-induced injury or surgical incision	A systematic electronic literature search was conducted to identify RCTs comparing the use of probiotics with a control in trauma patients.

	-small number of included RCTs with modest sample sizes		
Notes	**Author's Conclusion:** The use of probiotics is associated with a reduction in the incidence of nosocomial infections, VAP, and length of ICU stay but is not associated with an overall mortality advantage. However, the results should be interpreted cautiously due to the heterogeneity among study designs. Further large-scale, well-designed RCTs are needed		
Outcome measures/results	**Primary outcome measure:** incidence of nosocomial infections **Secondary outcome measures:** included the incidence of ventilator-associated pneumonia (VAP), length of ICU stay, mortality		Five studies involving 281 patients met our inclusion criteria. The use of probiotics was associated with a reduction in the incidence of nosocomial infections (5 trials; RR, 0.65; 95% CI, 0.45–0.94, *P* = .02), VAP (3 trials; RR, 0.59; 95% CI, 0.42–0.81, *P* = .001), and length of ICU stay (2 trials; SMD, −0.71; 95% CI, −1.09 to −0.34, *P* < .001) but no reduction in mortality (4 trials; RR, 0.63; 95% CI, 0.32–1.26, *P* = .19)

57. Adiamah A, Skorepa P, Weimann A et al. The Impact of Preoperative Immune Modulating Nutrition on Outcomes in Patients Undergoing Surgery for Gastrointestinal Cancer: A Systematic Review and Meta-analysis. Ann Surg 2019; 270: 247-256. doi:10.1097/SLA.0000000000003256			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic Review and Meta-Analysis 1++	**Countries:** Japan, Italy, Denmark, Germany, Turkey, Spain, Australia, China **Centers:** n/a **Setting:** n/a **Funding Sources:** Medical Research Council; Arthritis Research UK; National Institute for Health Research **Dropout rates:** n/a **Study limitations:** potential confounders such as compliance and potential for the controls to be taking in foods with similar ingredients as is found in immune modulating nutrition; no studies had a placebo-controlled arm; Compliance	**Total no. Studies:** 16 **Inclusion criteria:** Prospective RCTs reporting at least 1 relevant clinical outcome; human subjects ≥ age of 18 years undergoing surgery for gastrointestinal cancer; control arm was either an isocaloric isonitrogenous nonimmune-enhancing feed or normal diet with no supplementation **Exclusion criteria:** Studies which failed to fulfil the inclusion criteria such as nonrandomized or retrospective studies; Studies that only used singular components of recognized immune modulating nutrition; Studies that reported perioperative or postoperative	Evaluation of the impact of oral or enteral immune modulating nutrition administered a minimum of 3 days and restricted to the preoperative period on postoperative outcomes in patients undergoing surgery for gastrointestinal cancer

	and total amounts of immune modulating nutrition that each patient consumed were not reported adequately to allow calculations of a dose response	administration of immune modulating nutrition	
Notes	**Author's Conclusion:** pre- operative administration of immune modulating nutrition for a minimum of 5 days, either orally or enterally, leads to an appreciable and significant reduction in postoperative infectious complications and a tendency for a shortened length of stay		
Outcome measures/results	**Primary outcome**: infectious complications **Secondary outcomes**: length of stay, mortality, and non-infectious complications		- pooled OR for infectious complications after preoperative treatment with immune modulating nutrients was 0.52 (95% CI 0.38–0.71, P < 0.0001, I^2 = 16%) - pooled OR for noninfectious complications was 0.98 (95% CI 0.73–1.33, P = 0.91, I^2 = 0%) - pooled weighted mean differences was -1.57 (95% CI -2.48 to -0.66, P = 0.00007, I^2 = 34%). However, subgroup analysis of the group receiving supplements did not reach significance (OR - 1.06, 95% CI -2.76 to 0.63, P = 0.22, I^2 =63%) - pooled OR for mortality was 0.55 (95% CI 0.18–1.68, P = 0.29, I^2 = 0%)

58. Challine A, Rives-Lange C, Danoussou D et al. Impact of Oral Immunonutrition on Postoperative Morbidity in Digestive Oncologic Surgery: A Nation-wide Cohort Study. Ann Surg 2021; 273: 725-731. doi:10.1097/SLA.0000000000003282			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Cohort study 2+ NOS low	**Countries:** France **Centers:** n/a **Setting:** n/a **Funding Sources:** none **Dropout rates:** 0% **Study limitations:** Risk of Bias: low Inconsistency: high Indirectness: low Impreciseness: high Publication bias: n/a	**Total no. Patients:** 1771 **Inclusion criteria:** Patients were selected with ICD10 codes of cancer and digestive surgery act-procedures **Exclusion criteria:** Patients less than 18 years of age, with a second hospital stay for oncologic digestive surgery, or operated in emergency	Assessment of the effect of immunonutrition on 90-day morbidity, survival, and length of stay following surgery for digestive cancer.

	Health care databases could present a measurement bias; unable to measure the adherence of patients to the use of immunonutrition; several confounders may not have been measured: as a center effect		
Notes	**Author's Conclusion:** use of immunonutrition was not associated with a reduced 90-day morbidity, reduced infectious or non-infectious complications, or mortality rate. Immunonutrition was associated with a shorter length of stay.		
Outcome measures/results	**Primary outcome:** severe morbidity at 90 days after surgery **Secondary outcomes:** overall mortality and length of stay		- no significant difference between the 2 groups for 90-day severe morbidity [odds ratio (OR): 0.91, 95% confidence interval (95% CI): 0.73– 1.14] or in survival (hazard ratio: 0.89, 95% CI: 0.73 – 1.08) - length of stay were shorter in the immunonutrition-group [-1.26 days, 95% CI: - 2.4 to -0.1)]

59. Kelley KE, Fajardo AD, Strange NM et al. Impact of a Novel Preoperative Patient-centered Surgical Wellness Program. Ann Surg 2018; 268: 650-656. doi:10.1097/SLA.0000000000002932			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Controlled trial 2- NOS 9/9	**Countries:** USA **Centers:** n/a **Setting:** academic tertiary care medical center **Funding Sources:** National Institutes of Health, Welcome Trust, Howard Hughes Medical Institute or other external funding agencies. **Dropout rates:** n/a **Study limitations:** Risk of Bias: low Inconsistency: high Indirectness: moderate Impreciseness: low	**Total no. Patients:** 74 924 **Inclusion criteria:** preintervention group: attended the preadmission testing clinic prior to surgery between the dates of January 1, 2014 and December 31, 2015; intervention group: attended the preadmission testing hospitals within the time period of January 1, 2016 through January 31, 2018; nonintervention group: did not attend the preadmission testing clinic prior to their surgery **Exclusion criteria:** n/a	- 3 groups: preintervention group (n=9 202), intervention group (n=12 396) and non-intervention group (n= 53 326) - Intervention groups received a wellness bundle in a roller bag during preoperative screening at an urban academic medical center - wellness bundle consisted of a chlorhexidine bath solution, immuno-nutrition supplements, incentive spirometer, topical mupirocin for the nostrils, and smoking cessation information - Study staff performed structured patient interviews, observations, and standardized surveys at key intervals throughout the perioperative period

	Publication bias: n/a Not randomized nor was the between groups analysis matched; patients' self-reported data partly; smoking status not included in analysis		
Notes	**Author's Conclusion:** Adverse surgical outcomes cause significant morbidity and mortality to patients. A novel, preoperative, patient-centered well- ness program dramatically improved outcomes for surgical patients by reducing postoperative infectious complications		
Outcome measures/results	**Primary endpoint**: surgical complications		- Patients in the nonintervention and intervention groups were similar in demographics, comorbidity, and type of operations - Compliance with each element was high (80% mupirocin, 72% immuno-nutrition, 71% chlorhexidine bath, 67% spirometer) - intervention group had statistically significant reductions in surgical site infections, Clostridium difficile, catheter associated urinary tract infections, and patient safety indicator 90

60. Thornblade LW, Varghese TK, Jr., Shi X et al. Preoperative Immunonutrition and Elective Colorectal Resection Outcomes. Dis Colon Rectum 2017; 60: 68-75. doi:10.1097/DCR.0000000000000740			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Prospective cohort study 2+ NOS 9/9	**Countries:** USA **Centers:** multi-center **Setting:** n/a **Funding Sources:** Nestle Healthcare Nutrition **Dropout rates:** 0% **Study limitations:** Risk of Bias: low Inconsistency: n/a Indirectness: low Impreciseness: moderate Publication bias: n/a Patient compliance with the intervention was not measured. Residual	**Total no. Patients:** 3375 **Inclusion criteria:** patients undergoing elective gastrointestinal surgery; at one of the Surgical Care and Outcomes Assessment Program hospitals **Exclusion criteria:** underwent an emergency surgery or if they had an urgent condition for which they would not qualify for preoperative immunonutrition, age < 18	Surgeons used a preoperative checklist that recommended patients take oral immunonutrition (237mL, three times daily) for five days prior to elective colorectal resection.

	confounding including surgeon-level heterogeneity may influence estimates of the effect of immunonutrition		
Notes	**Author's Conclusion:** use of preoperative immunonutrition as part of the "strong for surgery" public health campaign helped to improve surgical outcome and was associated with fewer patients requiring a prolonged length of stay (≥8 days); the adoption of immune enhancing nutrition before elective surgery as a way to reduce prolonged length hospitalizations and improve the quality of surgical care		
Outcome measures/results	**primary outcome**: any serious adverse events **secondary outcome**: prolonged length of stay		- unadjusted rate of serious adverse events was 6.8% in the group receiving immunonutrition and 8.3% among those who did not receive treatment (p=0.25) - prolonged length of stay was 13.8% in the immunonutrition group and 17.3% in the untreated group (p=0.04). prolonged length of stay was more common among patients with than without serious adverse events (73.4% vs. 13.1%, p<0.001) - After matching, the rate of serious adverse events was 7.1% in the group receiving immunonutrition and 9.4% in those who did not (RR=0.76, 95% CI: 0.49–1.16, p=0.19) - relative risk of prolonged length of stay was 23% lower among patients receiving immunonutrition (15.6%) compared with the untreated group (20.4%) (RR=0.77, 95% CI: 0.58–1.01, p=0.05).

61. Buzquurz F, Bojesen RD, Grube C et al. Impact of oral preoperative and perioperative immunonutrition on postoperative infection and mortality in patients undergoing cancer surgery: systematic review and meta-analysis with trial sequential analysis. BJS Open 2020; 4: 764-775. doi:10.1002/bjs5.50314			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic Review and Meta-Analysis 1++ AMSTAR II 10/16	**Countries:** Italy, Spain, Greece, Japan, Denmark, USA, UK, Finland, Switzerland, France, Germany, New Zealand **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** Overall confidence in the results of the review: Critically Low Risk of bias of single studies: moderate Inconsistency: low Indirectness: low Impreciseness: moderate Publication bias: low High risk of performance bias because of unblinded studies; approximately half of studies did not report on adverse effects of immunonutrition; lack of blinding in the studies that had an active comparator; inadequate compliance among the studies included	**Total no. Studies:** 24 (22) **Inclusion criteria:** patients undergoing elective curative resection of a solid malignancy; Immunonutrition had to be administered within 30 days, and at the latest 5 days, before surgery. Continuation into the in-hospital postoperative period was allowed, but only by the oral route or tube feeding, RCT or prospective cohort study **Exclusion criteria:** patients under the age of 18years or with stage IV cancer	Evaluation of the potential clinical benefits of immunonutrition given in relation to the timing of surgery on postoperative infections and 30-day mortality in patients undergoing oncological surgery in comparison with patients not receiving immunonutrition.

Notes	**Author's Conclusion:** Immunonutrition reduced overall infectious complications, even after controlling for random error, and reduced surgical-site infection; quality of evidence was moderate, and mortality was not affected by immunonutrition (low quality). Oral immunonutrition merits consideration as a means of reducing overall infectious complications after cancer surgery.	
Outcome measures/results	**primary outcome**: overall infectious complications **secondary outcomes**: surgical-site infection and 30-day mortality	- overall infectious complications: significant effect was seen in favor of immunonutrition compared with the control group (RR 0·58, 95 percent c.i. 0·48 to 0·70; I^2 = 7 percent) - 95 percent prediction interval estimated the effect in future studies to be 0·43 to 0·78 - surgical-site infection and 30-day mortality: pooled RR in favor of immunonutrition was evident (RR 0·65, 95 percent c.i. 0·50 to 0·85; I^2 = 0 percent) - pooled RR for the 13 studies that reported on 30-day mortality in 1641 patients was 0·69 (95 per cent c.i. 0·33 to 1·40; I^2 =0 percent)

62.	**Gao B, Luo J, Liu Y et al. Clinical Efficacy of Perioperative Immunonutrition Containing Omega-3-Fatty Acids in Patients Undergoing Hepatectomy: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Ann Nutr Metab 2020; 76: 375-386. doi:10.1159/000509979**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis and systematic review 1++ AMSTAR II 8/16	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** Southwest Medical University Foundation (2018-ZRZD-010) and Doctoral Startup Fund of Affiliated Hospital of Southwest Medical University **Dropout rates:** n/a **Study limitations:** Overall confidence in the results of the review: Critically Low Risk of bias of single studies: moderate	**Total no. Studies:** 9 **Inclusion criteria:** RCTs; the experimental group received perioperative immunonutrition supplementation as the only intervention for patients who underwent hepatectomy, while the control group received placebo or regular nutrition; studies reporting at least one of the following outcomes: postoperative complications, liver failure, postoperative mortality, length of hospital stay **Exclusion criteria:** studies without a control group; case reports, letters, reviews, conference reports, or	experimental group received perioperative immunonutrition supplementation (including ω-3-FAs or Gln or Arg or nucleotides) as the only intervention for patients who underwent hepatectomy, while the control group received placebo or regular nutrition

	Inconsistency: low Indirectness: moderate Impreciseness: high Publication bias: n/a Only 9 RCTs, only articles in English included, variety of baseline characteristics and different schemes of immunonutrition supplementation	experiments; conference abstracts without the full text	
Notes	**Author's Conclusion:** This systematic review and meta-analysis showed that perioperative administration of immunonutrition containing ω-3-FAs can improve the overall postoperative complications, postoperative infectious complications, and incision infection, and it can shorten the length of hospital stay. Therefore, immunonutrition is clinically safe and feasible to be recommended as nutritional support for patients undergoing hepatectomy. However, considering the small number of patients included in this meta-analysis, more high-quality, large-sample, and multicenter RCTs are still required to verify the reliability of our conclusion.		
Outcome measures/results	overall postoperative complications; postoperative infectious complications; liver failure; postoperative mortality; length of hospital stay		- immunonutrition significantly reduced the incidence of overall postoperative complications (OR = 0.57, 95% CI: 0.34–0.95; p = 0.03) - incidence of overall postoperative infectious complications was significantly reduced in immunonutrition group than in control group (OR = 0.53, 95% CI: 0.37–0.75; p = 0.0003) - no significant difference in liver failure between the 2 groups (OR = 0.54, 95% CI: 0.23–1.24; p = 0.15) - no significant difference in postoperative mortality between both groups (OR = 0.69, 95% CI: 0.26–1.83; p = 0.46) - significantly shorter length of hospital stay in immunonutrition group compared with control group (MD = −3.80, 95% CI: −6.59 to −1.02; p = 0.007)

63. Wong CS, Praseedom R, Liau SS. Perioperative immunonutrition in hepatectomy: A systematic review and meta-analysis. Ann Hepatobiliary Pancreat Surg 2020; 24: 396-414. doi:10.14701/ahbps.2020.24.4.396			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis and systematic review 1++ AMSTAR II 12/16	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** no funding **Dropout rates:** n/a	**Total no. Studies:** 11 **Inclusion criteria:** RCT; patient undergoing hepatectomy (either open or laparoscopic approach; anatomical or non-anatomical	effects of immunonutrition on clinical outcomes of patients undergoing hepatectomy

	Study limitations: Overall confidence in the results of the review: Critically Low Risk of bias of single studies: moderate Inconsistency: moderate Indirectness: moderate Imprecisiseness: moderate Publication bias: low external validity limited to only adult patients who underwent elective liver resection or hepatectomy, small sample size, lack of high methodological quality clinical trials and presence of heterogeneity in outcome data	resection; for benign and malignant liver tumors); with reported outcomes comparing immunonutrition and control with or without standard nutritional supplementation **Exclusion criteria:** non-RCT, narrative or expert reviews, and animal studies or trials	
Notes	**Author's Conclusion:** In conclusion, wound infection rate was not significantly different between oral and parenteral IMN group. The length of hospital stay was significantly lower in parenteral IMN group than in oral IMN group. The mortality rates were not affected. Immunonutrition should be recommended routinely as part of the nutritional support in the Enhanced Recovery after Surgery (ERAS) protocol for hepatectomy.		
Outcome measures/results	primary outcomes: Wound infection (or surgical site infection), length of stay, bile leak, liver failure, ascites, ileus Secondary outcome: mortality		primary outcomes: - immunonutrition (IMN) significantly reduced post-operative wound infection (RR 0.65, 95% CI 0.43 to 0.96) - length of stay was significantly shorter in IMN group (MD −4.97 days, 95% CI −8.23 to −1.72) - bile leak and liver failure: no statistically significant difference (RR 0.64, 95% CI 0.38 to 1.06) and (RR 0.58, 95% CI 0.27 to 1.24) - ascites: significantly reduced in IMN group (RR 0.51, 95% CI 0.34 to 0.76) - Ileus: no statistically significant difference (RR 0.99, 95% CI 0.26 to 3.82) secondary outcome: - Mortality: no statistically significant difference (RR 0.74, 95% CI 0.25 to 2.17)

64.	**Yang FA, Chen YC, Tiong C. Immunonutrition in Patients with Pancreatic Cancer Undergoing Surgical Intervention: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Nutrients 2020; 12: 2798. doi:10.3390/nu12092798**

Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
Meta-Analysis and systematic review 1++ AMSTAR II 6/16	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** no external funding **Dropout rates:** n/a **Study limitations:** Overall confidence in the results of the review: Critically Low Risk of bias of single studies: moderate Inconsistency: low Indirectness: low Impreciseness: high Publication bias: n/a Administration of immunonutrition to patients at different times, amount of immunonutrition and duration of its administration were unclear, brand of the immunonutrition supplement was different	**Total no. Studies:** 6 **Inclusion criteria:** RCTs; enrolled patients with resectable pancreatic cancer who underwent the associated operation such as pancreaticoduodenectomy and irreversible electroporation; the trial compared preoperative, perioperative, or postoperative oral supplement of immunonutrition with standard diet, postoperative infectious and noninfectious complications, mortality, length of hospital stay, and immunity **Exclusion criteria:** included cancer other than pancreatic cancer; not compared with standard diet; and animal experiments	immunonutrition is administered to improve the outcome of patients with pancreatic cancer undergoing surgery
Notes	**Author's Conclusion:** We found that immunonutrition can significantly decrease the rate of postoperative infections, especially wound infection, and shorten the length of hospital stay. Furthermore, the effect of immunonutrition is significantly obvious in the subgroup analysis of preoperative group. We therefore recommend that patients with pancreatic cancer undergoing surgery take advantage of immunonutrition, especially in the preoperative period. Furthermore, well-designed randomized control trials are required to clarify the effect of immunonutrition.		
Outcome measures/results	postoperative total complications, postoperative infectious complications, wound infection, noninfectious complications, delayed gastric emptying, fistula development, postoperative mortality, length of hospital stay		- no significant difference in the amount of postoperative total complications (RR = 0.79; 95% CI = 0.56, 1.12; p = 0.18) - immunonutrition significantly decreased rate of infectious complications (RR = 0.47, 95% CI (0.23, 0.94), p = 0.03) - wound infections: significant difference (RR=0.44; 95% CI = 0.21, 0.91; p=0.03)

		- noninfectious complications: no significant difference (RR = 0.90; 95% CI = 0.66, 1.23; p = 0.52) - no significant difference in amount of postoperative delayed gastric emptying (RR = 1.17; 95% CI = 0.59, 2.31; p=0.65) - no significant difference in amount of postoperative fistula development (RR = 1.00; 95% CI = 0.56, 1.80; p = 1.00) - no significant difference in amount of postoperative mortality (RR=1.35; 95% CI = 0.27, 6.88; p=0.72) - significant difference in length of hospital stay (MD = −1.90, 95% CI (−3.78, −0.02), p = 0.05)

65. Li XK, Zhou H, Xu Y et al. Enteral immunonutrition versus enteral nutrition for patients undergoing oesophagectomy: a systematic review and meta-analysis. Interact Cardiovasc Thorac Surg 2020; 30: 854-862. doi:10.1093/icvts/ivaa022			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis and systematic review 1+ AMSTAR II 6/11	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** National Natural Science Foundation of China [81172032] and the Natural Science Foundation of Jiangsu Province [BK20181239] **Dropout rates:** n/a **Study limitations:** Overall confidence in the results of the review: Critically Low Risk of bias of single studies: moderate Inconsistency: high Indirectness: moderate Impreciseness: high Publication bias: n/a	**Total no. Studies:** 6 **Inclusion criteria:** RCTs, articles published in English **Exclusion criteria:** narrative or expert reviews, non-RCTs, studies with experimental data such as animal studies or trials, studies wherein the primary data were unable to be acquired and studies wherein essential information from the authors and articles was not published in English	enteral immunonutrition (EIN) or enteral nutrition (EN) for patients undergoing esophagectomy

	Exclusion of grey literature and non-English-language studies, no test for publication bias, partly incomplete data		
Notes	**Author's Conclusion:** The early-stage impact of EIN on immunological status in patients undergoing esophagectomy is still unclear. According to the results of this meta-analysis, whether EIN could improve the clinical outcomes or biological status after esophagectomy compared to standard EN is uncertain. Since the impact of EIN is unclear, current guidelines that strongly advise the use of EIN should be changed, as the utility of EIN is very uncertain. More appropriately powered clinical studies are warranted to confirm its effectiveness.		
Outcome measures/results	incidence of infectious complications and the length of hospital stay, blood indicators included CRP, IL-6, IL-8 and TNF-α		- infectious complications: no significant difference between the 2 groups (RR 0.77; 95% CI 0.37–1.62; P=0.50) - postoperative hospital stay: no significant difference between the EIN and EN groups (SMD = -0.07; 95% CI -0.36 to 0.22; P = 0.63) - IL6: no significant difference (SMD=-1.60; 95% CI -3.54 to 0.36; P=0.11) - CRP level was not significantly different between the 2 groups (SMD=-0.20; 95% CI -0.56 to 0.16; P=0.27) - IL8: no significant difference was found between the 2 groups (SMD = -0.11; 95% CI -1.66 to 1.44; P = 0.89) - TNF-α: no significant difference between the EIN and EN groups (SMD=-0.120; 95% CI -3.42 to 1.01; P = 0.29)

66. Zhang X, Chen X, Yang J et al. Effects of nutritional support on the clinical outcomes of well-nourished patients with cancer: a meta-analysis. Eur J Clin Nutr 2020; 74: 1389-1400. doi:10.1038/s41430-020-0595-6			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis 1+ AMSTAR II 10/16	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** Sichuan Science and Technology Department Youth Innovation Research Project (2018144) and National	**Total no. Studies:** 10 **Inclusion criteria:** participants were well-nourished patients, the information was available to identify the participants who met the criteria for malnutrition, RCT or non-RCT, the intervention group was administrated nutritional support before and/or after surgery	nutritional supplementation on well-nourished patients with cancer

	Natural Science Foundation of China (no. 71974135) **Dropout rates:** n/a **Study limitations:** Overall confidence in the results of the review: Critically Low Risk of bias of single studies: high Inconsistency: moderate Indirectness: moderate Impreciseness: high Publication bias: n/a Limited number of included studies, only short-term clinical outcomes, potentially publication bias	**Exclusion criteria:** observational studies, reviews, letters, case reports and news	
Notes	**Author's Conclusion:** Nutritional support, particularly immunonutritional supplementation, is likely to reduce infectious complications, morbidity and LOS without altering mortality and may be a safe and preferred choice for well-nourished patients undergoing surgery for cancer. Few studies have investigated the effects of nutritional supplementation on patients who are well nourished. Therefore, additional RCTs are warranted to determine the effects of nutritional support on well-nourished patients.		
Outcome measures/results	Mortality, morbidity, infectious complications, length of hospital stay		- Mortality rate: no significant differences (OR: 1.25, 95% CI: 0.33–4.70; I^2 = 0%, $P_{heterogeneity}$ = 0.82) - Morbidity: decreasing trend in the interventional group, but no statistical significance (OR: 0.85, 95% CI: 0.68–1.06; I^2 = 30%, $P_{heterogeneity}$ = 0.17) - Infectious complications: significantly lower in the intervention group (OR: 0.74, 95% CI: 0.57–0.96; I^2 = 35%, $P_{heterogeneity}$ = 0.14) - Length of hospital stay: not significantly different between the two groups (MD: −0.67, 95% CI: −1.89 to 0.51; I^2 = 66%, $P_{heterogeneity}$ = 0.01)

67.	Mingliang W, Zhangyan K, Fangfang F et al. Perioperative immunonutrition in esophageal cancer patients undergoing esophagectomy: the first meta-analysis of randomized clinical trials. Dis Esophagus 2020; 33. doi:10.1093/dote/doz111		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis 1++ AMSTAR II 7/16	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** National Natural Science Foundation Item, grant number 30871207, the National Natural Science Foundation Item, grant number 81874063, the National Natural Science Foundation Item, grant number 81672389, and the Anhui Province Science and Technology Key Project, grant number 1704a0802176 **Dropout rates:** n/a **Study limitations:** Overall confidence in the results of the review: Critically Low Risk of bias of single studies: low Inconsistency: low Indirectness: high Impreciseness: high Publication bias: n/a results of biochemical and immune indicators were diverse, less than 10 articles included, exclusion of gray	**Total no. Studies:** 7 **Inclusion criteria:** studies associated with perioperative EIN versus EN in EC patients undergoing esophagectomy; RCTs with a total sample size ≥ 30 patients; studies that provided primary data of postoperative infection complications and anastomotic leakage **Exclusion criteria:** studies in which EIN was used only before or after surgery, but not both; studies beyond the inclusion criteria or originally published in a language other than English	perioperative enteral immunonutrition vs. enteral nutrition in esophageal cancer patients undergoing esophagectomy

	literature and non-English language studies		
Notes	**Author's Conclusion:** In conclusion, this strict meta-analysis indicated that perioperative EIN provided no benefit in reducing the prevalence of infection complications and anastomotic leakage in EC patients undergoing esophagectomy. Further, large-scale RCTs should be conducted to confirm this conclusion.		
Outcome measures/results	infection complications, pneumonia, wound infection, sepsis, urinary tract infection, anastomotic leakage		- no significant difference between the two groups in overall infection complications (RR = 0.97, CI: 0.78–1.20, P = 0.76) or in occurrence of pneumonia (RR = 0.97, CI: 0.71–1.33, P = 0.84) - wound infection, was found in 214 patients in the EIN group and 201 patients in the EN group (RR = 0.80, CI: 0.46–1.40, P = 0.44), no statistical significance - sepsis: 262 patients in the EIN group and 244 patients in the EN group (RR = 1.35, CI: 0.67–2.71, P = 0.40), no statistical significance - urinary tract infection: 137 patients in the EIN group and 125 patients in the EN group (RR = 0.87, CI: 0.54–1.40, P = 0.56), no statistical significance - anastomotic leakage: no significant difference between the EN and EIN groups (RR = 0.59, CI: 0.33–1.04, P = 0.07)

68.	**Yu K, Zheng X, Wang G et al. Immunonutrition vs Standard Nutrition for Cancer Patients: A Systematic Review and Meta-Analysis (Part 1). JPEN J Parenter Enteral Nutr 2020; 44: 742-767. doi:10.1002/jpen.1736**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis and systematic review 1+ AMSTAR II 10/16	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** National Natural Science Foundation of China (no. 81571871 and 81770276), the Nn10 program and Distinguished Young Scholars Fund of Harbin Medical University Cancer Hospital, the Yuweihan Fund for Distinguished Young Scholars of Harbin Medical University, the Harbin Science and	**Total no. Studies:** 61 **Inclusion criteria:** adult cancer patients who underwent surgery; reported clinical outcomes comparing immunonutrition with standard nutrition supplementation, conventional nutrition supplementation, or physiological saline; included an experimental group that received at least 1 type of immunonutrition component; included a control group that did not receive any immunonutrition components; RCT	immunonutrition vs standard nutrition in cancer patients treated with surgery

	Technology Innovation Scholars Fund (2017RAXXJ087), and the Heilongjiang Province Postdoctoral Research Fund **Dropout rates:** n/a **Study limitations:** Overall confidence in the results of the review: Low Risk of bias of single studies: low Inconsistency: low Indirectness: low Impreciseness: moderate Publication bias: low different kinds and stages of surgical cancer and the long-time spans of the selected RCTs, differences in the timing and number of days of immunonutrition as well as the doses and active components of the immunonutrition formulas	**Exclusion criteria:** patients ≤ 18 years, reviews, retrospective studies, observational studies, case reports, animal studies, irrelevant studies, and duplicate studies	
Notes	**Author's Conclusion:** This systematic review and meta-analysis provides evidence that for surgical cancer patients, immunonutrition reduces postoperative infectious complications (moderate quality of evidence) and shortens the period of hospitalization (low quality) but does not reduce all-cause mortality (moderate quality). Patients who are malnourished before surgery and who receive arginine + nucleotides + ω-3 fatty acids (25–30 kcal/kg/d) via the gastrointestinal tract during the perioperative period (5–7 days) may show better clinical efficacy.		
Outcome measures/results	primary outcomes: postoperative infectious complications: wound infection, respiratory tract infection, urinary tract infection, sepsis, and anastomotic leakage Secondary outcomes: all-cause mortality and length of hospitalization		- significantly reduced risk of postoperative infectious complications (risk ratio [RR] 0.71 [95% CI, 0.64–0.79]) - significantly reduced risk of wound infection (RR 0.72 [95% CI, 0.60–0.87]), respiratory tract infection (RR 0.70 [95% CI, 0.59–0.84]), and urinary tract infection (RR 0.69 [95% CI, 0.51–0.94]), and anastomotic leakage (RR 0.70 [95% CI, 0.53– 0.91])

		- sepsis: no significant difference (n = 2322, fixed model: RR 0.75 [95% CI, 0.45–1.25], P = .27, I^2 = 0) - no significant between-group differences in all-cause mortality (fixed model: RR 1 [95% CI, 0.69–1.43], P = .99, I^2 = 0) - significantly reduced hospital stay (MD −2.12 days [95% CI −2.72 to −1.52])

69. Dushianthan A, Cusack R, Burgess VA et al. Immunonutrition for Adults With ARDS: Results From a Cochrane Systematic Review and Meta-Analysis. Respir Care 2020; 65: 99-110. doi:10.4187/respcare.06965			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis and systematic review 1++ AMSTAR II 16/16	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** Overall confidence in the results of the review: High Risk of bias of single studies: high Inconsistency: moderate Indirectness: low Impreciseness: moderate Publication bias: low Inclusion of studies with high risk of bias, significant dropouts, differences in patient populations	**Total no. Studies:** 10 **Inclusion criteria:** all studies involving mechanically ventilated adult participants with ARDS, intervention groups consisting of participants given enteral or parenteral immunonutrients, additionally supplemented with or as part of a nutritional formula **Exclusion criteria:** n/a	immunonutrition compared to standard non-immunonutrition formula feeding on mechanically ventilated adults with ARDS
Notes	**Author's Conclusion:** This Cochrane meta-analysis of 10 studies of varying quality examined the effects of omega-3 fatty acids and antioxidants in adults with ARDS. This intervention may produce little or no difference in all-cause mortality between groups. We are uncertain whether immunonutrition with omega-3 fatty acids and antioxidants improves ventilator days, ICU length of stay, or oxygenation due to the very low quality of evidence.		
Outcome measures/results	primary outcome: all-cause mortality secondary outcomes: 28-d mortality, ICU length of stay (LOS) and ICU-free days at day 28, ventilator days and ventilator-free days at		primary outcome: no difference in all-cause mortality (risk ratio = 0.79, 95% CI 0.59–1.07; low-quality evidence) Secondary outcomes

	day 28, hospital LOS, indices of oxygenation, other organ failure, nosocomial infection, adverse events	- uncertain evidence for use of omega-3 fatty acids and antioxidants in terms of mortality at 28 d (risk ratio = 0.64, 95% CI 0.49–0.84; I^2 = 0%) - uncertain evidence for use of omega-3 fatty acids and antioxidants for improvements in secondary outcomes of ICU LOS, duration of mechanical ventilation, ICU-free days at day 28 and ventilation-free days at day 28 - uncertain evidence for the use of omega-3 fatty acids and antioxidants in terms of improvements in Pa_{O2}/FI_{O2} ratio at day 4 and at day 7, reported new organ failures, nosocomial infections, and adverse events

70. Zhang B, Najarali Z, Ruo L et al. Effect of Perioperative Nutritional Supplementation on Postoperative Complications—Systematic Review and Meta-Analysis. J Gastrointest Surg 2019. 1-12			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis and systematic review 1++ AMSTAR II 10/16	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** Overall confidence in the results of the review: Critically Low Risk of bias of single studies: moderate Inconsistency: high Indirectness: low Impreciseness: low Publication bias: low No inclusion of studies specifically investigating effects of carbohydrate loading, diversity of interventions made it difficult to common on a specific guideline for the administration of	**Total no. Studies:** 56 **Inclusion criteria:** RCTs, involving participants ≥ 18 years who underwent any gastrointestinal surgery for any type of malignancy, studies that included patients with prior surgeries or distant metastases, **Exclusion criteria:** less than 30-day follow-up, included patients with chronic diseases	intervention involved the administration of a perioperative nutritional supplementation with immunonutrition, protein solution, or carbohydrate loading. Controls were defined as standard diet or control solutions with no nutritional value.

	perioperative nutritional supplements		
Notes	**Author's Conclusion:** In conclusion, this review confirmed that nutritional supplements reduce postoperative complications in patients undergoing surgery for gastrointestinal cancer. Further research may be justified to focus on defining the optimal duration of administration, route of administration, and type of nutrients in the formulations as well as to identify the specific subgroup of patients that will benefit from the treatment. The results of this systematic review should inform the design of future feasibility studies and RCTs that look at combining all three forms of nutritional supplements. These trials should use consistent definitions for postoperative complications and continue to inform the limited body of literature on length of hospital stay.		
Outcome measures/results	primary outcome: weighted proportion (incidence) of postoperative complications across all comparator groups secondary outcomes: postoperative infectious complications and length of hospital stay.		primary outcome: pooled RR of experiencing a postoperative complication was lower for patients in the perioperative nutritional supplementation group compared to control (RR 0.78; 95% CI, 0.72 to 0.85) secondary outcomes - decreased risk of experiencing postoperative infectious complications for patients in the perioperative nutritional supplementation group when compared to controls, pooled RR 0.71; 95% CI 0.64 to 0.79 - decreased risk of postoperative noninfectious complication among participants taking nutritional supplements compared to controls RR 0.79; 95% CI 0.71 to 0.87 - decrease in the pooled mean length of hospital stay among participants taking perioperative nutritional supple- mentation compared to control (pooled MD − 1.58 days; 95% CI − 1.83 to − 1.32)

71. Guan H, Chen S, Huang Q. Effects of Enteral Immunonutrition in Patients Undergoing Pancreaticoduodenectomy: A Meta-Analysis of Randomized Controlled Trials. Ann Nutr Metab 2019; 74: 53-61. doi:10.1159/000495468			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis and systematic review 1+ AMSTAR II 10/16	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** Overall confidence in the results of the review: Critically Low Risk of bias of single studies: moderate	**Total no. Studies:** 4 **Inclusion criteria:** studies designed as RCTs; patients who received PD, and intervention of trials was standard EN vs. EIN; published and available with full text in English; reported at least one of these clinical outcomes: overall postoperative complications, infectious complications, non-	enteral immunonutrition (EIN) vs. enteral nutrition (EN) in patients undergoing pancreaticoduodenectomy (PD)

	Inconsistency: low Indirectness: low Impreciseness: high Publication bias: n/a small number of included studies, language restriction to English, no study focused on total costs	infectious complications, mortality, length of hospital stay (LOS) **Exclusion criteria:** reports in which EIN and EN supplementation were not compared; no report of adequately postoperative complications, infectious and non-infectious complications, LOS, and mortality; case reports or reviews; no full text; studies on the same patient cohorts that were reported in more than 1 article	
Notes	**Author's Conclusion:** We found that EIN decreased the incidence of post- operative infectious complications and shortened the LOS. Immunonutrition should be encouraged in patients undergoing PD. However, adequately powered and well- designed RCTs are still needed to verify the results of this meta-analysis.		
Outcome measures/results	overall postoperative complications, postoperative infectious rate, postoperative noninfectious complications, LOS, postoperative mortality		- no significant difference in overall postoperative complications between EIN group and EN group (RR 0.81, 95% CI 0.62– 1.05; p = 0.11) - postoperative infectious complications rate was significantly lower in EIN group than in EN group (RR 0.58, 95% CI 0.37–0.92; p = 0.02) - no significant difference in postoperative noninfectious complications between EIN group and EN group (RR 0.94, 95% CI 0.69–1.28; p = 0.70) - significantly shorter LOS in the EIN group than that in the EN group (MD –1.79, 95% CI –3.40 to 0.18; p = 0.03) - no significant difference on postoperative mortality between EIN group and EN group (RR 2.43, 95% CI 0.37– 16.10; p = 0.36)

72.	**Cheng Y, Zhang J, Zhang L et al. Enteral immunonutrition versus enteral nutrition for gastric cancer patients undergoing a total gastrectomy: a systematic review and meta-analysis. BMC Gastroenterol 2018; 18: 11. doi:10.1186/s12876-018-0741-y**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis and systematic review 1+ AMSTAR II 6/16	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** National Natural Science Foundation (81473593 and 81473458)	**Total no. Studies:** 7 **Inclusion criteria:** RCT, English language **Exclusion criteria:** narrative or expert reviews, non-RCT, experimental data such as animal	enteral immunonutrition (EIN) vs. enteral nutrition (EN) in gastric cancer patients undergoing gastrectomy

	and the Jiangsu Qing Lan Project (JSQL-2014). Priority Academic Program Development of Jiangsu Higher Education Institutions (Integration of Chinese and Western Medicine) (PAPD) **Dropout rates:** n/a **Study limitations:** Overall confidence in the results of the review: Critically Low Risk of bias of single studies: moderate Inconsistency: moderate Indirectness: low Impreciseness: high Publication bias: n/a Exclusion of grey literature and non-English language studies, publish bias were not conducted because of the small number of included articles, partly incomplete data	studies or trials, unable to acquire primary data and essential information from authors, articles published not in English, GC patients combined with other cancers, patients with parenteral nutrition, patients have unresectable neoplasm, immune insufficiency, major organic disease, treatment with immunosuppressive drugs, corticosteroids or radiotherapy, severe preoperative infection	
Notes	**Author's Conclusion:** This synthesis analyses clearly show that EIN is better to EN in improving the immune function for patients with gastric cancer after surgery. Although the incidence of pulmonary infection, LHS and other clinical outcomes were not improved, EIN is clinically feasible and safe to be recommended as nutritional support in major gastric surgery.		
Outcome measures/results	incidence of pulmonary infection, incision infection, mortality, postoperative infectious complications, operating time, SIRS and the LHS, CD4+ and CD8+, IgG and IgM. serum protein e.g. proalbumin, lymphocytes		EIN, when beyond a 7-day time-frame post-operatively (D ≥ 7), increased level of - CD4+ (SMD = 0.99; 95% CI, 0.65–1.33; P < 0.00001), - CD4+/ CD8+ (SMD = 0.34; 95% CI, 0.02–0.67; P = 0.04), - IgM (SMD = 1.15; 95% CI, 0.11–2.20; P = 0.03), - IgG (SMD = 0.98; 95% CI, 0.55–1.42; P < 0.0001), - lymphocyte (SMD = 0.69; 95% CI, 0.32–1.06; P = 0.0003), - proalbumin (SMD = 0.73; 95% CI, 0.33–1.14; P = 0.0004).

		Those increased effects were not obvious within a 7-day time-frame post-operatively (D < 7). The levels of CD8+ and other serum proteins except proalbumin were not improved both on D ≥ 7 and D < 7. clinical outcomes - length of hospitalization (LHS): no significant difference between two groups (MD = - 1.42; 95% CI, - 4.50–1.66; P = 0.37) - operating time: no significant difference (SMD = - 0.43; 95% CI, - 1.65–0.78; P = 0.48) - systemic inflammatory response syndrome (SIRS): significantly reduced in EIN group (MD, - 0.89 days; 95% CI, - 1.40 to - 0.39; P = 0.005), - postoperative complications (RR, 0.29; 95% CI, 0.14–0.60; P = 0.001) were significantly reduced in EIN group - no significant differences between groups (RR = 1.02; 95% CI, 0.16–6.50; P = 0.98 for pulmonary infection; RR = 0.57; 95% CI, 0.28–1.14; P = 0.11 for postoperative complications; RR = 0.52; 95% CI, 0.18–1.53; P = 0.24 for incision infection; RR = 0.67; 95% CI, 0.12–3.89; P = 0.66 for mortality

73.	**Mocellin MC, Fernandes R, Chagas TR et al. A meta-analysis of n-3 polyunsaturated fatty acids effects on circulating acute-phase protein and cytokines in gastric cancer. Clin Nutr 2018; 37: 840-850. doi:10.1016/j.clnu.2017.05.008**
→ see No. 33	

74.	**Zhang C, Chen B, Jiao A et al. The benefit of immunonutrition in patients undergoing hepatectomy: a systematic review and meta-analysis. Oncotarget 2017; 8: 86843-86852. doi:10.18632/oncotarget.20045**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis and systematic review 1+ AMSTAR II 7/16	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** Natural Science Foundation of Liaoning Province (No. 201602874) **Dropout rates:** n/a **Study limitations:**	**Total no. Studies:** 8 **Inclusion criteria:** only patients who underwent hepatectomy; trials comparing outcomes in patients with and without preoperative, perioperative, or postoperative immunonutrition supplementation that included at least one from ω-3 FA, arginine, glutamine, and	patients who underwent hepatectomy with and without immunonutrition

	Overall confidence in the results of the review: Critically Low Risk of bias of single studies: moderate Inconsistency: low Indirectness: low Imprecisiseness: high Publication bias: n/a Sample sizes in several studies were relatively small, categories of diseases and administration routes differed, differences in the definition criteria of outcome variables	nucleotides, trials that assessed postoperative complications, length of hospital stay, and mortality, RCT **Exclusion criteria:** unoriginal studies, abstracts, letters, case reports, and conference papers, requisite information was lacking or original data could not be obtained from the authors, those not fulfilling the inclusion criteria	
Notes	**Author's Conclusion:** In conclusion, our meta-analysis reveals that perioperative administration of immunonutrition in patients undergoing hepatectomy may reduce the postoperative total complications, infectious complications, and length of hospital stay. This improvement in the postoperative clinical outcome is of more benefit when ω-3 FA-enriched supplementation is provided. The GRADEpro approach has been used to assess the quality of evidence of this meta-analysis. However, methodological differences do exist among some studies and the number of patients included in present meta-analysis is relatively small.		
Outcome measures/results	postoperative total complications, postoperative infectious complications, length of hospital stay, and postoperative mortality		- immunonutrition significantly reduced incidence of postoperative total complications (RR = 0.59; 95% CI, 0.46–0.75; $p < 0.0001$) - immunonutrition significantly reduced incidence of infectious complications (RR = 0.46; 95% CI, 0.32–0.68; $p < 0.0001$) - length of hospital stay was significantly shorter in the ω-3 FA-enriched group (SMD = −0.49; 95% CI, −0.81 to −0.16; $p = 0.004$) - mortality in the ω-3 FA-enriched group was lower than in the control group, but not significantly so (RR = 0.46; 95% CI, 0.16–1.31; $p = 0.15$)

75. Song GM, Liu XL, Bian W et al. Systematic review with network meta-analysis: comparative efficacy of different enteral immunonutrition formulas in patients underwent gastrectomy. Oncotarget 2017; 8: 23376-23388. doi:10.18632/oncotarget.15580			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Network Meta-Analysis and systematic review 1- AMSTAR II 8/16	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** Overall confidence in the results of the review: Critically Low Risk of bias of single studies: moderate Inconsistency: high Indirectness: low Impreciseness: high Publication bias: n/a no subgroup analysis based on nutrition status possible, possibility of publication bias, time of measuring outcomes were varying from one to another, studies with small sample size	**Total no. Studies:** 11 **Inclusion criteria:** all adults with histologically diagnosed GC who were scheduled for gastrectomy; all EIN formulas, regardless of administration time; other active EIN formulas or SEN; postoperative infectious complications (ICs), postoperative non-infectious complications (NICs) and LOS **Exclusion criteria:** patients with unresectable neoplasm, administration of corticosteroids or immunosuppressive agents, previous abdominal radiotherapy, active preoperative infection, underlying cardiovascular pathology, and renal or hepatic function impairment, duplication with poor methodology and insufficient data; nonoriginal research	comparing EIN (enteral immunonutrition) formulas with standard enteral nutrition (SEN) in GC patients underwent gastrectomy
Notes	**Author's Conclusion:** In summary, we identified several important conclusions with significant implications for clinical practice and further research by performing this systematic review and network meta-analysis. Firstly, EIN is an effective nutrition support regime of promoting recovery of GC patients underwent gastrectomy. Secondly, Arg+Gln+ω-3-FAs and Arg+RNA+ω-3-FAs are the optimal regimes of reducing ICs and LOS; it must be noted is that, however, the use of Arg+RNA in controlling ICs, NICs and LOS are not preferentially recommended compared to SEN. Moreover, most findings in our study generated from small numbers with small sample sizes, and most importantly, the administration time of nutrition support, time of measuring outcomes and nutrition status of patients are different among eligible studies, so these findings in our study should be cautiously interpreted.		
Outcome measures/results	reducing infectious complications (ICs), noninfectious complications (NICs) and length of hospital stay (LOS)		- EIN (RR 0.56, 95% CI 0.36-0.86; MD -0.42, 95% CI -0.74—0.10), Arg+RNA+ω-3-FAs (RR 0.37, 95% CI 0.22-0.63; MD -0.42, 95% CI -0.75—0.07), Arg+Gln+ω-3-FAs (RR 0.22, 95% CI 0.05-0.94; MD -0.69, 95% CI -1.22—1.07) reduced ICs and LOS.

		- network meta-analysis confirmed the potential of Arg+RNA+ω- 3-FAs for ICs (OR 0.27, 95% CrI 0.12–0.49) and Arg+Gln+ω-3-FAs for CIs (OR 0.22, 95% CrI 0.02–0.84) and LOS (SMD -0.63, 95% CrI -1.07—0.13), and indicated that Arg+RNA+ω-3-FAs was superior to Arg+RNA and Arg+Gln for ICs as well

76.	**Tan HB, Danilla S, Murray A et al. Immunonutrition as an adjuvant therapy for burns. Cochrane Database Syst Rev 2014. doi:10.1002/14651858.CD007174.pub2: CD007174. doi:10.1002/14651858.CD007174.pub2**
→ see No. 26	

77.	**Howes N, Lewis SJ, Thomas S. Immunonutrition for patients undergoing surgery for head and neck cancer. Cochrane Database Syst Rev 2014. doi:10.1002/14651858.Cd010954. doi:10.1002/14651858.Cd010954**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic review 1++	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** National Institute for Health Research via Cochrane Infrastructure, Cochrane Programme Grant or Cochrane Incentive funding to Cochrane ENT **Dropout rates:** n/a **Study limitations:** complications were poorly defined, follow-up timeframes differed considerably across studies, 7 studies came from one center with relatively small sample sizes	**Total no. Studies:** 19 **Inclusion criteria:** RCTs, including quasi-randomized trials, studies irrespective of language or publication status, all adult patients undergoing an elective surgical procedure for head and neck cancer under a general anesthetic **Exclusion criteria:** non-randomized studies,	review compared how people recover after surgery for head and neck cancer if they have been given either 'immunonutrition' or a standard feed before and after or only after the surgery immunonutrition versus standard care (intravenous fluids)and/ or polymeric nutritional supplements.
Notes	**Author's Conclusion:** The risk of postoperative fistula formation may be reduced with immunonutrition, but we found no evidence of an effect of immunonutrition on any of the other outcomes that we assessed. The studies included in this review were generally small or at high risk of bias (or both). We judged the overall quality of the evidence to be low for the outcomes length of hospital stay and all-cause mortality, and very low for wound infection and adverse events. Further research should include larger, better quality studies.		

Outcome measures/results	primary outcomes: length of hospital stay (days), wound infection, fistula formation and adverse events/tolerance of feeds secondary outcomes: all-cause mortality and postoperative complications	primary outcomes: - no evidence of a difference in length of hospital stay (mean difference -2.5 days, 95% CI -5.11 to 0.12) - no evidence of an effect of immunonutrition on wound infection (RR 0.94, 95% CI 0.70 to 1.26) - fistula formation may be reduced with immunonutrition; absolute risks were 11.3% and 5.4% in the standard care and immunonutrition groups, with a RR of 0.48 (95% CI 0.27 to 0.85) - no evidence of a difference in terms of tolerance of feeds ('adverse events') between treatments (RR 1.33, 95% CI 0.86 to 2.06) secondary outcomes: - no evidence of a difference between treatments in all-cause mortality (RR 1.33, 95% CI 0.48 to 3.66) - Other postoperative complications such as pneumonia and urinary tract infections were not commonly reported

78.	**Shen J, Dai S, Li Z, Dai W, Hong J, Huang J, et al. Effect of Enteral Immunonutrition in Patients Undergoing Surgery for Gastrointestinal Cancer: An Updated Systematic Review and Meta-Analysis. Front Nutr. 2022;9:941975.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic review and Meta-Analysis 1+ AMSTAR II 11/16	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** Overall confidence in the results of the review: Low Risk of bias of single studies: moderate Inconsistency: low Indirectness: low Impreciseness: low Publication bias: low	**Total no. Studies:** 35 **Inclusion criteria:** participants: patients with gastrointestinal cancer and underwent surgery; intervention: EIN; control: standard diet (an isocaloric and isonitrogenous enteral nutrition supplement) or no supplement (a normal diet without supplements); outcomes: at least one investigated postoperative outcomes, such as complications, mortality, and length of hospital stay; study design: randomized controlled trials (RCTs) **Exclusion criteria:** study intervention contained only one	This meta-analysis aimed to investigate the effectiveness of enteral immunonutrition (EIN) administration in patients undergoing surgery for gastrointestinal cancer.

	Study includes unavoidable heterogeneity, such as variations in operation, disease severity, duration of intervention, and definition of complications; some subgroup analyses used small sample sizes	component of EIN; articles were not published in English; the data was unavailable	
Notes	**Author's Conclusion:** According to this systematic review and meta-analysis, EIN is safe and beneficial for reducing overall complications, infectious complications, and length of hospital stay, but it has no efficacy for reducing non-infectious complications in patients undergoing surgery for gastrointestinal cancer (including gastric cancer, colorectal cancer, esophageal cancer, periampullary cancer, or pancreatic cancer). In terms of infectious complications, EIN primarily minimizes the incidence of surgical site infection, abdominal abscess, anastomotic leakage, bacteremia, SIRS duration, and antibiotic therapy duration. Therefore, perioperative EIN administration is recommended for malnourished patients undergoing surgery for gastrointestinal cancer, especially for patients with colorectal cancer. Overall, more well-designed and large-scale RCTs are required to clarify the unanswered questions and further evaluate the effect of EIN in patients undergoing gastrointestinal cancer surgery to provide reasonable theoretical guidelines for clinical practice.		
Outcome measures/results	Overall complications, infectious complications, incidence of surgical site infection, abdominal abscess, anastomotic leakage, bacteremia, duration of systemic inflammatory response syndrome (SIRS), duration of antibiotic therapy in the specific infectious complications, other infectious complications, length of hospital stay, non-infectious complications, mortality, enteral nutrition-related complications		- Compared with the control group, EIN group had a significantly decreased incidence of overall complications (RR = 0.79, $p < 0.001$). - Infectious complications in patients who received EIN were considerably lower than in the control group (RR = 0.66, $p < 0.001$). - Compared to the control group, the incidence of surgical site infection, abdominal abscess, anastomotic leakage, bacteremia, duration of systemic inflammatory response syndrome (SIRS), and duration of antibiotic therapy was significantly lower in the specific infectious complications treated with EIN. - no significant difference between the two groups with other infectious complications. - a substantial shortening in the length of hospital stay was shown in EIN group compared with the control group. - no significant effect of EIN was demonstrated in non-infectious complications and mortality. The enteral nutrition-related complications had no significant difference between two groups.

79.	**Lee SY, Lee J, Park HM, Kim CH, Kim HR. Impact of Preoperative Immunonutrition on the Outcomes of Colon Cancer Surgery: Results from a Randomized Controlled Trial. Ann Surg. Epub ahead of print.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**

RCT 1+ ROB 7/9	**Countries:** South Korea **Centers:** n/a **Setting:** n/a **Funding Sources:** Chonnam National University Hwasun Hospital, Institute for Biomedical Science (grant number HCRI19014) **Dropout rates:** n/a **Study limitations:** Risk of Bias: low Inconsistency: n/a Indirectness: low Impreciseness: moderate Publication bias: n/a Impact of immunonutrition on nutritionally high-risk patients might have been masked because of the small number of malnourished patients; no evaluation of patients' compliance to the use of nutritional supplements; study was conducted in a single institution in Korea may lead to problems with external validity	**Total no. Patients:** 177 **Inclusion criteria:** primary colon cancer, aged 20–80 years, who provided written informed consent to participate **Exclusion criteria:** emergency surgery, difficulty in oral intake, pregnancy, and scheduled ostomy surgery	Patients with primary colon cancer were enrolled and randomly assigned (1:1) to receive preoperative immunonutrition plus a normal diet (n = 88) or a normal diet alone (n = 88). Patients in the immunonutrition group received oral nutritional supplementation (400 mL/day) with arginine and ω-3 fatty acids for 7 days before elective surgery.
Notes	**Author's Conclusion:** In patients undergoing colon cancer surgery, preoperative immunonutrition was not associated with the occurrence of infectious complications. Routine administration of preoperative immunonutrition cannot be justified in colon cancer surgery. Further studies are needed to investigate the association between preoperative immunonutrition and infectious complications in patients at a high risk of malnutrition.		
Outcome measures/results	primary outcome: rate of infectious complications secondary outcome: postoperative complication rate, change in body weight, and length of hospital stay	- rates of infectious (17.7% vs. 15.9%, P = 0.751) and total (31.6% vs. 29.3%, P= 0.743) complications were not different between the two groups. - Old age was the only significant predictive factor for the occurrence of infectious complications (odds ratio = 2.990, 95% confidence interval 1.179–7.586, P = 0.021).	

		- length of hospital stay (7.6 ± 2.5 vs. 7.4 ± 2.3 days, P = 0.635) and overall change in body weight (P = 0.379) were similar between the two groups. - only the immunonutrition group showed weight recovery after discharge (+0.4 ± 2.1 vs. -0.7 ± 2.3 kg, P = 0.002).

5. Präoperative Ernährung

5.1 Welche Patienten profitieren von einer präoperativen Ernährungstherapie?

<u>Empfehlung 13</u>

Patienten mit hohem metabolischem Risiko sollen eine Ernährungstherapie präoperativ erhalten (A) sogar, wenn dadurch die Operation verschoben wird (BM).

Ein Zeitraum von 10-14 Tagen kann empfohlen werden (0)

Empfehlungsgrad A/0 - Konsens 92 % Zustimmung

<u>Empfehlung 14</u>

Die orale/enterale Zufuhr soll gegenüber der parenteralen Ernährung bevorzugt werden. (A) (BM, HE, QL).

Empfehlungsgrad A – Starker Konsens 100 % Zustimmung

1. Burden S, Todd C, Hill J, Lal S Pre-operative nutrition support in patients undergoing gastrointestinal surgery. Cochrane Database Syst Rev 2012; 11:CD008879.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Review 1++	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** Post Doctoral Fellowship Grant from Macmillan Cancer Support **Dropout rates:** n/a **Study limitations:** - varying quality among included studies - Blinding was only undertaken in two of the included trials - Incomplete outcome data among included studies - exclusion of patients who had received pre-operative	**Total no. Patients:** 13 RCTs **Inclusion criteria:** randomized controlled trials; All non-emergency GI surgical patients; Nutrition support intervention by any route using any nutritional formulation containing both macro and micronutrients; the nutritional formulation had a carbohydrate, fat and nitrogen source with vitamins and minerals administered over any time (up to 3months prior to surgery to 24 hours pre-operatively); manipulated dietary intake to increase calories and protein **Exclusion criteria:** studies evaluating a single nutrient or IE	We performed this review to evaluate if nutritional support intervention by any route prior to surgery improves clinical outcomes for elective GI surgical patients and to determine if nutritional support interventions provide any benefit to nutritional intake or nutritional status prior to elective GI surgery.

	chemotherapy, radiotherapy or immunosuppressive treatment in some trials (external bias and thus affect the generalizability of the results) -differing nutritional status of patients among included studies (malnourished vs. well-nourished patients)	agent or any combination of nutritional components that	
Notes	**Author's Conclusion:** There have been significant benefits demonstrated with pre-operative administration of IE nutrition in some high-quality trials. However, bias was identified which may limit the generalizability of these results to all GI surgical candidates and the data needs to be placed in context with other recent innovations in surgical management (e.g.-ERAS). Some unwanted effects have also been reported with components of IE nutrition in critical care patients and it is unknown whether there would be detrimental effects by administering IE nutrition to patients who could require critical care support after their surgery. The studies evaluating PN demonstrated that the provision of PN to predominantly malnourished surgical candidates reduced post-operative complications; however, these data may not be applicable to current clinical practice, not least because they have involved a high degree of 'hyperalimentation'. Trials evaluating enteral or oral nutrition were inconclusive and further studies are required to select GI surgical patients for these nutritional interventions.		
Outcome measures/results	**Primary outcome measure:** Complications (Infective - including pneumonia, wound infections, abdominal abscess. Non-infective - including anastomotic leak, wound dehiscence, organ failure or thromboembolism); Length of hospital stay **Secondary outcome measures:** Nutritional aspects including weight, anthropometric measurements, hand grip strength and subjective global assessment; Quality of life (including patient reported outcomes): Within group and between group changes in macro nutrient (calories and protein/nitrogen) intake; Biochemical parameters including albumin, prealbumin and C-reactive protein; 30-day perioperative mortality; Adverse effects from feed and route of feeding All outcomes will be included up to 3 months post-operatively	The searches identified 9900 titles and, after excluding duplicates, 6433 titles were initially screened. After the initial title screen, 6266 were excluded. Abstracts were screened for 167 studies and 33 articles were identified as meeting the inclusion criteria, of which 13 were included in the review after an assessment of the complete manuscripts. Seven trials evaluating IE nutrition were included in the review, of which 6 were combined in a meta-analysis. These studies showed a low to moderate level of heterogeneity and significantly reduced total post-operative complications (risk ratio (RR) 0.67 CI 0.53 to 0.84). Three trials evaluating PN were included in a meta-analysis and a significant reduction in post-operative complications was demonstrated (RR 0.64 95% CI 0.46 to 0.87) with low heterogeneity, in predominantly malnourished participants. Two trials evaluating enteral nutrition (RR 0.79, 95% CI 0.56 to 1.10) and 3 trials evaluating standard oral supplements (RR 1.01 95% CI 0.56 to 1.10) were included, neither of which showed any difference in the primary outcomes.

2. Veteran Affairs Perioperative total parenteral nutrition in surgical patients. The Veterans Affairs Total Parenteral Nutrition Cooperative Study Group. N Engl J Med 1991; 325:525-532.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n=64 (13.9%) **Study limitations:** n/a	**Total no. Patients:** n=459 • Intervention group n=192 • Control group n=203 **Inclusion criteria:** patients older than 21 years admitted to a participating VA Medical Center before nonemergency laparotomy or thoracotomy (Laparotomy: any nonvascular intraperitoneal operation, excluding inguinal or ventral herniorrhaphy; thoracotomy: any non-cardiac intrathoracic operation, excluding mediastinoscopy or mediastinotomy), **Exclusion criteria:** expected death of their primary disease within 90 days, TPN in the preceding 15 days, TPN is contraindicated or essential, operation in the preceding 30 days, major current illness (cardiac, neurologic, hepatic, renal, coagulopathy, psychiatric), TPN	Intervention group - TPN administration for 7 to 15 days preoperative and 3 days postoperative (daily caloric goal of 100kcal above the resting metabolic expenditure) Control group - no TPN (or forced enteral feedings) before surgery or for the first 72 hours after surgery. Thereafter, TPN or tube feedings could be instituted if clinically indicated
Notes	*Patients (not excluded) underwent nutritional screening and were considered malnourished if they met either or both criteria: 1)score of 100 or less on the Nutrition Risk Index; 2)any two of the following: current weight was 95% of the ideal weight or less, serum albumin level of 39.2 g per liter or less, serum prealbumin level of 186mg per liter or less.* Patients who were too well nourished to meet either criterion were not offered study participation but were assigned to the well-nourished nonrandomized group and followed to monitor postoperative complications. Patients were stratified according to the severity of the patient's underlying malnutrition **Author's Conclusion:**		

	The use of preoperative TPN should be limited to patients who are severely malnourished unless there are other specific indications.	
Outcome measures/results	**Primary outcome measure:** complications within 90 days after surgery **Secondary outcome measures:** mortality, all complications (major or minor), infectious complications, noninfectious complications, major complications	The rates of major complications during the first 30 days after surgery in the two groups were similar (TPN group, 25.5 percent; control group, 24.6 percent), as were the overall 90-day mortality rates (13.4 percent and 10.5 percent, respectively). There were more infectious complications in the TPN group than in the controls (14.1 vs. 6.4 percent; P = 0.01; relative risk, 2.20; 95 percent confidence interval, 1.19 to 4.05), but slightly more noninfectious complications in the control group (16.7 vs. 22.2 percent; P = 0.20; relative risk, 0.75; 95 percent confidence interval, 0.50 to 1.13). The increased rate of infections was confined to patients categorized as either borderline or mildly malnourished, according to Subjective Global Assessment or an objective nutritional assessment, and these patients had no demonstrable benefit from TPN. In contrast, severely malnourished patients who received TPN had fewer noninfectious complications than controls (5 vs. 43 percent; P = 0.03; relative risk, 0.12; 95 percent confidence interval, 0.02 to 0.91), with no concomitant increase in infectious complications.

3. Bozzetti F, Gavazzi C, Miceli R, Rossi N, Mariani L, Cozzaglio L, Bonfanti G, Piacenza S Perioperative total parenteral nutrition in malnourished, gastrointestinal cancer patients: a randomized, clinical trial. JPEN J Parenter Enteral Nutr 2000; 24:7-14.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries:** n/a **Centers:** Surgical Oncology A of the Istituto Nazionale per Lo Studio e la Cura dei Tumori of Milan **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n=17 (15,9%) **Study limitations:** n/a	**Total no. Patients:** n=107 • Intervention group n=43 • Control group n=47 **Inclusion criteria:** patients with newly detected histologically proven gastric or colorectal carcinoma requiring surgical treatment in addition to weight loss of 10% or more in the previous 6 previous months **Exclusion criteria:** age of >80 years, patients requiring urgent surgery because of bleeding, obstruction or serve	Intervention group -TPN for 10 days preoperatively and 9 days postoperatively (1.5-fold of the resting energy expenditure, 34.6 ± 6.3kcal nonprotein per kilogram body weight, 0.25 ± 0.04 g of nitrogen per kilogram body weight) Control group - no preoperative nutrition support and subsequently administration of IV fluids administered according to standard prescription (940 kcal nonprotein, 85 g amino acid)

		organ failure(jaundice, cardiac or respiratory failure etc.), contraindicating preoperative TPN as planned by protocol	
Notes	*Patients were stratified* for age (<65years,>65years)and tumor localization (gastric, colorectal) **Author's Conclusion:** This study shows that 10 days of preoperative TPN that is continued postoperatively is able to reduce the complication rate by approximately one third and to prevent mortality in severely malnourished patients with gastrointestinal cancer.		
Outcome measures/results	**Primary outcome measure:** occurrence of postoperative complications **Secondary outcome measures:** postoperative mortality, length of hospitalization		Complications occurred in 37% of the patients receiving TPN vs 57% of the control patients (p=.03). Noninfectious complications mainly accounted for this difference, which was 12% vs 34%, respectively (p=.02). Mortality occurred in only 5 of the control group patients (p=.05). The total length of hospitalization for TPN patients was longer than for control (p=.00), whereas the length of postoperative stay in the two groups did not differ significantly.

4. Von Meyenfeldt MF, Meijerink WJ, Rouflart MM, Builmaassen MT, Soeters PB Perioperative nutritional support: a randomised clinical trial. Clin Nutr 1992; 11:180-186.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** n/a	**Total no. Patients:** n=200 • TPN n=51 • TEN n=50 • Depleted control group n=50 • Non-depleted reference group n=49 **Inclusion criteria:** newly detected, histologically proven gastric or colorectal carcinoma requiring surgical treatment, no treatment for other malignant tumors **Exclusion criteria:** age >80years, normal nutritional status	pre-operative parenteral nutrition (TPN) - preoperative parenteral nutrition for at least 10 days (150% of the calculated basal energy expenditure (BEE)), postoperative TPN until orally resumption of 120% BEE pre-operative enteral nutrition (TEN) - preoperative enteral nutrition for at least 10 days (either by nasogastric tube or by mouth; 150% of the calculated basal energy expenditure depleted control group (D) -no nutritional support, surgery without delay non-depleted reference group (ND)

Notes	Missing description of nutritional regime of depleted control group and non-depleted reference group (ND) Patients were stratified for percent weight loss (PWL) (<,> 15%), age (<,> 65 years) and tumor localization (gastric/colorectal). depletion was defined in this study by means of a 'nutritional index' (serum albumin, total lymphocyte count, percent ideal weight) Non-depleted patients with a nutritional index >1.31 and served as reference group and were monitored according trial guidelines. **Author's Conclusion:** We conclude that pre-operative nutritional support, in patients with severe depletion, results in a reduction in major complications to a degree that justifies its routine use in this selected group of patients.	
Outcome measures/results	Occurrence of complications, mortality	Depleted control patients suffered significantly more septic complications than did patients in the non-depleted reference group ($p<0.05$). There was no significant difference, however, in septic complications between either of the nutritional support groups and the non-depleted control group. In high risk patients, with weight loss >10% of body weight and over 500ml blood loss during operation, a significant decrease in major complications was observed ($p<0.05$) as a result of nutritional support.

5. Hennessey DB, Burke JP, Ni-Dhonochu T, Shields C, Winter DC, Mealy K (2010) Preoperative hypoalbuminemia is an independent risk factor for the development of surgical site infection following gastrointestinal surgery: a multi-institutional study. Ann Surg 2010; 252:325-329.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
retrospective trial	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** n/a	**Total no. Patients:** n=524 • Patients with SSI n=105 • Patients without SSI n=419 **Inclusion criteria:** patients who underwent operations on the gastrointestinal tract including gastroduodenal, gallbladder, small intestine, and colon and rectum **Exclusion criteria:** Patients who underwent esophageal surgery and appendectomies	We performed a retrospective trial of patients who underwent gastrointestinal surgery to determine the relationship between preoperative albumin and the development of (Surgical site infection) SSI .Therefore data were recorded prospectively on each patient in the database, which was completed immediately postoperatively by the operating surgeon (age, gender, operation class (elective or emergency), and operation type (gastric, hepatobiliary, small bowel or colonic), anesthesia, ASA grade, wound classification (clean, clean/contaminated, contaminated, dirty). diagnosis and classification of SSI, duration of procedure use of prophylactic antibiotics, preoperative serum albumin levels). Diagnosis of SSI in each case was by the surgeon or attending doctor. Infection was determined according to Centre for Disease Control and Prevention definitions of wound infection and was confirmed with positive wound cultures.
Notes	**Author's Conclusion:**		

	Hypoalbuminemia is an independent risk factor for the development of SSI following gastrointestinal surgery and is associated with deeper SSI and prolonged inpatient stay.	
Outcome measures/results	to determine the relationship between preoperative serum albumin and SSI (Surgical site infection)	A total of 105 patients developed an SSI (20%). The median time to the development of SSI was 7 (5–10) days. Having an emergency procedure (P = 0.003), having a procedure over 3 hours in duration (P = 0.047), being American Society of Anesthetics grade 3 (P = 0.03) and not receiving preoperative antibiotics (P = 0.007) were associated with SSI while having a laparoscopic procedure reduced the likelihood of SSI (P = 0.004). Patients who developed an SSI had a lower preoperative serum albumin (30 [25–34.5] vs. 36 [32–39], P < 0.001). On multivariate analysis, hypoalbuminemia was an independent risk factor for SSI development (relative risk, RR = 5.68, 95% confidence interval: 3.45–9.35, P < 0.001). Albumin <30 mg/dL was associated with an increased rate of deep versus superficial SSI (P = 0.002). The duration of inpatient stay was negatively correlated with preoperative albumin (R2 = -0.319, P < 0.001).

6. Wada N, Kurokawa Y, Tanaka K et al. Perioperative Nutritional Support With Beta-hydroxy-beta-methylbutyrate, Arginine, and Glutamine in Surgery for Abdominal Malignancies. Wounds : a compendium of clinical research and practice 2018; 30: 251-256			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1- ROB 4/7	**Countries:** Japan **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** 2% **Study limitations:** Risk of Bias: moderate Inconsistency: n/a Indirectness: low Impreciseness: high Publication bias: n/a small sample size, small amount of HMB/Arg/Gln administered	**Total no. Patients:** 61 **Inclusion criteria:** ≥ 20 years of age, adequate organ function, and planned open surgery for abdominal malignancies **Exclusion criteria:** patients needing emergency surgery, history of laparotomy with repeated incision, continuous corticosteroid use, uncontrolled or insulin-treated diabetes, or active infection	HMB/Arg/Gln group: compound consisting of 1.2 g of HMB, 7 g of L-Arg, and 7 g of L-Gln was administered after being dissolved in 250 mL of tap water. Patients in the placebo group received an equivalent amount of isocaloric juice with a similar taste as the HMB/Arg/Gln compound. In addition to a regular hospital diet, the 250-mL supplements were provided once daily for 3 days preoperatively and once daily for 7 days postoperatively
Notes	**Author's Conclusion:** The study results show the incidence of wound complications would not be reduced by perioperative nutritional support with a compound consisting of HMB/Arg/Gln in patients who underwent open surgery for abdominal malignancies. The efficacy of HMB/Arg/Gln for increasing serum GH levels needs to be validated in another large-scale RCT.		

Outcome measures/results	primary outcome: incidence of wound complications secondary outcomes: incidence of postoperative complications; duration of hospital stay after surgery; total-body skeletal muscle mass (TSM); handgrip strength; skin water content, serum growth hormone levels	- incidences of wound complications (20%) were the same in the 2 groups (2-sided P = 1.000; 1-sided P = .500) - incidences of other complications: similar between 2 groups: 4 patients (13%) in HMB/Arg/Gln group and 6 patients (20%) in placebo group - no significant differences in body composition, handgrip strength, or skin water content between the 2 groups - serum growth hormone (GH) levels were significantly higher for patients whose total intake was > 80% of planned volume in the HMB/Arg/Gln group

5.2 Wann besteht die Indikation zur präoperativen Einnahme einer Trinknahrung oder enteralen Ernährung?

<u>Empfehlung 15</u>

Bei Patienten mit Mangelernährung und/oder hohem metabolischen Risiko soll vor großen abdominellen Eingriffen eine Trinknahrung (oral nutritional supplements) verabreicht werden. (BM, HE)

Empfehlungsgrad A – Starker Konsens 100 % Zustimmung

7. Elia M, Normand C, Norman K, Laviano A , Norman K A systematic review of the cost and cost effectiveness of using standard oral nutritional supplements in the hospital setting. Clin Nutr 2016; 35: 370-380.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-analysis 1+	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** n/a	**Total no. Patients:** 9 publications **Inclusion criteria:** interventional and observational studies aiming to assess the effects of ONS interventions on economic outcomes; papers or abstracts reported in English; Studies of adults and children (>1 year of age) of any nutritional status (malnourished and well nourished) treated as hospital inpatients in any country; Studies of ONS alone or with other types of intervention, such as dietary advice (dietary counselling) or enteral tube feeding; only standard ONS were included which were defined as a commercially available, ready to consume, multi-nutrient (complete or incomplete), liquid or semi-solid product providing a mixture of macronutrients and micronutrients and produced by specialist medical nutrition manufacturers; Studies of interventions with ONS, with or without other interventions, were	We performed this meta-analysis to examine the cost and cost effectiveness of using standard (non-disease specific) oral nutritional supplements (ONS) administered in the hospital setting only.

		compared with no ONS (or routine care, which may include ONS in a proportion of patients); Studies comparing ONS with another type of nutritional intervention, such as dietary advice **Exclusion criteria:** Animal studies; studies in pregnant and lactating women; Studies of disease-specific formulas adapted to the needs of specific diseases and/or digestive or metabolic disorders; immune modulating formulas; Studies that included exercise as an intervention, ONS in combination with drug therapy such as anabolic steroids, and studies of one type of ONS v. another	
Notes	-small number of included publications (n=9): four full text papers, two abstracts and three reports, one of which contained 11 cost analyses of controlled cohort studies - the overall quality of the studies with respect to the combined clinical and economic outcomes, were judged to have at least a moderate risk of bias, with substantial variation between studies **Author's Conclusion:** This review suggests that standard ONS in the hospital setting produce a cost saving and are cost effective. The evidence base could be further strengthened by prospective studies in which the primary outcome measures are economic.		
Outcome measures/results	**Primary outcome measure:** cost or cost effectiveness, (no restrictions on the type of effectiveness outcomes) **Secondary outcome measures:** any functional and/or clinically relevant effect pertinent to cost-effectiveness analysis		Nine publications comprising four full text papers, two abstracts and three reports, one of which contained 11 cost analyses of controlled cohort studies, were identified. Most of these were based on retrospective analyses of randomized controlled trials designed to assess clinically relevant outcomes. The sample sizes of patients with surgical, orthopedic and medical problems and combinations of these varied from 40 to 1.16 million. Of 14 cost analyses comparing ONS with no ONS (or routine care), 12 favored the ONS group, and among those with quantitative data (12 studies) the mean cost saving was 12.2%. In a meta-analysis of five abdominal surgical studies in the UK, the mean net cost saving was £746 per patient (se £338; P = 0.027). Cost savings were typically associated with significantly improved outcomes, demonstrated through the following meta-analyses: reduced mortality

		(Risk ratio 0.650, P < 0.05; N = 5 studies), reduced complications (by 35% of the total; P < 0.001, N = 7 studies) and reduced length of hospital stay (by ∼2 days, P < 0.05; N = 5 surgical studies) corresponding to ∼13.0% reduction in hospital stay. Two studies also found ONS to be cost effective, one by avoiding development of pressure ulcers and releasing hospital beds, and the other by gaining quality adjusted life years.

8. Burden S, Todd C, Hill J, Lal S Pre-operative nutrition support in patients undergoing gastrointestinal surgery. Cochrane Database Syst Rev 2012; 11:CD008879.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Review 1++	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** Post Doctoral Fellowship Grant from Macmillan Cancer Support **Dropout rates:** n/a **Study limitations:** - varying quality among included studies - Blinding was only undertaken in two of the included trials - Incomplete outcome data among included studies - exclusion of patients who had received pre-operative chemotherapy, radiotherapy or immunosuppressive treatment in some trials (external bias and thus affect the generalizability	**Total no. Patients:** 13 RCTs **Inclusion criteria:** randomized controlled trials; All non-emergency GI surgical patients; Nutrition support intervention by any route using any nutritional formulation containing both macro and micronutrients; the nutritional formulation had a carbohydrate, fat and nitrogen source with vitamins and minerals administered over any time (up to 3months prior to surgery to 24 hours pre-operatively); manipulated dietary intake to increase calories and protein **Exclusion criteria:** studies evaluating a single nutrient or IE agent or any combination of nutritional components that	We performed this review to evaluate if nutritional support intervention by any route prior to surgery improves clinical outcomes for elective GI surgical patients and to determine if nutritional support interventions provide any benefit to nutritional intake or nutritional status prior to elective GI surgery.

	of the results) -differing nutritional status of patients among included studies (malnourished vs. well-nourished patients)		
Notes	**Author's Conclusion:** There have been significant benefits demonstrated with pre-operative administration of IE nutrition in some high-quality trials. However, bias was identified which may limit the generalizability of these results to all GI surgical candidates and the data needs to be placed in context with other recent innovations in surgical management (e.g.-ERAS). Some unwanted effects have also been reported with components of IE nutrition in critical care patients and it is unknown whether there would be detrimental effects by administering IE nutrition to patients who could require critical care support after their surgery. The studies evaluating PN demonstrated that the provision of PN to predominantly malnourished surgical candidates reduced post-operative complications; however, these data may not be applicable to current clinical practice, not least because they have involved a high degree of 'hyperalimentation'. Trials evaluating enteral or oral nutrition were inconclusive and further studies are required to select GI surgical patients for these nutritional interventions.		
Outcome measures/results	**Primary outcome measure:** Complications (Infective - including pneumonia, wound infections, abdominal abscess. Non-infective - including anastomotic leak, wound dehiscence, organ failure or thromboembolism); Length of hospital stay **Secondary outcome measures:** Nutritional aspects including weight, anthropometric measurements, hand grip strength and subjective global assessment; Quality of life (including patient reported outcomes): Within group and between group changes in macro nutrient (calories and protein/nitrogen) intake; Biochemical parameters including albumin, prealbumin and C-reactive protein; 30-day perioperative mortality; Adverse effects from feed and route of feeding All outcomes will be included up to 3 months post-operatively	The searches identified 9900 titles and, after excluding duplicates, 6433 titles were initially screened. After the initial title screen, 6266 were excluded. Abstracts were screened for 167 studies and 33 articles were identified as meeting the inclusion criteria, of which 13 were included in the review after an assessment of the complete manuscripts. Seven trials evaluating IE nutrition were included in the review, of which 6 were combined in a meta-analysis. These studies showed a low to moderate level of heterogeneity and significantly reduced total post-operative complications (risk ratio (RR) 0.67 CI 0.53 to 0.84). Three trials evaluating PN were included in a meta-analysis and a significant reduction in post-operative complications was demonstrated (RR 0.64 95% CI 0.46 to 0.87) with low heterogeneity, in predominantly malnourished participants. Two trials evaluating enteral nutrition (RR 0.79, 95% CI 0.56 to 1.10) and 3 trials evaluating standard oral supplements (RR 1.01 95% CI 0.56 to 1.10) were included, neither of which showed any difference in the primary outcomes.

9. MacFie J, Woodcock NP, Palmer MD, Walker A, Townsend S, Mitchell CJ (2000) Oral dietary supplements in pre- and postoperative surgical patients: a prospective and randomized clinical trial. Nutrition 2000; 16:723-728.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**

Prospective, randomized, controlled trial 1+	**Countries:** n/a **Centers:** Gastroenterology Unit at Scarborough Hospital **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n=12 (10, 7%) **Study limitations:** n/a	**Total no. Patients:** n=112 • Group 1 n=24 • Group 2 n=24 • Group 3 n=27 • Group 4 n=2 **Inclusion criteria:** patients requiring elective major gastrointestinal surgery **Exclusion criteria:** dementia, major concurrent metabolic problems, such as uncontrolled diabetes, advanced liver disease, uremia	Group I (pre-& post-op supplements) -oral dietary supplements (ODS) in addition to normal diet both pre- and for a minimum of 7days postoperatively Group II (pre-op supplements) - ODS in addition to normal diet preoperatively Group III (post-op supplements - ODS in addition to normal dies postoperatively (minimum of 7days) Group IV (no supplements) - no supplements Composition ODS (Intake of a minimum of two cartons a 200mL daily) -variety of flavors: 1.5 kcal, 0.05 g protein, d 0.18 g carbohydrate per mL. -fruit-flavored supplement (alternative) :1.25 kcal, 0.025 g protein, and 0.285 g carbohydrate per mL
Notes	No blinding **Author's Conclusion:** These results suggest that the routine use of perioperative ODS in well-nourished patients undergoing major gastrointestinal surgery confers no clinical or functional benefit.		
Outcome measures/results	nutritional status, voluntary food intake, weight loss, serum albumin, morbidity and mortality, anxiety and depression, postoperative activity levels		The mean daily energy intake from preoperative ODS was 507 ± 140 kcal, significantly more than the 252 ± 195 kcal in the postoperative period ($P < 0.001$). The postoperative voluntary food intake in patients receiving ODS was not significantly different from that in patients receiving normal diet alone (1090 versus 1268 kcal, 46.2 versus 49.1 g protein, $P > 0.05$). All groups demonstrated an overall weight loss, with no significant differences between the groups, and there was no demonstrable effect on clinical outcome. At 6 mo. postoperatively there were no differences between the study groups in terms of levels of activity.

10. Smedley F, Bowling T, James M, Stokes E, Goodger C, O'Connor O, Oldale C, Jones P, Silk D Randomized clinical trial of the effects of preoperative and postoperative oral nutritional supplements on clinical course and cost of care. Br J Surg 2004; 91:983-990.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries:** n/a **Centers:** The North West London Hospitals National Health Service (NHS) Trust	**Total no. Patients:** n= 179 • SS n= 32 • SC n= 41 • CS n= 35	Supplement contained 1.5 kcal and 0.05 g protein per ml and was administered as oral nutritional supplementation (Intake ad libitum, volume consumed was recorded) SS

	(Central Middlesex Hospital), London; University Hospital of North Staffordshire NHS Trust, Stoke-on-Trent; Chelsea and Westminster Hospitals NHS Trust, London **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n=27 (15,1%) **Study limitations:**	• CC n= 44 **Inclusion criteria:** patients undergoing elective moderate to major lower gastrointestinal surgery **Exclusion criteria:** age under 18 years, pregnancy, overt dementia, emergency or laparoscopic surgery, receipt of other forms of preoperative nutritional support, inability to take ONS for a minimum of 7 days before operation	- pre- and postoperative supplements SC - preoperative supplements; no postoperative supplements CS - postoperative supplements; no preoperative supplements CC -no supplements pre- and postoperatively
Notes	Two-phase trial: -Phase I: started before operation, when operating electively was decided in the outpatient setting, and ended 24 h before surgery. -Phase II started on the first day the patient was able to take free fluids or a light diet after operation, and ended 4 weeks after discharge from hospital. They were stratified according to nutritional status before randomization using a combination of body mass index, history of weight loss and age, according to previously validated criteria, to ensure even distribution of poorly nourished individuals. **Author's Conclusion:** Perioperative oral nutritional supplementation started before hospital admission for lower gastrointestinal tract surgery significantly diminished the degree of weight loss and incidence of minor complications, and was cost-effective.		
Outcome measures/results	**Primary outcome measure:** Postoperative change in bodyweight. **Secondary outcome measures:** clinical complications, length of hospital stay, nutritional status, quality of life, cost of care		Some 179 patients were randomized, of whom 27 were withdrawn and 152 analyzed (CC 44, SS 32, CS 35, SC 41). Dietary intake was similar in all four groups throughout the study. Mean energy intake from preoperative supplements was 536 and 542 kcal/day in the SS and SC groups respectively; that 2 weeks after discharge from hospital was 274 and 361 kcal/day in the SS and CS groups respectively. There was significantly less postoperative weight loss in the SS group than in the CC and CS groups ($P < 0{\cdot}050$), and significantly fewer minor complications in the SS and CS groups than the CC group ($P < 0{\cdot}050$). There were no differences in the rate of major complications, anthropometrics and quality of life. Mean overall costs were greatest in the CC group, although differences between groups were not significant.

<table>
<tr><th colspan="4">11. Keele AM, Bray MJ, Emery PW, Duncan HD, Silk DB Two phase randomised controlled clinical trial of postoperative oral dietary supplements in surgical patients. Gut 1997; 40:393-399.</th></tr>
<tr><th>Study Type/
Evidence Level</th><th>Study details/limitations</th><th>Patient characteristics</th><th>Interventions</th></tr>
<tr><td>RCT
1+</td><td>Countries: n/a
Centers: n/a
Setting: n/a
Funding Sources:
Nutricia
Research
Dropout rates: n= 14 (14%)
Study limitations: n/a</td><td>Total no. patients: n=100
• Intervention group n= 43
• Control group n= 43
Inclusion criteria: patients who have undergone gastrointestinal surgery
Exclusion criteria: Patients who underwent laparoscopic surgery, had diabetes or overt dementia, had received preoperative enteral or parenteral nutrition, or had undergone previous abdominal radiotherapy</td><td>Phase 1: the inpatient phase
Intervention group
-postoperative standard hospital diet supplemented ad libitum with an oral dietary supplement containing 1,5kcal/ml and 0,05g/ml protein (consumption of the supplements in small, frequent amounts, in between meals)
Control group
-postoperative standard hospital diet
Phase 2: the outpatient phase
Intervention group
-Intake of supplements (1,5kcal/ml and 0,05g/ml protein) ad libitum in addition to their normal diet for four months
Control group
-no supplementation</td></tr>
<tr><td>Notes</td><td colspan="3">Phase 1: nutrient Intake was assessed from day 1 until day 7 of the study period, partially drunk supplements were measured, Nutritional status was assessed preoperatively on day 3 of the study period, and on discharge:: weight, BMI, Percentage usual body weight (%UBW) , Midarm circumference (MAC) and triceps skinfold thickness (TSF), Midarm muscle circumference (MAMC) was calculated according to the formula MAMC (cm)=MAC (cm)-0-3142 TSF (mm), Hand grip, serum albumin, Nutrition risk index (NRI) was calculated according to the formula NRI= 1,519 albumin (g/l)+0-417 %/6UBW, (where a score of 97,5-100 indicated borderline malnutrition, 83-5-97-5 mild malnutrition, and <83-5 severe malnutrition), fatigue score Phase 2: Nutrient intake was assessed using four day food diaries (Patients were instructed to record their intake over a weekend and two weekdays, during the week before their outpatient appointment; Measurements of nutritional status were repeated (see above) - Treatment regimens of the four groups of patients:
Phase1 Phase 2
Group 1 Supplements Supplements
Group 2 Supplements Control
Group 3 Control Control
Group 4 Control Supplements
-randomization is mentioned, but method not specified
Author’s Conclusion:
The prescription of oral dietary supplements to patients who have undergone gastrointestinal surgery results in clinically significant benefits. These benefits, however, are restricted to the inpatient phase.</td></tr>
<tr><td>Outcome measures/results</td><td colspan="2">Primary outcome measure:
Nutritional Intake, Nutritional status and fatigue levels, complications</td><td>During the inpatient phase, patients treated with oral supplements had a significantly improved nutritional intake and lost less weight (2.2, 950/0 confidence interval (95% CI) 0*9 kg) compared</td></tr>
</table>

		with control patients (4.2 (0.78) kg, p< 0-001). Supplemented patients maintained their hand grip strength whereas control patients showed a significant reduction in grip strength (p<0-01). Subjective levels of fatigue increased significantly above preoperative levels in control patients (p<0-01) but not in the supplemented group. Twelve patients in the control group developed complications compared with four in the supplemented group (p<0.05). In the outpatient phase, supplemented patients had improved nutrient intakes but there were no significant differences in indices of nutritional status or wellbeing between the groups.

12. Espaulella J, Guyer H, Diaz-Escriu F, Mellado-Navas JA, Castells M, Pladevall M Nutritional supplementation of elderly hip fracture patients. A randomized, double-blind, placebo-controlled trial. Age Ageing 2000; 29:425-431.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1	**Countries:** n/a **Centers:** n/a **Setting: Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** Spanish Ministry of Health **Dropout rates:** n= 43 (25.1%) **Study limitations:** n/a	**Total no. patients:** n= 171 • Intervention group n= 85 (n= 61 available for 6-months analysis) • Control group n= 86 (n= 67 available for 6-months analysis) **Inclusion criteria:** patients aged 70 and over hospitalized for fracture of the proximal femur **Exclusion criteria:** patients with dementia, patients who needed intravenous nutrition, patients whose fracture were pathological or not due to accidental falls	Intervention group - nutritional supplementation containing 149 calories per dose (200mL), 20g protein, 800mg Calcium, 25IU vitamin D3, other vitamins and minerals; Intake began within 48 hours of study entry for 60 days once a day Control group -placebo providing 155 calories, mainly derived from carbohydrates; Intake began within 48 hours of study entry for 60 days once a day
Notes	**Author's Conclusion:** Based on our results, we cannot recommend routine nutritional supplementation of all elderly hip fracture patients. While nutritional supplementation may be useful in decreasing complications, this reduction does not result in improvement in functional recovery and nor does it decrease fracture-related mortality. Selected patients may, however, benefit from nutritional supplementation.		
Outcome measures/results	**Primary outcome measure:**		The two groups were comparable at study entry. We observed no differences in return to functional status 6 months post-fracture (61% intervention group vs 55% in control group) nor in fracture-related mortality (13% in intervention group vs 10%

	Functional (Barthel Index, Mobility Index, use of walking aids) and nutritional status (Albumin, BMI, Mid-arm circumference), complications, mortality	in control group). The intervention group suffered fewer in-hospital [odds ratio 1.88 (95% CI 1.01 - 3.53), P = 0.05] and total complications [odds ratio 1.94 (95% CI 1.02-3.7), P = 0.04] than the control group.

13. Burden ST, Hill J, Shaffer JL, Campbell M, Todd C An unblinded randomised controlled trial of preoperative oral supplements in colorectal cancer patients. J Hum Nutr Diet 2011; 24:441-448.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** NHS Fellowship Award, Central Manchester Foundation Trust and Central Manchester Foundation Trust small awards **Dropout rates:** n= 9 (7,2%) **Study limitations:** n/a	**Total no. Patients:** n=125 • Intervention group n = 54 • Control group n = 62 **Inclusion criteria:** patients with CRC (colorectal cancer) where surgery was their planned treatment option, age of >18 years, informed consent, a minimum period of 10 days before surgery (minimum period of oral supplementation) **Exclusion criteria:** pregnant, enrolled in another trial, no informed consent, inoperable tumor	Intervention group -daily Intake of 400 mL of an oral supplementary drink (Milk-based supplements (630 kJ and 6 g protein per 100 mL; or a fruit juice (630 kJ and 4 g protein per 100 mL) dietary advice starting at time of enrolment until surgery Control group -dietary advice (same as intervention group: increasing energy and protein from food based on an information leaflet) only
Notes	No blinding **Author's Conclusion:** There was no evidence that preoperative supplements were beneficial in reducing the number of complications, although there may be some benefit for surgical site infections in selected weight-losing preoperative patients.		
Outcome measures/results	**Primary outcome measure:** total post-operative complications **Secondary outcome measures:** infectious complications, surgical site infections (SSI), chest infections, urinary tract infections (UTI)		In the intervention group, 24 (44%) patients had a complication compared to 26 (42%) in the control group (*P* = 0.780). In the intervention and control groups, there were eight (15%) and 16 (25%) surgical site infections, respectively (*P* = 0.140) and seven (13%) and 11 (17%) chest infections, respectively (*P* = 0.470). Subgroup analysis for hypothesis generation included 83 (71%) weight-losing patients, where there was a significant reduction in surgical site infections using the Buzby definition (*P* = 0.034), although this was not the case for the Centre for Disease Control definition (*P* = 0.052).

Empfehlung 16

Patienten mit gastrointestinalem Karzinom sollte eine mit (Arginin, Omega-3-Fettsäuren, Ribonukleotide) angereicherte Trinknahrung präoperativ für 5-7 Tage angeboten werden. (BM, HE)

Empfehlungsgrad B – Konsens 92 % Zustimmung

14. Bruns ERJ, Argillander TE, Van Den Heuvel B et al. Oral Nutrition as a Form of Pre-Operative Enhancement in Patients Undergoing Surgery for Colorectal Cancer: A Systematic Review. Surg Infect (Larchmt) 2018; 19: 1-10. doi:10.1089/sur.2017.143			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic review 1+ AMSTAR II 9/16	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** Overall confidence in the results of the review: Critically Low Risk of bias of single studies: moderate Inconsistency: high Indirectness: moderate Impreciseness: moderate Publication bias: n/a Number of studies was restricted, and the overall methodological quality was only moderate	**Total no. Studies:** 6 **Inclusion criteria:** answered the clinical question as defined by the population, intervention, control, outcome (PICO) format, RCT or prospective cohort study, patients ≥ 60 and undergoing colorectal surgery, administered oral nutrition for at least 48 h pre-operatively **Exclusion criteria:** studies investigating the effect of nutrition as a part of a multimodal prehabilitation program or parenteral nutrition, review articles, (retrospective) case-controlled studies, case reports, opinion papers, animal studies, studies not in English	oral pre-operative nutritional support as a part of prehabilitation in patients undergoing surgery for colorectal cancer
Notes	**Author's Conclusion:** Current studies are too heterogeneous to conclude that pre-operative oral nutritional support could enhance the condition of patients undergoing colorectal surgery. Patients at risk have a relatively lean body mass deficit (sarcopenia) rather than an absolute malnourished status. Compliance is an important element of prehabilitation. Targeting patients at risk, combining protein supplements with strength training, and defining standardized patient-related outcomes will be essential to obtain satisfactory results.		
Outcome measures/results	primary outcome: overall complication rate		- overall complication rate: not significantly different between intervention and control groups (OR 0.82; 95% confidence interval [CI] 0.52 - 1.25)

	secondary outcomes: incision infection rate, anastomotic leakage rate, length of hospital stay	- incision infection rate: no advantage for pre-operative nutritional support (OR 0.57; 95% CI 0.30 - 1.09) - anastomotic leakage rate: none of the studies demonstrated a significant difference between the treatment arms - length of hospital stay: because of the large clinical and statistical heterogeneity among studies, no meta-analysis was undertaken for this outcome

15. Gillis C, Buhler K, Bresee L et al. Effects of Nutritional Prehabilitation, With and Without Exercise, on Outcomes of Patients Who Undergo Colorectal Surgery: A Systematic Review and Meta-analysis. Gastroenterology 2018; 155: 391-410 e394. doi:10.1053/j.gastro.2018.05.012			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis and systematic review 1+ AMSTAR II 12/16	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** no funding **Dropout rates:** n/a **Study limitations:** Overall confidence in the results of the review: Low Risk of bias of single studies: high Inconsistency: high Indirectness: moderate Impreciseness: high Publication bias: low Small number of studies of small sample, statistical heterogeneity, some studies with high risk of bias	**Total no. Studies:** 9 **Inclusion criteria:** original prospective cohort or RCT study on the use of nutrition-only prehabilitation or multimodal prehabilitation in adults ≥ 18 years awaiting colorectal resection surgery, compared to a control **Exclusion criteria:** invasive preoperative nutrition support requiring hospitalization, including parenteral and/or enteral nutrition, studies that included carbohydrate loading- only or specialized immunonutrition products	nutrition-only (oral nutritional supplements and/or counseling) and multi-modal (oral nutritional supplements and/or counseling with exercise) with or without exercise in prehabilitation after colorectal resection
Notes	**Author's Conclusion:** In conclusion, our systematic review and meta-analysis revealed that nutrition is a key component of prehabilitation interventions. Nutrition prehabilitation alone and when combined with exercise significantly reduced LOS post-colorectal surgery. The available evidence also suggests that multimodal prehabilitation with nutrition would make a complementary addition to ERPs by promoting an earlier functional recovery four and eight weeks after colorectal surgery.		

Outcome measures/results	length of hospital stay (LOS)	- receipt of any prehabilitation significantly reduced days spent in hospital compared with controls (weighted mean difference of length of hospital stay, –2.2 days; 95% CI, –3.5 days to –0.9 days)

16. Kong SH, Lee HJ, Na JR et al. Effect of perioperative oral nutritional supplementation in malnourished patients who undergo gastrectomy: A prospective randomized trial. Surgery 2018; 164: 1263-1270. doi:10.1016/j.surg.2018.05.017			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1- ROB 4/7	**Countries:** Korea **Centers:** n/a **Setting:** n/a **Funding Sources:** Abbott Laboratories, Lake Bluff, IL **Dropout rates:** 11% **Study limitations:** Risk of Bias: moderate Inconsistency: n/a Indirectness: low Impreciseness: moderate Publication bias: n/a low compliance to ONS postoperatively	**Total no. Patients:** 144 **Inclusion criteria:** ≥ 20 years; undergoing distal, total, proximal, or pylorus-preserving gastrectomy; assessed as being moderately or severely, malnourished, according to the patient-generated subjective global assessment (PG-SGA) or with a BMI ≤ 18.5 kg/m^2; did not receive preoperative chemotherapy; able to take oral meals **Exclusion criteria:** underwent wedge resection, gastric bypass, or gastrotomy (non- resection); well-nourished according to PG-SGA and a BMI ≥ 18.5; underwent an emergency operation; pregnancy; could not consume the oral nutritional supplement	preoperative ONS versus standard care without a preoperative ONS in malnourished patients who undergo gastrectomy - patients in the ONS group received Ensure powder sachets. Each sachet contains 500 kcal, 18 grams of protein, 34 grams of carbohydrate, 9 grams of fat and vitamins and minerals, and is not enriched with any immune modulating compounds. Duration of ONS intake was 2 weeks before surgery, 1 sachet per day. After surgery: patients in the ONS group continued to take 2 ONS servings per day that provided 500 kcal along with their usual meals for 2 weeks. - Patients in the control group did not receive any ONS and maintained usual meals for 2 weeks before the surgery
Notes	**Author's Conclusion:** In conclusion, despite of the limitation of unintended early termination of the study, we conclude that preoperative ONS does not reduce the overall incidence of complications after gastrectomy when indicated for patients with BMI <18.5 or for patients with moderately or severely malnourished status as determined by the PG-SGA. However, standard ONS that is not enriched with immune-compounds could reduce the incidence, severity, and du- ration of complications after gastrectomy in severely malnourished patients. A comprehensive assessment using the PG-SGA may better predict which patients can benefit from this effect compared with BMI alone.		
Outcome measures/results	primary outcome: postoperative complications (Clavien-Dindo classification ≥II) secondary outcomes: body weight changes, biochemical parameters, quality of life survey results		- overall incidence of complications with Clavien-Dindo classification grade 2 or more tended to be lower in the ONS group, but not significant (29.2% versus 37.1%, P=.346)

		- no mortality observed in either of the groups, and lengths of hospital stay and readmission rates were not different between the 2 groups - changes in body weight: not significantly different between the 2 groups - total lymphocyte count: significantly higher in the ONS group on the 4th visit day (1,810 ± 597 versus 1,570 ± 492, P=.0157) and the 5th visit day (1,895 ± 707 versus 1638 ± 544, P = .0242) - total iron-binding capacity tended to be higher in the ONS group, including during the baseline period, but no difference between the 2 groups when the baseline differences were compensated (P=.9775) - no difference between the 2 groups in the biochemical examinations - quality of life was not significantly affected by ONS, dietary symptoms, such as nausea, vomiting, appetite loss, constipation, and diarrhea, were not increased using ONS

5.3 Wann besteht die Indikation zur präoperativen parenteralen Ernährung?

<u>Empfehlung 18</u>

Bei Patienten mit Mangelernährung und/oder hohem metabolischen Risiko, bei denen eine bedarfsgerechte orale /enterale Ernährung nicht möglich ist, soll eine präoperative parenterale Ernährung durchgeführt werden (A) (BM).

Ein Zeitraum von 10-14 Tagen kann empfohlen werden (0).

Empfehlungsgrad A/0 – Starker Konsens 100 % Zustimmung

17. Veteran Affairs Perioperative total parenteral nutrition in surgical patients. The Veterans Affairs Total Parenteral Nutrition Cooperative Study Group. N Engl J Med 1991; 325:525-532.
→ see No. 2

18. Klein S, Kinney J, Jeejeebhoy K, Alpers D, Hellerstein M, Murray M, Twomey P Nutrition support in clinical practice: review of published data and recommendations for future research directions. Summary of a conference sponsored by the National Institutes of Health, American Society for Parenteral and Enteral Nutrition, and American Society for Clinical Nutrition. Am J Clin Nutr 1997; 66:683-706.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Review 2+	**Countries:** n/a **Centers:** n/a	**Total no. Patients:** n/a **Inclusion criteria:** n/a	We performed a critical review of the current medical literature evaluating the clinical use of nutrition support; the goal was to assess our current body of

	Setting: n/a **Funding Sources:** Clintec Nutrition, McGaw Inc, Mead Johnson Nutritional Groups, Ross Laboratories, The American Dietetic Association **Dropout rates:** n/a **Study limitations:** n/a	**Exclusion criteria:** n/a	knowledge and to identify the issues that deserve further investigation. The panel was divided into five groups to evaluate the following areas: nutrition assessment, nutrition support in patients with gastrointestinal diseases, nutrition support in wasting diseases, nutrition support in critically ill patients, and perioperative nutrition support. The findings from each group are summarized in this report. Each conclusion was graded on the basis of the strength of the supporting data. This document is not meant to establish practice guidelines for nutrition support. The use of nutritional therapy requires a careful integration of data from pertinent clinical trials, clinical expertise in the illness or injury being treated, clinical expertise in nutritional therapy, and input from the patient and his/her family.
Notes	**Author's Conclusion:** The development of modern nutrition support has been hailed as one of the major advances in patient care in this century. To continue to improve the nutritional management of patients, it is important to have a clear understanding of the published data evaluating the use of nutrition support and to target areas that deserve future investigation. This document represents a careful review of the identified published literature evaluating nutritional assessment and the clinical efficacy of enteral and parenteral nutrition. The interpretation of data presented here does not always reflect uniformity of opinion among all members of each subcommittee but does represent a consensus of the entire group. The applicability of data obtained from published clinical trials to current practice is limited because of shortcomings in study design and the absence of studies addressing some important clinical issue. In addition, changes that have occurred in both medical and nutritional therapy may limit the application of data from earlier clinical trials to current practice. Therefore, practice guidelines for nutrition support cannot be based solely on this report. Indeed, more than a half of the A.S.P.E.N. Guidelines and the Georgtown University School of Medicine Conference practice guidelines for TPN are based on expert opinion rather than research-based-evidence. Nevertheless, this document should serve to inform the practitioner of the existing literature within the five areas reviewed by this conference. This document also serve as a challenge to obtain the objective evidence needed to determine the most clinically effective and cost-effective use of nutritional therapy.		
Outcome measures/results	nutrition assessment, nutrition support in patients with gastrointestinal diseases, nutrition support in wasting diseases, nutrition support in critically ill patients, perioperative nutrition support		Conclusion Nutrition Assessment: 1. Malnutrition is a continuum that starts with inadequate nutrient intake, followed by a progressive series of metabolic, functional, and body compositional changes. (B) 2. There is no "gold standard" for determining nutritional status because (a) there is no universally accepted clinical definition of malnutrition, (b) all current assessment parameters are affected by illness and injury, (c) it is difficult to isolate the effect of malnutrition from the influence of the disease on clinical outcome and, (d) it is not clear which of the commonly used nutrition assessment techniques is the most reliable because of the paucity of comparative data. (B) 3. Most current nutrition assessment techniques are based on their ability to predict clinical outcome. However, the validity of any of these techniques to truly measure "nutritional risk " has not been proved and the effect of nutritional therapy to

		influence outcome in patients judged to be “malnourished” has not been consistent in PRCTs. (4) 4. Muscle function testing represents a promising new approach for evaluating the adequacy of nutrient intake and identifying patients who are at increased risk for medical complications. However, additional data and more widespread availability of the technology are needed before this approach can be incorporated into clinical practice. (B) Conclusion Short Bowel Syndrome 1.Enteral and parenteral nutrition support can prevent malnutrition and is essential for survival in selected patients with SBS.(B) 2. Appropriate manipulation of enteral feeding and the use of oral rehydration therapy can obviate the need for TPN in selected patients with SBS.(B) Conclusion Inflammatory Bowel Disease 1.Enteralnutrition support is likely to have a therapeutic effect in patients with Crohn’s disease, but no PRCT has compared such nutritional therapy with placebo.(B) 2. Steroid therapy is more effective than enteral nutritional therapy in inducing clinical remission in patients with Crohn’s disease. (A) 3. Noncompliance limits the usefulness of monomeric and oligomeric diet therapy. (A) 4. Clinical outcome in response to monomeric, oligomeric, and polymeric formulas is similar. (A) 5. Bowel rest is not necessary to achieve clinical remission. (A) 6. TPN has not been shown to be an effective primary therapy for patients with ulcerative or Crohn’s colitis. (A) 7. Enteral nutrition or TPN promotes growth in pediatric patients with growth retardation. (B) Conclusion Acute Pancreatitis 1. Neither enteral nutrition nor TPN has a beneficial effect on clinical outcome in patients with mild or moderate pancreatitis. (A) 2. Patients who have a protracted clinical course, such as those with serve disease or complications, often require nutrition support to prevent the adverse effects of nutrient deprivation. The timing, route, and nutrient formulation for optimal nutritional therapy are not clear because of paucity of clinical trials. (C) 3. Enteral feeding can be safely administered to patients with pancreatitis. Jejunal tube feeding is often tolerated without an exacerbation of symptoms in patients with mild or moderate disease and in patients who have had surgery for

		complications of pancreatitis. (A) However, the site of feeding (gastric vs duodenal vs jejuna) and the nutrient formulation (elemental vs polymeric; low fat vs normal fat) that cause the least risk for exacerbating disease symptoms are not known. 4. The use of intravenous lipid emulsions is safe in patients with acute pancreatitis, provided hypertriglyceridemia (>400mg/dL) is avoided. (A) Conclusion Liver Disease 1. Providing adequate enteral nutrition or TPN therapy improves some parameters of liver function in patients with chronic alcoholic liver diseases. (A) 2. The aggregate of data are inconclusive to determine whether enteral nutrition or TPN decrease morbidity and mortality in patients with alcoholic liver diseases. (A) 3. BCAA-enriched TPN increases recovery from acute hepatic encephalopathy compared with high-dextrose solutions that do not contain amino acids; BCAA-enriched solutions have not been shown to be superior to standard amino acids formulas. (A) 4. In patients who are protein-intolerant because of chronic or latent hepatic encephalopathy, BCAA-enriched formulas permit greater protein intake without inducing encephalopathy than do standard protein formulas. (A) Conclusion Wasting disorders 1. The routine use of adjunctive short-term enteral nutrition or TPN does not decrease complications or mortality in patients who are receiving chemotherapy or radiation therapy for cancer. (A) However, many of the reported PRCTs have serious limitations in study design that may limit their applicability to current medical practice. (C) 2. Long-term enteral nutrition or TPN may beneficial by maintaining hydration, providing nutrients, increasing comfort, and improving survival in patients unable to eat or absorb adequate nutrients for a prolonged period. (B) However, no PRCTs have evaluated this issue. 3. Use of TPN is associated with an increased rate of infection (including non-catheter-related infections) in patients treated with chemotherapy. (A) It is possible that technical advances in line insertion, improved methods of catheter care, and the trend toward lower calorie and/or fat administration may decrease the incidence of TPN-induced infections bus this has not been proven in PRCTs.(C) 4. Standard TPN given after bone marrow transplantation does not decrease treatment toxicity, graft-vs-host disease, or bacteremia; does not increase lean tissue accrual; and does not affect short-term (<6-month) survival. However, one PRCT found short-term TPN increase long-term survival (>6-month) and decrease the rate of tumor relapse. (A)

		5. The impressive loss of tissue mass and function that occurs in patients with wasting disorders makes restoration of disordered body composition a reasonable clinical goal, until definitive studies are performed to evaluate this hypothesis.(C) 6. TPN, enteral, and oral nutrition support may prevent or reverse weight loss and replenish body cell mass in patients with AIDS who have poor food intake or malabsorption and do not have an active opportunistic infection. Nutritional therapy does not have beneficial effects on body composition in patients with AIDS who have systematic infection. (B) 7. Despite the striking weight loss or stunting that often occurs in children with cancer or AIDS, routine use of TPN in these children does not improve quality of life, growth or survival. (B) Nutrition support may increase muscle mass in children who are malnourished prior to therapy. (B) 8. Many decisions relevant to nutrition practice for patients with wasting disorders cannot be based solely on definitive, research-based evidence because of the absence of clinically relevant PRCTs. (C) Conclusion Critical Illness 1. Critically ill patients are hypermetabolic and have increased nutrient requirements. Although it has been assumed that nutrition support is clinically beneficial in this patient's population, this hypothesis has not been tested by well-designed clinical trials. (C) 2. In the absence of carefully designed clinical trials, the rationale for nutrition support is based mostly on clinical judgment, and nutrition support is considered in patients who are unlikely to consume adequate nutrient intake for a "prolonged" period. Although it is not known how long a critically ill patient can tolerate lack of nutrient intake without adverse consequences, the loss of lean tissue that occurs in severely catabolic patients (20 to 40g of nitrogen/day) suggests that critical depletion of lean tissue may occur after 14 days of starvation. Therefore, nutrition support should be initiated in patients who are not expected to resume oral feeding for 7 to 10 days. (C) 3. Trauma patients fed by enteral nutrition have fewer complications than those given TPN. (B) However, it is not clear whether enteral nutrition support provides a specific benefit or whether TPN itself or overfeeding by TPN is associated with increased infections. 4. No definitive conclusions can be made regarding the clinical efficacy of specialized nutrient formulations (containing w-3 fatty acids, arginine, nucleic acids, glutamine, and/or BCAAs) because of conflicting results from various studies. Conclusion Perioperative Nutrition Support

		1. TPN given to “malnourished” (defined by weight loss, plasma proteins, or prognostic indices) patients with gastrointestinal cancer for 7 to 10 days before surgery decreases postoperative complications by approximately 10%. (A) 2. Routine use of early postoperative TPN in “malnourished” (defined by weight loss, plasma proteins, or prognostic indices) general surgical patients who do not receive preoperative TPN increases postoperative complications by approximately 10%. (A) 3. Postoperative nutrition support is necessary for patients unable to eat for long periods after surgery to prevent adverse effects of starvation. The exact duration of starvation that can be tolerated without increased morbidity is unknown. The opinion of this subcommittee is that wound healing and recovery from surgery may be impaired if TPN is not started within 5 to 10 days after operation in patients who are unable to eat or tolerate enteral feedings. (C) 4. In the majority of currently published PRCTs evaluating the use of perioperative TPN, the quantity and type of substrates given were not optimal by current standards. For example, calories were often given in amounts substantially greater than metabolic needs. Therefore, it is possible that outcomes in many of these trials would be different if the trials were repeated using our present-day understanding of caloric needs and other metabolic requirements in specific patients’ groups. (C) 5. Postoperative enteral feeding given to underweight elderly women after surgery for hip fracture speeds recovery of mobility, decreases postoperative complications, and decreases the length of hospital stay. (A)

19. Bozzetti F, Gavazzi C, Miceli R, Rossi N, Mariani L, Cozzaglio L, Bonfanti G, Piacenza S Perioperative total parenteral nutrition in malnourished, gastrointestinal cancer patients: a randomized, clinical trial. JPEN J Parenter Enteral Nutr 2000; 24:7-14.
→ see No. 3

20. Meyenfeldt von MF, Meijerink WJ, Rouflart MM, Builmaassen MT, Soeters PB Perioperative nutritional support: a randomised clinical trial. Clin Nutr 1992; 11:180-186.
→ see No. 4

21. Jie B, Jiang ZM, Nolan MT, Zhu SN, Yu K, Kondrup J Impact of preoperative nutritional support on clinical outcome in abdominal surgical patients at nutritional risk. Nutrition 2012; 28:1022-1027.

Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
Cohort study 2+	**Countries:** n/a **Centers:** Peking Union Medical College Hospital (PUMCH), Beijing University Third Hospital (BUTH) **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** n/a	**Total no. Patients:** n= 1085 **Inclusion criteria:** admission for non-emergency abdominal surgery; age 18 to 80 y; well oriented to time and place, speaking/understanding Chinese; a hospital LOS of at least 4 d; provision of a written informed consent **Exclusion criteria:** n/a	We performed this cohort study to evaluate the effect of preoperative nutritional support in abdominal surgical patients at nutritional risk as defined by the Nutritional Risk Screening Tool 2002 (NRS-2002). Therefore, data were collected on the nutritional risk screening (NRS-2002), the application of perioperative nutritional support, surgery, complications, and length of stay
Notes	-Parenteral nutrition: administered intravenously and consisted of a combination of amino acids, carbohydrate, and fat with a non-protein energy at least 10 kcal · kg^{-1} · d^{-1} (according to the American Gastroenterological Association statement) -Enteral nutrition: oral nutrient supplementation and tube feeding that provided at least 10 kcal · kg^{-1} · d^{-1} (according to the guideline from European Society of Parenteral and Enteral Nutrition) - and a minimum of 3 d of PN or EN after surgery was considered postoperative nutritional support, a minimum of 7 d of parenteral nutrition or enteral nutrition before surgery was considered adequate preoperative nutritional support. **Author's Conclusion:** To our knowledge, this is the first study to evaluate the effect of preoperative nutritional support on clinical outcomes in patients at nutritional risk as defined by the NRS-2002. Of the patients with an NRS score of at least 5, a lower complication rate was found in patients who received preoperative nutritional support. In addition, the hospital LOS was not prolonged by the preoperative nutritional support because of the shorter postoperative hospital LOS in the preoperative nutrition group. This finding suggests that adequate preoperative nutritional support (≥7 d) should be provided to a patient with an NRS score of at least 5.		
Outcome measures/results	**Primary outcome measure:** Complication rate **Secondary outcome measure:** Length of stay		In total 1085 patients were recruited, and 512 of them were at nutritional risk. Of the 120 patients with an NRS score at least 5, the complication rate was significantly lower in the preoperative nutrition group compared with the control group (25.6% versus 50.6%, *P* = 0.008). The postoperative hospital stay was significantly shorter in the preoperative nutrition group than in the control group (13.7 ± 7.9 versus 17.9 ± 11.3 d, *P* = 0.018). Of the 392 patients with an NRS score from 3 to 4, the complication rate and the postoperative hospital stay were similar between patients with and those without preoperative nutritional support (*P* = 1.0 and 0.770, respectively).

22. Fukuda Y, Yamamoto K, Hirao N, Nishikawa K, Maeda S, Haraguchi N, Miyake M, Hama N, Miyamoto A, Ikeda M, Nakamori S, Sekimoto M, Fujitani K, Tsujinaka T Prevalence of Malnutrition Among Gastric Cancer Patients Undergoing Gastrectomy and Optimal Preoperative Nutritional Support for Preventing Surgical Site InfectionsAnn Surg Oncol 2015; Suppl 3: 778-785.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Retrospective trial 2+	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** -retrospective trial (no investigation of relationship between nutritional parameters and clinical outcomes among malnourished patients receiving appropriate nutritional support possible)	**Total no. Patients:** *n= 800* • Malnourished patients n= 152 • Well-nourished patients n= 648 **Inclusion criteria:** patients with gastric cancer underwent surgery; **Exclusion criteria:** Patients who received neoadjuvant chemotherapy, underwent gastrojejunal bypass , underwent combined resection of other cancers	The aim of this study was to explore the prevalence of malnutrition among patients with gastric cancer undergoing gastrectomy and the influence of nutritional support on the incidence of postoperative surgical site infections (SSIs). Therefore, we analyzed the patients nutritional risk factors and examined the optimal nutritional support in terms of both duration and calorie intake.
Notes	-Definition malnourished: Malnourished patients were screened based on at least one of the following four criteria: (i) weight loss[10 % within 6 months; (ii) body mass index (BMI) <18.5 kg/ m2; (iii) subjective global assessment (SGA) Grade C; (iv) serum albumin \3.0 g/dl, according to the ESPEN guidelines (Patients who only met the criterion of BMI \18.5 kg/m2 were considered lean but well-nourished and were excluded from NST recommendations) -Energy Intake: Adequate energy support was defined as the provision of ≥25 kcal/kg ideal body weight per day, while energy intake was calculated as the total number of calories, including oral intake, enteral nutrition (EN), and total or peripheral parenteral nutrition (PN) -Preoperative nutritional intervention periods (NIPs) were divided into the following four groups: no intervention or inadequate energy intake, and adequate energy intake for 1–9, 10–13, and C14 days. **Author's Conclusion:** Malnutrition, a risk factor for SSI, was prevalent in gastric cancer patients preoperatively. Well managed preoperative nutritional support decreased the incidence of postoperative SSIs in malnourished patients.		
Outcome measures/results	Occurrence of Postoperative Surgical Site Infections (SSIs), Nutritional risk factors, nutritional support (duration and calorie intake)		Overall, 152 patients (19.0 %) were classified as malnourished. The incidence of SSIs was significantly higher in malnourished patients than in well-nourished patients (35.5 vs. 14.0 %; p\0.0001). The incidence of SSIs in malnourished patients was significantly lower in the well-supported group receiving adequate energy support for at least 10 days than in the poorly-supported group, which received inadequate or no energy support or adequate energy support for \10 days (17.0 vs. 45.4 %; p =

		0.0006). In multivariate analysis, well-managed nutritional support was identified as an independent factor associated with fewer SSIs (odds ratio 0.14; 95 % confidence interval 0.05–0.37;p = 0.0002).

23.	**Gillis C, Buhler K, Bresee L et al. Effects of Nutritional Prehabilitation, With and Without Exercise, on Outcomes of Patients Who Undergo Colorectal Surgery: A Systematic Review and Meta-analysis. Gastroenterology 2018; 155: 391-410 e394. doi:10.1053/j.gastro.2018.05.012**
→ see No. 15	

103.	**Hughes MJ, Hackney RJ, Lamb PJ et al. Prehabilitation Before Major Abdominal Surgery: A Systematic Review and Meta-analysis. World J Surg 2019; 43: 1661-1668. doi:10.1007/s00268-019-04950-y**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis and systematic review 1+	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** heterogeneity of the included trials	**Total no. Studies:** 15 **Inclusion criteria:** trials assessing prehabilitation prior to abdominal surgery **Exclusion criteria:** pediatric studies, cardiac/thoracic only surgery, pharmaceutical interventions, nutritional interventions alone, non-randomized controlled trials	prehabilitation before major abdominal surgery
Notes	**Author's Conclusion:** In summary, this meta-analysis has shown that prehabilitation results in improved morbidity rates after abdominal surgery and could be implemented routinely. Future research should be aimed at ascertaining the exact components and timing of the prehabilitation regimen (including nutritional supplementation) and the ideal target patients and operative procedures in order to maximize implementation.		
Outcome measures/results	primary outcome: occurrence of any complication within 30 days post-operatively secondary outcomes: post-operative pulmonary morbidity; post-operative length of stay (LOS); preoperative, post-intervention maximal inspiratory pressure (MIP); post-intervention change in six-minute walking test (6MWT)		- significant reduction in overall morbidity was observed in the prehabilitation group (OR 0.63 95% CI 0.46–0.87 I^2 34%, p = 0.005) - prehabilitation was associated with a significant reduction in composite pulmonary morbidity compared with controls (OR 0.40 95% CI 0.23–0.68, I^2 = 0%, p = 0.0007) - LOS: no significant difference was observed between prehabilitation groups compared with controls (WMD -2.39 95% CI -4.86 to 0.08 I^2 = 0%, p = 0.06) - no significant difference was observed in the MIP recorded at the pre-operative stage after the prehabilitation process had been completed (WMD 11.46 95% CI -2.09 to 25.0, I^2 = 77%, p = 0.10) - no significant difference in 6MWT was observed between those who had undergone the prehabilitation protocol versus the control groups (WMD 9.06 [95% CI -35.68, 53.81] p = 0.69, I^2 = 88%)

104.	Huang ZX, Zhang HH, Zhang WT, Shi MM, Ren JH, Xu LB, et al. Effect of Short-Term Preoperative Parenteral Nutrition Support for Gastric Cancer Patients with Sarcopenia: a Propensity Score Matching Analysis. J Gastrointest Surg. 2022;26:1362-1372.		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Case Control Study 2- NOS 7/9	**Countries:** China **Centers:** Department of Gastrointestinal Surgery, the First Affiliated Hospital of Wenzhou Medical University **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** Risk of Bias: moderate Inconsistency: n/a Indirectness: low Impreciseness: moderate Publication bias: n/a Definition of sarcopenia was based on muscle mass alone, retrospective study, effect of other confounding factors cannot be ruled out	**Total no. Patients:** 428 **Inclusion criteria:** patients with incomplete clinical data, patients with gastrointestinal dysfunction, nonsarcopenic patients, patients who received PN support > 7 days or ≤ 2 before surgery, and patients who received EN **Exclusion criteria:** n/a	Estimation of the effectiveness of short-term preoperative parenteral nutrition (PN) in GC patients with sarcopenia.
Notes	**Author's Conclusion:** In summary, using PSM analysis, we found that short-term preoperative PN support did not show a significant benefit in GC patients with sarcopenia, it also increased their financial burden. Short-term preoperative PN support is associated with decreased postoperative complications in patients with hypoalbuminemia based on subgroup analysis. This finding suggests that short-term preoperative PN support (3–7 days) should not be the conventional choice for GC patients with sarcopenia unless these patients also present with albumin levels < 35 g/L.		
Outcome measures/results	Incidence of postoperative complications, intra-abdominal infection, hospitalization costs, risk factors for postoperative complications, postoperative surgical complications	- In total, 428 patients met the inclusion criteria, and the propensity scores identified 166 matched pairs of patients with sarcopenia. - The overall incidence of postoperative complications between both groups was not significantly different (P = 0.728). - The PN group had a lower rate of intra-abdominal infection (P = 0.032) and higher hospitalization costs (P < 0.001) than the control group. - Multivariate analysis demonstrated that age, Charlson score, and TNM stage were independent risk factors for postoperative complications.	

		- subgroup analysis revealed that short-term preoperative PN support is associated with decreased postoperative surgical complications in patients with albumin levels < 35 g/L (P = 0.025).

6. Postoperative Ernährung

6.1 Welche Patienten profitieren besonders von einer frühen postoperativen Ernährung?

<u>Empfehlung 19</u>

Eine enterale Ernährung soll innerhalb von 24 Stunden bei den Patienten begonnen werden, bei denen ein oraler Kostaufbau noch nicht möglich ist (A).

Dies gilt insbesondere bei:

- **Patienten, bei denen die orale Kalorienzufuhr voraussichtlich in den nächsten 7 Tagen < 50% sein wird (BM) (KKP)**
- **Patienten nach großen Kopf-Hals Operationen und gastrointestinalen Resektionen wegen Tumor (BM) (KKP)**
- **Patienten mit Polytrauma und/oder schwerem Schädel-Hirn-Trauma (BM) (KKP)**
- **Patienten mit Mangelernährung zum Zeitpunkt der Operation (BM) (KKP)**

Empfehlungsgrad A/KKP – Starker Konsens 100 % Zustimmung

1. Klek S, Sierzega M, Szybinski P, Szczepanek K, Scislo L, Walewska E, Kulig J Perioperative nutrition in malnourished surgical cancer patients - a prospective, randomized, controlled clinical trial. Clin Nutr 2011; 30:708-713.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
prospective RCT 2+	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** n/a	**Total no. patients:** n= 167 • SEN n= 43 • IMEN n= 41 • SPN n= 41 • IMPN n= 42 **Inclusion criteria:** patients' severe nutritional risk (according to one of the following ESPEN criteria: weight loss > 10–15% within 6 months; BMI < 18 kg/m2; subjective global assessment, Grade C; serum albumin < 30 g/L (with no evidence of hepatic or renal dysfunction)), patients scheduled for gastrectomy or pancreaticoduodenectomy due to malignancy, age between 18 and	All patients received parenteral nutrition before surgery for 14 days standard enteral nutrition (SEN) - standard oligopeptic diet (1 ml = 1 kcal) at least until postoperative day 7 immunomodulating enteral nutrition (IMEN) - immunomodulating enteral diet (1 ml = 1.25 kcal, higher amount of minerals and vitamins) at least until postoperative day 7 standard parenteral nutrition (SPN) - standard parenteral) at least until postoperative day 7 immunomodulating parenteral nutrition (IMPN) - parenteral diet supplemented with glutamine of 0.1 g/kg/day and omega-3-unsaturated fatty acids of 0.1 g/kg/day Preoperatively and at least until postoperative day 7

		80 years, Karnoffsky's performance status > 80, adequate major organ function **Exclusion criteria:** patients with unresectable disease, well-nourished or in poor general condition (Karnoffsky's performance score < 80)	
Notes	**Author's Conclusion:** Results demonstrated that postoperative nutritional intervention generates comparable results regardless of the route and formula used and that preoperative intervention is of the utmost importance.		
Outcome measures/results	**Primary outcome measures:** rate of infectious complications **Secondary outcome measures:** morbidity and mortality rates, postoperative hospital stay		The incidence of individual complications was comparable among all four groups ($p > 0.05$). Infectious complications occurred in 23 of 84 patients with standard diets and in 20 of 83 patients receiving immunomodulatory formula (odds ratio 0.84; 95% CI 0.42 to 1.69). There were no significant differences in infectious complications' ratio in patients receiving enteral (24/84 patients) and parenteral formulas (19/83 patients). Neither immunomodulating formulas nor enteral feeding significantly affected the length of hospitalization, overall morbidity and mortality rates.

2. Bozzetti F, Gianotti L, Braga M, Di Carlo V, Mariani L Postoperative complications in gastrointestinal cancer patients: the joint role of the nutritional status and the nutritional support. Clin Nutr 2007; 26:698-709.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic Review 2+	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** n/a	**Total no. patients:** n=1410 **Inclusion criteria:** randomized clinical trials (RCTs), patients with histologically documented gastrointestinal malignancy and were candidate for major open elective surgery, **Exclusion criteria:** clinically relevant organ dysfunction (type I diabetes, morbid obesity or other severe	We reviewed patients enrolled in previous RCTs, who received different types of nutritional support such as TPN, EN, IEEN or SIF before and/or after abdominal surgery. We investigated the potential joint prognostic role of baseline demographic and nutritional parameters, type of nutritional support and intraoperative factors upon the occurrence of postoperative complications.

		comorbidities) or ongoing infections, patients receiving a concurrent heavy treatment with steroids or immunosuppressive or cytotoxic agents	
Notes	Nutritional regimes: • immune-enhancing enteral nutrition (IEEN; *n*=500), • enteral nutrition (EN; *n*=393) • total parenteral nutrition (TPN; *n*=368) • standard intravenous fluids (SIF; *n*=149) we considered only the route of administration and composition of the admixture as the main criteria for defining the groups, regardless the time of start and/or duration of nutrition **Author's Conclusion:** Pancreatic surgery, advanced age, weight loss and low serum albumin are independent risk factors for the onset of postoperative complications. Nutritional support, particularly IEEN, significantly reduced postoperative morbidity.		
Outcome measures/results	Postoperative complications, considered as minor or major (if lethal or requiring re-operation, or transfer to intensive care unit) Body weight (BW; kg), degree of weight loss (with respect to usual BW in the previous 6 months), hemoglobin (g/L), serum albumin (g/L), total circulating lymphocyte count ($\times 10^9$/L). Type of surgery, duration of surgery, operative blood loss, rate of homologous blood transfused ,	Major and minor complications occurred in 101 (7.2%) and 446 (31.6%) patients, respectively. Factors correlated with postoperative complications at multivariate analysis were pancreatic surgery, (p<0.001), advanced age (p=0.002), weight loss (p=0.019), low serum albumin (p=0.019) and nutritional support (p=0.001). Nutritional support reduced morbidity versus SIF with an increasing protective effect of TPN, EN, and IEEN. This effect remained valid regardless the severity of risk factors identified at the multivariate analysis and it was more evident by considering infectious complications only.	

3. Moore FA, Feliciano DV, Andrassy RJ, McArdle AH, Booth FV, Morgenstein-Wagner TB, Kellum JM,Jr, Welling RE, Moore EE Early enteral feeding, compared with parenteral, reduces postoperative septic complications. The results of a meta-analysis. Ann Surg 1992; 216:172-183.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-analysis 1+	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** n/a	**Total no. patients:** n= 230 (8 RCTs) • Total enteral nutrition (TEN) n= 118 • Total parenteral nutrition (TPN) n= 112 **Inclusion criteria:** Initiation of nutritional support within 72	We performed this meta-analysis of RCTs to compare the nutritional efficacy of early enteral (TEN) and parenteral nutrition in high-risk surgical patients.

		postoperative hours; Vivonex TEN or study TPN solution as initial postoperative feeding; Moderately to severely stressed (i.e., high-risk surgical) patients; Daily documentation of postoperative complications **Exclusion criteria:** Preexisting diseases including advanced diabetes, chronic inflammatory bowel disease; conditions precluding of TEN (e.g., bowel obstruction); severe head injury (Glasgow Coma Scale ≤ 5); any reason for preclusion of aggressive nutritional support (e.g., low flow state), Hospitalization of ≥ 10 days before study enrollment; prior surgical procedures during study enrollment hospital stay; preoperative nutritional support; nonstudy nutritional solution used immediately after operation	
Notes	Two-part meta-analysis: phase 1: summary statistics were evaluated for each treatment group from the eight study sites, and dropouts were excluded. Phase 2: individual patient data were used to permit comparisons among five patient subgroups, and dropouts were included. **Author's Conclusion:** In conclusion, this meta-analysis attests to the feasibility of early postoperative TEN in high-risk surgical patients and that these patients have reduced septic morbidity rates compared with those administered TPN.		
Outcome measures/results	Phase 1 outcome measures: Diet intake and nutritional responses (e.g., nitrogen balance); change in body weight; time to start of nutritional support; biochemical responses (e.g., total protein); GI intolerance; postoperative complications; length of time in hospital, ICU; cost of hospitalization Phase 2 outcome measures:	The combined data gave sufficient patient numbers (TEN, n = 118; TPN, n = 112) to adequately address whether route of substrate delivery affected septic complication incidence. Phase I (dropouts excluded) meta-analysis confirmed data homogeneity across study sites, that TEN and TPN groups were comparable, and that significantly fewer TEN patients experienced septic complications (TEN, 18%; TPN, 35%; p = 0.01). Phase II meta-analysis, an intent-to-treat analysis (dropouts included), confirmed that fewer TEN patients developed septic complications. Further	

	10-day complications rates; types of complications; 10- and 30-day mortality rates	breakdown by patient type showed that all trauma and blunt trauma subgroups had the most significant reduction in septic complications when fed enterally.

4. Kudsk KA, Croce MA, Fabian TC, Minard G, Tolley EA, Poret HA, Kuhl MR, Brown RO Enteral versus parenteral feeding. Effects on septic morbidity after blunt and penetrating abdominal trauma. Ann Surg 1992; 215:503-511.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries:** n/a **Centers:** Presley Memorial Trauma Center At the University of Tennessee **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n= 2(2%) **Study limitations:** n/a	**Total no. patients:** n=98 • TPN n= 45 • ENT n= 51 **Inclusion criteria:** age of >18, patients with an intra-abdominal injury Requiring laparotomy; Abdominal trauma index (ATI) of at least 15 **Exclusion criteria:** n/a	Enteral feeding group -formula composition: 16,7% protein, 19,2% BCAA; 73,9% CHO, 9,4% fat, 150/1 calorie/nitrogen; nutritional support started within 24hours of injury and continued until patients tolerated a diet Parenteral feeding group -formula composition: 17% amino acids, 15,6% BCAA, 74% CHO, 9% fat, 150/1 calorie/nitrogen; ; nutritional support started within 24hours of injury
Notes	**Author's Conclusion:** The authors recommend that the surgeon obtain enteral access at the time of initial celiotomy to assure an opportunity for enteral delivery of nutrients, particularly in the most severely injured patients.		
Outcome measures/results	**Primary outcome measures:** Septic morbidity, frequency of infections, amount of delivered nutrition, clinical outcome **Secondary outcome measures:** Length of hospital stay, number of ventilator days, number of days receiving tube feedings or TPN, number of and on antibiotics, failure of ENT nutrition requiring cross-over to TPN, number of units of blood administered in the first 24 hours and during total hospitalization, maximum bilirubin level occurring in the first 15 days, calculated nitrogen balances on days 1,4,7 and 10	To investigate the importance of route of nutrient administration on septic complications after blunt and penetrating trauma, 98 patients with an abdominal trauma index of at least 15 were randomized to either enteral or parenteral feeding within 24 hours of injury. Septic morbidity was defined as pneumonia, intra-abdominal abscess, empyema, line sepsis, or fasciitis with wound dehiscence. Patients were fed formulas with almost identical amounts of fat, carbohydrate, and protein. Two patients died early in the study. The enteral group sustained significantly fewer pneumonias (11.8% versus total parenteral nutrition 31.%, p less than 0.02), intra-abdominal abscess (1.9% versus total parenteral nutrition 13.3%, p less than 0.04), and line sepsis (1.9% versus total parenteral nutrition 13.3%, p less than 0.04), and sustained significantly fewer infections per patient (p less than 0.03), as well as significantly fewer infections per infected patient (p less than 0.05). Although there were no differences in infection rates in patients with injury severity score less than 20 or abdominal trauma index less than or equal to 24, there were significantly fewer infections in patients with an injury severity score greater than 20	

		(p less than 0.002) and abdominal trauma index greater than 24 (p less than 0.005). Enteral feeding produced significantly fewer infections in the penetrating group (p less than 0.05) and barely missed the statistical significance in the blunt-injured patients (p = 0.08). In the subpopulation of patients requiring more than 20 units of blood, sustaining an abdominal trauma index greater than 40 or requiring reoperation within 72 hours, there were significantly fewer infections per patient (p = 0.03) and significantly fewer infections per infected patient (p less than 0.01). There is a significantly lower incidence of septic morbidity in patients fed enterally after blunt and penetrating trauma, with most of the significant changes occurring in the more severely injured patients.

5. Kompan L, Kremzar B, Gadzijev E, Prosek M Effects of early enteral nutrition on intestinal permeability and the development of multiple organ failure after multiple injury. Intensive Care Med 1999; 25:157-161.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries:** n/a **Centers:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** n/a	**Total no. patients:** **Inclusion criteria:** patients with an Injury Severity Score (ISS) of > 25 and a Glasgow Coma Score of ≥ 12 points, admitted in shock ; patients who recovered from shock ± as evidenced by their shock index of 1 and systolic blood pressure ≥ 100 mmHg ± in the 6 h after admission to ICU **Exclusion criteria:**	Group A -enteral nutrition started not later than 6 h after admission to the ICU Group B - enteral nutrition started later than 24 h after admission; during the first 24 h following admission patients received total parenteral feeding
Notes	In both groups parenteral solutions were added to meet nutritional requirements **Author's Conclusion:** In contrast with normal volunteers, the patients started on EN later than 24 h after admission to the ICU demonstrated increased intestinal permeability on the second day after sustaining multiple injury. Also, they had a more severe form of MOF than the group placed on EN immediately upon admission. However, early EN had no influence on the length of ICU stay or the time of mechanical ventilation.		
Outcome measures/results	Multiple organ failure (MOF) scores; intestinal permeability (Lactulose and mannitol clearance)		The lactulose/mannitol (L/M) test was performed in patients on days 2 and 4 after trauma, and in 5 healthy volunteers. MOF scores were calculated daily. The mean MOF score from day 4 onwards was 1.84 in group A versus 2.81 in group B (p < 0.002), and was correlated with the time of initiation of EN after injury and the L/M

		ratio on day 2. The median L/M ratio on day 2 was 0.029 for group A and 0.045 for group B, while on day 4 it was 0.020 and 0.060, respectively. On day 2 after trauma, the L/M ratio was significantly higher in group B ($p < 0.05$) than in normal volunteers (median 0.014) and was positively correlated with the time of starting EN.

6. Perel P, Yanagawa T, Bunn F, Roberts I, Wentz R, Pierro A Nutritional support for head-injured patients. Cochrane Database Syst Rev 2006:CD001530.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic Review 1++	**Countries:** n/a **Centers:** n/a **Funding Sources:** Imperial Gift Foundation Boshi-Aiiku-kai (Aiiku Association for Maternal Health and Welfare) **Dropout rates:** n/a **Study limitations:** -lack of report on the effect of alternative feeding strategies on death and disability among included studies -missing data on mortality and disability data for all the included trials (possibility of bias due to the selective publication of trials outcome showing stronger treatment effects) -poor quality of included studies (inadequate or unclear allocation concealment; no attempt to do	**Total no. patients:** n= 434 (11 RCTs) **Inclusion criteria:** randomized controlled trials of timing or route of nutritional support following acute traumatic brain injury; People of all ages with acute traumatic brain injury of any severity; Patients with multiple injuries were included if the injuries included head injury; Randomized controlled trials comparing: Early versus delayed nutritional support; Parenteral versus enteral nutritional support; Gastric versus jejunal enteral nutrition; Mixed nutrition (enteral plus parenteral) was regarded as enteral if the enteral calories exceeded 50% of calorie intake; reported outcome measures: All-cause mortality at the end of follow-up, Death and disability at the end of follow-up; Length of hospital stay, frequency of infections **Exclusion criteria:** n/a	To determine the best timing (early or delayed), and route (enteral or parenteral) of nutritional supplementation following head injury, a systematic review of randomized controlled trials was conducted.

	an intention to treat analysis, admitted excluding from the final analysis patients who had died.)		
Notes	**Author's Conclusion:** This review suggests that early feeding may be associated with a trend towards better outcomes in terms of survival and disability. Further trials are required. These trials should report not only nutritional outcomes but also the effect on death and disability.		
Outcome measures/results	All-cause mortality at the end of follow-up, Death and disability at the end of follow-up; Length of hospital stay, frequency of infections.		A total of 11 trials were included. Seven trials addressed the timing of support (early versus delayed), data on mortality were obtained for all seven trials (284 participants). The relative risk (RR) for death with early nutritional support was 0.67 (95% CI 0.41 to 1.07). Data on disability were available for three trials. The RR for death or disability at the end of follow-up was 0.75 (95% CI 0.50 to 1.11). Seven trials compared parenteral versus enteral nutrition. Because early support often involves parenteral nutrition, three of the trials are also included in the previous analyses. Five trials (207 participants) reported mortality. The RR for mortality at the end of follow-up period was 0.66 (0.41 to 1.07). Two trials provided data on death and disability. The RR was 0.69 (95% Cl 0.40 to 1.19). One trial compared gastric versus jejunal enteral nutrition, there were no deaths and the RR was not estimable.

7.	**Berkelmans GHK, Fransen LFC, Dolmans-Zwartjes ACP et al. Direct Oral Feeding Following Minimally Invasive Esophagectomy (NUTRIENT II trial): An International, Multicenter, Open-label Randomized Controlled Trial. Ann Surg 2020; 271: 41-47. doi:10.1097/SLA.0000000000003278**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1++	**Countries:** Netherlands, Sweden **Centers:** multi-center, Catharina Hospital, Eindhoven, the Netherlands; Hospital Group Twente,	**Total no. patients:** 148 **Inclusion criteria:** patients aged 18 years or above scheduled to undergo a minimally invasive esophagectomy with intrathoracic Ivor Lewis anastomosis	Two groups:

ROB 4/7	Almelo, the Netherlands and the Karolinska University Hospital, Stockholm, Sweden **Setting:** n/a **Funding Sources:** KWF Kankerbestrijding (Dutch Cancer Society, project number 10495) and Covidien/Medtronic. **Dropout rates:** 11% **Study limitations:** Risk of Bias: moderate Inconsistency: n/a Indirectness: low Impreciseness: high Publication bias: n/a finding that median time to functional recovery was 7 days in the intervention group and 8 days in the control group was lower than expected before start of the study; complication rate may be a factor in the current results	**Exclusion criteria:** inability to tolerate oral intake, inability to receive a feeding jejunostomy, diagnosed with a preoperative swallowing disorder or achalasia, a Karnofsky Performance Status <80, or malnourishment (defined as >15% weight loss in the period before surgery); Patients with metastases found during surgery or patients who received a total gastrectomy were	intervention group (direct oral feeding) (n= 65): started directly with a liquid oral diet slowly increasing calories each day. From postoperative day 15, patients could eat solid foods without restrictions control group (n=67): Patients in the control group (standard of care) had a delay in start of oral intake and were only allowed to drink clear liquids up to 250cc/day. They received tube feeding via the jejunostomy and started oral intake on postoperative day 5, expanding this diet exactly the same as in the oral group. Fourteen days after initiation of oral intake, all patients could start a solid oral diet.
Notes	**Author's Conclusion:** direct start of oral feeding after esophagectomy does not affect functional recovery compared with starting oral intake 5 days postoperatively. Importantly, direct start of oral intake did not increase incidence or severity of postoperative complications.		
Outcome measures/results	**Primary outcome:** the day of functional recovery **Secondary outcomes:** pulmonary complications; anastomotic leakage and nutritional status; pneumonia rate, and other surgical complications scored by predefined definitions.		- Functional recovery was 7 days for patients receiving direct oral feeding compared with 8 days in the control group (P = 0.436). - Anastomotic leakage rate did not differ in the intervention (18.5%) and control group (16.4%, P = 0.757) - Pneumonia rates were comparable between the intervention (24.6%) and control group (34.3%, P = 0.221) - Other morbidity rates were similar, except for chyle leakage, which was more prevalent in the standard of care group (P = 0.032).

6.3 Welche Patienten profitieren von einer enteralen Sondennahrung?

Empfehlung 21

Bei Patienten mit Mangelernährung und/oder hohem metabolischen Risiko sollte insbesondere bei Ösophagus- und Magenresektion sowie partieller Duodenopankreatektomie die intraoperative Platzierung einer nasojejunalen Sonde oder Feinnadelkatheterjejunostomie (FKJ) erfolgen (BM).

Empfehlungsgrad B – Starker Konsens 100 % Zustimmung

Empfehlung 22

Eine Sondenernährung soll innerhalb von 24 Stunden begonnen werden (BM)

Empfehlungsgrad A – Starker Konsens 97 % Zustimmung

8. Markides GA, Alkhaffaf B, Vickers Nutritional access routes following oesophagectomy--a systematic review. Eur J Clin Nutr 2011; 65:565-573.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-analysis 1++	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** *-small number of included RCTs* *-average quality due to* methodological problems - present heterogeneity among studies -no clear definition of health status of selected patients -variety of selection and performance bias -small number of included patients per trial	**Total no. patients:** n= 344 (5RCTs, one Case-Control-study) • Patients with a nutritional support n= 188 • Control n= 164 **Inclusion criteria:** RCTs, studies with the use of access route(s) for nutrition following esophagectomy (regardless of the type); patients undergoing esophagectomy **Exclusion criteria:** other gastro-intestinal operations	We searched for RCTs to examine the current body of evidence behind nutritional support routes in esophagectomy patients by means of systematic review and meta-analysis.
Notes	Case-control studies were later introduced due to the small numbers of RCTs **Author's Conclusion:**		

	In conclusion, evidence supporting an optimal route for nutritional support in post-esophagectomy patients is weak. Given this, results from studies examining other types of gastro-intestinal surgery must be drawn upon to make clinical decisions, which is sub-optimal. If enteral feeding routes are to be used, jejunostomy may be superior to nasoduodenal or nasojejunal tubes.	
Outcome measures/results	**Primary outcome measures:** procedure-related complication rates at 30 days, changes in nutritional status as(defined as biochemically) **Secondary outcome measures:** length of hospital stay, overall complication rates at 30 days	There was a significant variation in the routes assessed (including intravenous fluid therapy, peripheral and central line nutrition, feeding jejunostomy, nasojejunal and nasoduodenal tubes) and the methodological quality of each study, with small patient numbers. No route was found to be superior over another in the RCTs. In the case-control trial, the combination of enteral parenteral nutrition led to shorter hospital stay compared with parenteral feeding alone. Nasojejunal and nasoduodenal tubes are associated with a significant rate of dislodgement. There is absence of strong direct evidence supporting a single feeding access route in esophagectomy patients.

9. Gerritsen A, Besselink MG, Gouma DJ, Steenhagen E, Borel Rinkes IH, Molenaar IQ Systematic review of five feeding routes after pancreatoduodenectomy. Br J Surg 2013; 100:589-598.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Review 1+	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** *-moderate quality of included studies* - only two RCTS (of 7) directly compared outcomes of two different feeding routes - rare report on feeding related Outcome measures (such as time to resumption of normal oral diet, serum albumin levels or weight loss during hospital stay)	**Total no. patients:** n= 3474 (15 studies) **Inclusion criteria:** studies concerning feeding after Pancreatoduodenectomy (both pylorus-preserving PD and classical Whipple); reporting on length of hospital stay; with the full text available in English; If multiple series with overlapping cohorts were available from one center, only the most recent study was included **Exclusion criteria:** review articles; opinion papers; case reports; animal studies; studies not reporting results of different routes separately; studies with combined feeding routes, unclear definitions	The present systematic review of the literature compared outcomes of feeding an oral diet and enteral and parenteral feeding routes after PD, focusing on both efficacy and safety.

	- definitions of various endpoints, definition of oral diet and regular standards of care varied widely among the studies - subgroup analysis of the primary outcome in patients with delayed gastric emptying could not be performed, (missing reports on outcomes for the subgroups of patients with and without delayed gastric emptying)	of feeding protocols or any supplements in addition to the standard formula	
Notes	**Author's Conclusion:** There is no evidence to support routine enteral or parenteral feeding after PD. An oral diet may be considered as the preferred routine feeding strategy after PD.		
Outcome measures/results	***Primary outcome measure:*** Length of hospital stay **Secondary outcome measures:** Time to resumption of normal diet, Duration of artificial feeding, overall morbidity, incidence of delayed gastric emptying, postoperative pancreatic fistula, tube-related complications, mortality		Of 442 articles screened, 15 studies with 3474 patients were included. Data on five feeding routes were extracted: oral diet (2210 patients), enteral nutrition via either a nasojejunal tube (NJT, 165), gastrojejunostomy tube (GJT, 52) or jejunostomy tube (JT, 623), and total parenteral nutrition (TPN, 424). Mean(s.d.) length of hospital stay was shortest in the oral diet and GJT groups (15(14) and 15(11) days respectively), followed by 19(12) days in the JT, 20(15) days in the TPN and 25(11) days in the NJT group. Normal oral intake was established most quickly in the oral diet group (mean 6(5) days), followed by 8(9) days in the NJT group. The incidence of delayed gastric emptying varied from 6% (3 of 52 patients) in the GJT group to 23·2% (43 of 185) in the JT group, but definitions varied widely. The overall morbidity rate ranged from 43·8% (81 of 185) in the JT group to 75% (24 of 32) in the GJT group. The overall mortality rate ranged from 1·8% (3 of 165) in the NJT group to 5·4% (23 of 424) in the TPN group.

10. Han-Geurts IJ, Hop WC, Verhoef C, Tran KT, Tilanus HW Randomized clinical trial comparing feeding jejunostomy with nasoduodenal tube placement in patients undergoing oesophagectomy. Br J Surg 2007; 94:31-35.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** n/a	**Total no. patients:** n= 150 • Nasoduodenal tube group n=71 • Jejunostomy group n= 79 **Inclusion criteria:** patients undergoing esophageal resection, written informed consent before surgery **Exclusion criteria:** n/a	Nasoduodenal tube group -enteral feeding via nasoduodenal tube with a standard solution (1·0 kcal/ml; given as a continuous infusion commencing at 30 ml/h and increasing to 84 ml/h on the third day as tolerated); nutritional support started on postoperative day 1 until an adequate diet containing solid food was possible (oral diet started approximately 10 days after surgery and, if no anastomotic leakage was present) Jejunostomy group - enteral feeding via jejunostomy catheter with a standard solution (1·0 kcal/ml; given as a continuous infusion commencing at 30 ml/h and increasing to 84 ml/h on the third day as tolerated); nutritional support started on postoperative day 1 until an adequate diet containing solid food was possible (oral diet started approximately 10 days after surgery and, if no anastomotic leakage was present)
Notes	**Author's Conclusion:** Nasoduodenal tube feeding is safe and efficient after esophageal resection		
Outcome measures/results	**Primary outcome measures:** catheter-related complications **Secondary outcome measures:** Surgical and non-surgical complications, time interval between surgery and tolerance to full enteral feeding, total duration of enteral support		Full enteral feeding took 3 days to be established in both groups. Minor catheter-related complications occurred in 28 patients (35%) in the jejunostomy group, and in 21 (30%) in the nasoduodenal group (P = 0·488). One patient had jejunostomy leakage that required reoperation. Enteral nutrition was given for a median of 11 days in the jejunostomy group and for 10 days in the nasoduodenal group. Nine patients who had a jejunostomy and five with a nasoduodenal tube did not tolerate full enteral feeding (P = 0·411)

11. Zhu X, Wu Y, Qiu Y, Jiang C, Ding Y Comparative analysis of the efficacy and complications of nasojejunal and jejunostomy on patients undergoing pancreaticoduodenectomy. JPEN J Parenter Enteral Nutr;2014; 38: 996-1002. [391]			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries:** n/a **Centers:** n/a **Setting:** n/a	**Total no. patients:** n= 68 • JT group n= 34 • NJT group n=34 **Inclusion criteria:**	enteral feeding via a jejunostomy tube (JT group) -PN was given for 5 days from the first day after surgery (nitrogen 0.25 g/kg body weight per day; caloric intake 125.4 kJ/kg (30.0 kcal/kg) per day; lipid intake 1.1 g/kg per day; nonprotein calories as dextrose 5.0 g/kg per day; fat emulsion at a rate of

	Funding Sources: Jiangsu Province Government Foundation **Dropout rates:** n/a **Study limitations:** n/a	clinical history, symptoms, signs, and imaging material to define PD (pancreaticoduodenectomy) indication; no obvious contraindication for PD; understanding the objective and adverse reactions of the study, and fully completing the informed consent form **Exclusion criteria:** patients with manifest metabolic diseases (e.g., diabetes mellitus and hyperthyroidism), severe hemorrhagic disease, ongoing infection, inflammatory bowel diseases, or severe renal abnormality	2:1; source standard lipid emulsion (20% emulsion, 5.5 ml/kg per day, long chain triglycerides/medium chain triglycerides 1:1; 1.5 g amino acids/kg per day) -100 ml of 5% glucose and sodium chloride injection (GNS) within 24 h after surgery and 500 ml of 5% GNS on post operation day 2 (POD2); On POD3, 250 ml of an enteral formula (500 kcal/500 ml) and 250 ml of 5% GNS were given; Amount of enteral route was increased day by day and PN adjusted according to the amount of EN (total caloric intake of PN and EN was 125.4 kJ/kg (30.0 kcal/kg) per day); PN was stopped on POD6, Oral intake started on POD 7 and EN was stopped when the patients tolerated an oral diet with oral intake >1000 kcal/day. enteral feeding via a nasojejunal tube (NJT group) -see above
Notes	**Author's Conclusion:** Nasojejunal feeding is safer than jejunostomy, and it is associated with only minor complications. Nasojejunal feeding can significantly decrease the incidence of delayed gastric emptying and shorten the postoperative hospital stay.		
Outcome measures/results	**Primary outcome measure:** Postoperative complications **Secondary outcome measure:** tube related complications, index on catheter efficiency		There were 15 cases with infectious complications in the JT group and 13 cases in the NJT group, and there was no significant difference in the rate of infectious complications between the 2 groups. The rate of intestinal obstruction and delayed gastric emptying was significantly decreased in the NJT group ($P < .05$). Catheter-related complications were more common in the JT group as compared with the NJT group (35.3% vs 20.6%, $P < .05$). The time for removal of the feeding tube and nasogastric tube was significantly decreased in the NJT group. The postoperative hospital stay in the NJT group was significantly decreased ($P < .05$), and there was no hospital mortality in this study.

12.	**Kang YK, Dong L, Ge Y et al. Short-term clinical outcomes of enteral nutrition versus parenteral nutrition after surgery for pancreatic cancer: a meta-analysis. Translational cancer research 2019; 8: 1403-1411. doi:10.21037/tcr.2019.07.47**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**

Systematic Review 1++ AMSTAR II 13/16	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** none **Dropout rates:** n/a **Study limitations:** Risk of Bias of single studies: n/a Inconsistency: moderate Indirectness: low Impreciseness: low Publication bias: n/a small sample sizes, not possible to analyze preoperative data, lack of data on important indices	**Total no. patients:** 486 **Inclusion criteria:** randomized controlled trials reporting the short-term (seven to ten days after surgery) clinical outcomes between EEN (including oral intake, jejunostomy and nasojejunum) and TPN; at least 15 participants in each group; patients pathologically diagnosed with pancreatic ductal adenocarcinoma (PDAC) and underwent PD; nutritional supports initiating on the first postoperative day and lasted more than ten days; patients treated with isonitrogenous and isocaloric nutrients; studies available to get complete data. **Exclusion criteria:** duplicated papers failing to provide supplementary information; unfinished studies or unavailable data	EEN (including oral intake, jejunostomy and nasojejunum) vs. TPN
Notes	**Author's Conclusion:** EEN was better than TPN at improving the nutritional status and bowel function as well as to decreasing complication rate and hospital stay after PD in patients with pancreatic cancer. Novel nutrition support should be also investigated and developed as an adjunctive therapy to pancreatic cancer patients.		
Outcome measures/results	nutritional status, bowel function, complication rate and hospital stay		After surgery, patients in EEN group had significantly higher plasma total protein than those in TPN group (WMD: 1.83, 95% CI: 0.33–3.32, P=0.02; P for heterogeneity =0.72, I2=0%), while the albumin level was similar between the groups (WMD: 0.25, 95% CI:–4.07–4.56, P=0.91; P for heterogeneity <0.00001, I2=95%). Patients in EEN group had shorter exhaust time (WMD: –0.66, 95% CI: –0.81 to –0.51, P<0.00001; P for heterogeneity =0.28, I2 =21%) and bowel movement time (WMD: –2.27, 95% CI: –2.61 to –1.94, P<0.00001; P for heterogeneity =0.17, I2 =44%) than those in TPN group after surgery. EEN group had lower rate of short-term total complication (RR: 0.68, 95% CI: 0.51–0.92, P=0.01; P for heterogeneity =0.19, I2=33%) and postoperative hemorrhage rate (RR: 0.22, 95% CI: 0.06–0.75, P=0.02; P for heterogeneity =0.82, I2=0%) than TPN group, while there was no significant difference in infection rate (RR: 0.68, 95% CI:

		0.38–1.22, P=0.20; P for heterogeneity =0.87, I2=0%), pancreatic fistula rate (RR: 0.63, 95% CI: 0.35–1.16, =0.14; P for heterogeneity =0.45, I2 =0%) and delayed gastric emptying rate (RR: 0.72, 95% CI: 0.39–1.33, P=0.29; P for heterogeneity =0.27, I2=23%) between the groups. In addition, EEN group had shorter hospital stay (WMD: –1.53, 95% CI: –2.12 to –0.94, P<0.001; P for heterogeneity =0.49, I2=0%).

13. Cai J, Yang G, Tao Y et al. A meta-analysis of the effect of early enteral nutrition versus total parenteral nutrition on patients after pancreaticoduodenectomy. HPB (Oxford) 2020; 22: 20-25. doi:10.1016/j.hpb.2019.06.002			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic Review 1++ AMSTAR II 11/16	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** PUMC Youth Fund and the Fundamental Research Funds for the Central Universities and the Chinese Academy Medical Science Innovation Fund for Medical Students **Dropout rates:** n/a **Study limitations:** Risk of Bias: n/a Inconsistency: low Indirectness: low Impreciseness: low Publication bias: n/a small number of studies, non-availability of some original data	**Total no. patients:** 1.258 **Inclusion criteria:** RCT or Non-RCT (NRCT) with parallel-controlled design; patients underwent pancreaticoduodenectomy; the trial groups consisted of at least two of EN group, TPN group, or EN combined with PN group; EN was started prior to 48 h after surgery; main outcomes such as postoperative complications, postoperative hemorrhage, postoperative infections, and LOS were described; studies were published in English and the relevant data were available. **Exclusion criteria:** duplicate publication; non-comparative studies; animal trials, non-related studies, review articles, and case reports.	At least two of EN group, TPN group, or EN combined with PN group
Notes	**Author's Conclusion:** Compared with TPN, EEN is a safe strategy and can significantly shorten the LOS in patients after pancreaticoduodenectomy. For patients with gastro-intestinal tolerance, EEN can be considered a priority; otherwise, PN combined with EEN is also a safe strategy.		

Outcome measures/results	overall postoperative complications, DGE, post-operative hemorrhage, POPF, mortality, LOS, biliary fistula, intra-abdominal infection, wound infection and lung infection	<u>Meta-analysis results of EEN versus TPN</u> The mean difference in LOS between the two groups was significant (P < 0.001). The final mean difference was −1.46 (95% CI −2.04, −0.89) days, which meant that LOS in the EEN group was shorter than that of the TPN group. However, no significant difference was shown in other complications. <u>Meta-analysis results of EEN and PN versus EEN or TPN</u> There was no significant difference in the comparison of all items.

14.	**Tanaka M, Heckler M, Mihaljevic AL et al. Meta-analysis of effect of routine enteral nutrition on postoperative outcomes after pancreatoduodenectomy. Br J Surg 2019; 106: 1138-1146. doi:10.1002/bjs.11217**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic Review 1++ AMSTAR II 13/16	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** Risk of Bias: high Inconsistency: moderate Indirectness: low Impreciseness: low Publication bias: n/a small sample size in the original studies, heterogenous products of artificial nutrition, heterogenous patient population	**Total no. patients:** 995 **Inclusion criteria:** All RCTs that compared at least two arms of nutritional management (enteral nutrition, non-enteral nutrition) where all patients regularly began oral intake after pancreatoduodenectomy were considered. **Exclusion criteria:** Review articles without original data were excluded.	Regular oral diet with routine enteral nutrition was considered to comprise the intervention group of the eligible RCTs, whereas regular oral diet with or without parenteral nutrition was defined as the control group.
Notes	**Author's Conclusion:** As a supplement to regular oral diet, routine enteral nutrition, especially via a percutaneous enteral tube, may improve postoperative outcomes after pancreatoduodenectomy		
Outcome measures/results	Time to oral intake after surgery, first passage of flatus after surgery, infectious complications, postoperative pancreatic fistula,		<u>Enteral versus non-enteral nutrition</u> Enteral nutrition, compared with non-enteral nutrition, significantly reduced the incidence of infection (OR 0.66, 95% CI 0.43 to 0.99; P = 0.046; I^2 = 31%) shortened

	delayed gastric emptying, postpancreatectomy hemorrhage, postoperative length of stay, 30-day mortality or hospital death	the hospital stay (MD –2.89 (95% CI –4.99 to –0.80) days; P = 0.007; I^2 = 79%) and reduced the time to first flatus (MD –1.75 (–2.58 to –0.93) days; P < 0.001; I^2 = 82%) <u>Enteral versus parenteral nutrition</u> Enteral nutrition, compared with parenteral nutrition, significantly reduced the incidence of infection (OR 0.70, 95% CI 0.45 to 0.96; P = 0.045; I^2 = 10%), and shortened the hospital stay (MD –1.59 (95% CI –2.53 to –0.64) days; P = 0.001; I^2 = 17%) and time to first flatus (MD –1.75 (–2.58 to –0.93) days; P < 0.001; I^2 = 82%). <u>Percutaneous enteral feeding versus parenteral nutrition, and nasojejunal tube feeding versus parenteral nutrition</u> In the analysis of feeding via the percutaneous route versus parenteral feeding, there was a lower incidence of infection (OR 0.47, 95% CI 0.25 to 0.87; P = 0.017; I^2 = 0%), a shorter hospital stay (MD –1.56 (95% CI –2.13 to –0.98) days; P < 0.001; I^2 = 0%) and a significantly shorter time to first flatus (MD –2.10 (–2.48 to –1.72) days; P < 0.001; I^2 = 0%) in the percutaneous route group.

6.4 Welchen Patienten nutzt eine enterale Ernährung nach der Entlassung aus dem Krankenhaus?

<u>Empfehlung 25</u>

Bei Patienten, die perioperativ einer Ernährungstherapie bedurften, sollte die regelmäßige Erfassung des Ernährungsstatus während des Krankenhausaufenthaltes mit poststationärer Fortsetzung einschließlich Ernährungsberatung sowie ggf. oraler/enterale Supplementierung erfolgen. (BM)

Empfehlungsgrad B – Starker Konsens 100 % Zustimmung

<table>
<tr><th colspan="4">15. Wobith M, Wehle L, Haberzettl D et al. Needle Catheter Jejunostomy in Patients Undergoing Surgery for Upper Gastrointestinal and Pancreato-Biliary Cancer-Impact on Nutritional and Clinical Outcome in the Early and Late Postoperative Period. Nutrients 2020; 12. doi:10.3390/nu12092564</th></tr>
<tr><th>Study Type/ Evidence Level</th><th>Study details/limitations</th><th>Patient characteristics</th><th>Interventions</th></tr>
<tr><td>Cohort study
2-
NOS 6/9</td><td>Countries: Germany
Centers: n/a
Setting: n/a
Funding Sources: no external funding
Dropout rates: 14%
Study limitations:
Risk of Bias: moderate
Inconsistency: n/a
Indirectness: low
Impreciseness: moderate
Publication bias: n/a
retrospective analysis and potential selection bias</td><td>Total no. patients: 102
Inclusion criteria: n/a
Exclusion criteria: n/a</td><td>patients undergoing surgery for cancer of the upper gastrointestinal tract, who had undergone NCJ placement during surgery</td></tr>
<tr><td>Notes</td><td colspan="3">Author’s Conclusion: In metabolic risk patients undergoing major surgery for cancer the option of NCJ placement offers safe access for the continuation of enteral feeding after discharge. This may be helpful for individual shared decision-making in order to attenuate postoperative weight loss and to maintain body cell mass.</td></tr>
<tr><td>Outcome measures/results</td><td colspan="2">complications, nutritional status, weight, phase angle</td><td>- no severe complications after the NCJ placement
- supplementing enteral nutrition via NCJ did not improve nutritional status of patients postoperatively, significant postoperative decline of weight and phase angle, especially in the first to third month after surgery, which could be stabilized until 4–6 months after surgery</td></tr>
</table>

		- in patients with upper gastrointestinal and pancreato-biliary cancer, supplementing enteral nutrition during the postoperative course and continued after discharge may attenuate unavoidable weight loss and a reduction of body cell mass within the first six months

16. Meng Q, Tan S, Jiang Y et al. Post-discharge oral nutritional supplements with dietary advice in patients at nutritional risk after surgery for gastric cancer: A randomized clinical trial. Clin Nutr 2021; 40: 40-46. doi:10.1016/j.clnu.2020.04.043			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1- ROB 4/7	**Countries:** China **Centers:** Department of General Surgery/Shanghai Clinical Nutrition Research Center, Zhongshan Hospital, Fudan University, China **Setting:** n/a **Funding Sources:** National Natural Science Foundation of China (81372197, 81900484), Project funded by China Postdoctoral Science Foundation (2019M661370), Shanghai Sailing Program (18YF1404700), Municipal Natural Science Foundation of Shanghai of China (19ZR1409100), Construction Program of Key but Weak Disciplines of Shanghai Health Commission-Clinical Nutrition (2019ZB0105), and Youth Science Foundation of Zhongshan Hospital, Fudan University (2016ZSQN56)	**Total no. patients:** 353 **Inclusion criteria:** discharged after surgery for gastric cancer and a nutritional risk score of 3 or greater based on the Nutritional Risk Screening 2002 (NRS 2002) tool **Exclusion criteria:** unable to take food orally, already receiving nutritional support therapy, pregnant, < 18 years old	patients receive either ONS with dietary advice (ONS group) or dietary advice alone (control group) Patients in the ONS group received dietary advice and an oral intake of Nutren® Optimum at a 500 mL daily dosage for 3 months after discharge as a supplement to regular meals. Dietary advice was defined as instructions that aimed to increase energy and nutrients intake by dietary means, such as increasing the amount of protein-rich and high fat foods in the diet. The product of ONS is a balanced nutritional supplement that contains about 100 kcal energy, 4.1 g protein, 3.9 g fat, 11.7 g carbohydrate, 1.2 g/100 mL of fiber, as well as vitamins and minerals per 100 mL

	Dropout rates: 5% **Study limitations:** Risk of Bias: moderate Inconsistency: n/a Indirectness: low Impreciseness: moderate Publication bias: n/a Data on nutritional requirements and intake from normal food are lacking, single-center, non-blinded study, unable to capture data on long-term outcomes, using low skeletal muscle mass to define sarcopenia		
Notes	**Author's Conclusion:** In conclusion, the present study revealed that post-discharge ONS with dietary advice in patients at nutritional risk after surgery for gastric cancer improved nutritional outcomes, skeletal muscle maintenance, chemotherapy tolerance and some quality of life variables. These findings strongly support the concept of the introduction of post-discharge ONS with dietary advice to this patient cohort.		
Outcome measures/results	primary outcomes: nutritional outcomes and sarcopenia prevalence secondary outcomes: chemotherapy tolerance, the 90-day readmission rate, quality of life		- after 3 months of intervention, BMI and SMI were significantly higher in the ONS group than in the control group ($P < 0.05$), weight were similar between the two groups, patients in the ONS group had a significantly lower weight loss than those in the control group ($P < 0.05$) - after 3 months of intervention, incidence of sarcopenia was significantly lower in the ONS group than in the control group ($P < 0.05$) - 90-day readmission rate in the ONS group was a little lower than that in the control group, no significance (1.8% versus 3.0%, $P > 0.05$) - ONS group had significantly less chemotherapy modifications, including delay, dose reduction, or termination, when compared with the control group (26.0% versus 43.6%, $P = 0.004$) - significantly less fatigue and appetite loss were reported in the ONS group ($P < 0.05$). No significant differences between the two groups were noted in the other outcomes regarding the quality of life ($P > 0.05$)

17.	Hatao F, Chen KY, Wu JM et al. Randomized controlled clinical trial assessing the effects of oral nutritional supplements in postoperative gastric cancer patients. Langenbecks Arch Surg 2017; 402: 203-211. doi:10.1007/s00423-016-1527-8		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1- ROB 5/7	**Countries:** Japan **Centers:** The University of Tokyo Hospital in Tokyo, Japan, and The National Taiwan University Hospital in Taiwan **Setting:** n/a **Funding Sources:** EN Otsuka Pharmaceutical Co., Ltd. **Dropout rates:** 28% **Study limitations:** Risk of Bias: moderate Inconsistency: n/a Indirectness: low Impreciseness: moderate Publication bias: n/a conducted at only two hospitals, sample size for total gastrectomy patients was less than originally planned, could not calculate the caloric values of the patients' daily meals after discharge, preoperative nutritional status differed	**Total no. patients:** 157 **Inclusion criteria:** ≥ 20 years of age, able to ingest food orally, scheduled to receive curative total gastrectomy or distal gastrectomy, no prior treatment for gastric cancer, any preoperative nutritional state **Exclusion criteria:** scheduled to receive function-preserving gastrectomy, Ileus, no residual intestinal function, severe liver and/or renal disorders, abnormalities of glucose metabolism such as severe diabetes mellitus (HbA1c ≥ 7.0 %), allergy to any ingredient of milk, wheat, soybeans, or Salmon, pregnant, possibly pregnant, or lactating, active double cancer and/or multiple cancers	In both groups, standard surgery for gastric cancer was performed. In the treatment group, intervention with ONS was performed until 12 weeks after discharge. In the control group, patients were fed the usual postoperative diet.
Notes	**Author's Conclusion:** This is the first feasibility report on the effects of ONS in postoperative gastric cancer patients. Our exploratory cross- national study showed ONS to be significantly associated with diminished weight loss after total, but not distal gastrectomy. Further studies are needed to determine whether or not ONS can improve the prognosis of gastric cancer patients.		
Outcome measures/results	primary outcome: postoperative percent weight changes at 12 weeks after surgery secondary outcomes: changes in body composition, hematologic and biochemical data, and QOL	- the control and ONS group patients who underwent total gastrectomy, at 12 weeks after discharge, weights had decreased to 85.6 and 88.5 % of the preoperative values, respectively	

		- amount of weight loss after total gastrectomy was significantly smaller in the ONS ($p < 0.05$) - weight loss after distal gastrectomy did not differ significantly between groups - in control group, weight loss was significantly greater after total gastrectomy than after distal gastrectomy - no significant difference in the loss of skeletal muscle mass after a distal or total gastrectomy between the ONS and the control groups - no significant difference in the percentage of body fat loss after either distal or total gastrectomy between groups - losses of both skeletal muscle mass and body fat in the control group were significantly greater after total gastrectomy than after distal gastrectomy - hematological and blood chemistry results did not differ significantly between groups - no significant difference between the ONS and control groups in QOL

18.	**Kong SH, Lee HJ, Na JR et al. Effect of perioperative oral nutritional supplementation in malnourished patients who undergo gastrectomy: A prospective randomized trial. Surgery 2018; 164: 1263-1270. doi:10.1016/j.surg.2018.05.017**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Randomized clinical trial 1- ROB 4/7	**Countries:** Korea **Centers:** n/a **Setting:** n/a **Funding Sources:** Abbott Laboratories, Lake Bluff, IL **Dropout rates:** 11% **Study limitations:** Risk of Bias: moderate Inconsistency: n/a Indirectness: low Impreciseness: moderate Publication bias: n/a Low compliance to ONS postoperatively	**Total no. patients:** 144 **Inclusion criteria:** ≥ 20 years; undergoing distal, total, proximal, or pylorus-preserving gastrectomy; assessed as being moderately or severely, malnourished, according to the patient-generated subjective global assessment (PG-SGA) or with a BMI ≤ 18.5 kg/m^2; did not receive preoperative chemotherapy; able to take oral meals **Exclusion criteria:** underwent wedge resection, gastric bypass, or gastrotomy (non- resection); well-nourished according to PG-SGA and a BMI ≥ 18.5; underwent an emergency operation; pregnancy;	preoperative ONS versus standard care without a preoperative ONS in malnourished patients who undergo gastrectomy - patients in the ONS group received Ensure powder sachets. Each sachet contains 500 kcal, 18 grams of protein, 34 grams of carbohydrate, 9 grams of fat and vitamins and minerals, and is not enriched with any immune modulating compounds. Duration of ONS intake was 2 weeks before surgery, 1 sachet per day. After surgery: patients in the ONS group continued to take 2 ONS servings per day that provided 500 kcal along with their usual meals for 2 weeks. - Patients in the control group did not receive any ONS and maintained usual meals for 2 weeks before the surgery

		could not consume the oral nutritional supplement	
Notes	**Author's Conclusion:** In conclusion, despite of the limitation of unintended early termination of the study, we conclude that preoperative ONS does not reduce the overall incidence of complications after gastrectomy when indicated for patients with BMI <18.5 or for patients with moderately or severely malnourished status as determined by the PG-SGA. However, standard ONS that is not enriched with immune-compounds could reduce the incidence, severity, and du- ration of complications after gastrectomy in severely malnourished patients. A comprehensive assessment using the PG-SGA may better predict which patients can benefit from this effect compared with BMI alone.		
Outcome measures/results	primary outcome: postoperative complications (Clavien-Dindo classification ≥II) secondary outcomes: body weight changes, biochemical parameters, quality of life survey results		- overall incidence of complications with Clavien-Dindo classification grade 2 or more tended to be lower in the ONS group, but not significant (29.2% versus 37.1%, P=.346) - no mortality observed in either of the groups, and lengths of hospital stay and readmission rates were not different between the 2 groups - changes in body weight: not significantly different between the 2 groups - total lymphocyte count: significantly higher in the ONS group on the 4th visit day (1,810 ± 597 versus 1,570 ± 492, P=.0157) and the 5th visit day (1,895 ± 707 versus 1638 ± 544, P = .0242) - total iron-binding capacity tended to be higher in the ONS group, including during the baseline period, but no difference between the 2 groups when the baseline differences were compensated (P=.9775) - no difference between the 2 groups in the biochemical examinations - quality of life was not significantly affected by ONS, dietary symptoms, such as nausea, vomiting, appetite loss, constipation, and diarrhea, were not increased using ONS

7. Bariatrische Chirurgie

<u>Empfehlung 27</u>

Nach bariatrischer Chirurgie soll ein früher oraler Kostaufbau durchgeführt werden. (BM)

Empfehlungsgrad A – Starker Konsens 100 % Zustimmung

<table>
<tr><th colspan="4">1. Azagury DE, Ris F, Pichard C, Volonté F, Karsegard L, Huber Ol Does perioperative nutrition and oral carbohydrate load sustainably preserve muscle mass after bariatric surgery? A randomized control trial. Surg Obes Relat Dis 2015; 11:920-926.</th></tr>
<tr><th>Study Type/
Evidence Level</th><th>Study details/limitations</th><th>Patient characteristics</th><th>Interventions</th></tr>
<tr><td>RCT
1+</td><td>Countries: n/a
Centers: n/a
Setting: n/a
Funding Sources: n/a
Dropout rates: n = 5 (2.5%)
Study limitations:
-absence of blinding
- no establishment of objective criteria for discharge and the decision was left to the surgeon’s judgment, potentially creating a bias on LOS
-missing monitoring of insulin resistance (valuable proof of short-term impact of CHL)
- no systematically assessment of the patient’s compliance (Residual CHL drink left over by the patient was not measured)</td><td>Total no. patients: n = 203
• Intervention group n = 97
• Control group n = 101
Inclusion criteria:
patients >18 years and older scheduled to undergo LRYGB ((Laparoscopic Roux-en-Y gastric bypass)
Exclusion criteria:
prior history of bariatric surgery</td><td>Intervention group
-800 mL of oral isotonic glucose 12 hours before anesthesia and 400 mL 2 hours before (CHL composition: 12.5 g of carbohydrate per 100 mL, 12% monosaccharide, 12% disaccharide, 76% polysaccharide, 250 mOsm/kg and 50 kcal); peripheral parenteral nutrition ((50 g protein, 150 g carbohydrates, 60 g lipids, 750 mOsm, 1400 kcal) starting 2hours postoperatively until oral intake was deemed and at a minimum up to postoperative day 4
Control group
-patients were kept nil-by-mouth as of midnight the day before surgery; postoperative administration of a saline perfusion until oral fluid intake was deemed adequate</td></tr>
<tr><td>Notes</td><td colspan="3">Body composition was measured one day before surgery, one month and one-year postop, using Bioelectrical Impedance Analysis (BIA).
Author’s Conclusion:</td></tr>
</table>

	In a highly homogeneous group of morbidly obese patients with one-year follow-up, CHL and short-term parenteral nutrition did not lead to significant or sustained LBM preservation or modification in EBWL. There was no significant decrease in complications or length of stay. Our study confirms the safety of these interventions, even in previously unstudied Type 2 diabetic patients.	
Outcome measures/results	**Primary outcome measure:** lean body mass (LBM) at one month and one year postoperative **Secondary outcome measures:** length of stay (LOS), weight loss, 30-day complication rate	Of the 203 randomized patients, 198 were included in the analysis. All 101 patients in the control group completed the one-year follow up and 76 completed the BIA. In the intervention group, 93 of 97 patients completed the one-year follow-up and 71 completed the BIA. At one- and 12-months follow-up, body composition, LBM, or EBWL were comparable. There was no difference in operative outcomes, complications rates, or length of stay. There was no adverse effect in the intervention group.

2. Sherf Dagan S, Tovim TB, Keidar A et al. Inadequate protein intake after laparoscopic sleeve gastrectomy surgery is associated with a greater fat free mass loss. Surg Obes Relat Dis 2017; 13: 101-109. doi:10.1016/j.soard.2016.05.026			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
prospective cohort study 2+	**Countries:** Israel **Centers:** n/a **Setting:** private hospital and university hospital **Funding Sources:** Research Projects and Fellowships Fund on Food and Nutrition with Implications on Public Health (Grant number: 3-10470) **Dropout rates:** 20% **Study limitations:** use of BIA and not DXA for body composition measurement, use of 3-day food diary for all time points, no differentiation between protein sources or proteins with different biological value	**Total no. Patients:** 96 **Inclusion criteria:** 18–65 years old, BMI > 40 kg/m^2 or BMI > 35 kg/m^2 with co-morbidities, approval of the Assuta Hospital's committee to undergo bariatric surgery, ultrasound diagnosed nonalcoholic fatty liver disease **Exclusion criteria:** excessive alcohol consumption, mental illness or cognitive deterioration, and previous bariatric surgery, diabetic patients who were treated with antidiabetic medications other than Metformin exclusively at a stable dose for at least 6 months, medical history for co-morbidities was obtained from the patients' medical records	association between daily protein intake and relative FFM loss at 6 (M6) and 12 (M12) months after LSG surgery

Notes	**Author's Conclusion:** A large proportion of the patients during the first year after LSG, do not meet the currently recommended daily protein intake of at least 60 g/d. Our data emphasize the importance of an adequate protein intake after LSG and supports the currently recommended protein intake goal of ≥ 60 g/d as an efficient strategy to better preserve FFM post-LSG.	
Outcome measures/results	energy intake, absolute protein intake, physical activity, FFM	- after LSG, energy intake drastically decreased at M3 and slightly increased at M6 and at M12 - total absolute protein intake significantly decreased at M3 and slightly increased at M6 and at M12 in both genders - most of the patients did not report adequate protein intake according to the recommended goal of ≥ 60 g/d at the first 6 months after LSG (43.8% of the men and 24.4% of the women) - hours spent in physical activity per week increased significantly from baseline at all time points among both genders - for both genders, FFM significantly decreased at M6 and then stabilized at M12, whereas FM continued to decrease during all the 12 months follow-up - protein intake of ≥ 60 g/d was associated with a significantly lower relative FFM loss than protein intake of o 60 g/d at M6 among women (8.9 ± 6.5% versus 12.4 ± 4.1%; P = .039) and this trend was also found among men (9.5 ± 5.5% versus 13.4 ± 6.0%; P = .068) - logistic regression for the prediction of FFM loss of ≥ 10% at M6, indicated that protein intake ≥60 g/d is a strong protective factor (OR = 0.29, 95% CI .09–.96, P = .043)

3. Muschitz C, Kocijan R, Haschka J et al. The Impact of Vitamin D, Calcium, Protein Supplementation, and Physical Exercise on Bone Metabolism After Bariatric Surgery: The BABS Study. J Bone Miner Res 2016; 31: 672-682. doi:10.1002/jbmr.2707			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries:** Austria **Centers:** St. Vincent Hospital, Medical Department II, in Vienna, Austria **Setting:** n/a **Funding Sources:** not supported by any grant or pharmaceutical company **Dropout rates:** 16,4%	**Total no. Patients:** 238 **Inclusion criteria:** obese premenopausal women and men (≥ 25 years) with BMI ≥ 38 kg/m^2 and total body weight ≤ 160kg **Exclusion criteria:** any prior oral calcium and/or vitamin D supplementation consistent with recommended dosages to prevent	1) intervention group receiving: 28,000 IU cholecalciferol/wk. for 8 weeks before bariatric surgery, 16,000 IU/wk. and 1000 mg calciummonocitrate/d after surgery, daily BMI-adjusted protein supplementation and physical exercise (Nordic walking, strength perseverance, and equipment training) 2) 2) a non-intervention group: no preoperative loading, nutritional supplementation, or obligatory physical exercise

	Study limitations: lack of structured randomization, not designed to evaluate any potential clinical risks or benefits, lack of data on patients in the non-intervention group on their dietary behavior and physical activities after surgery	osteoporosis, any antiresorptive or anabolic bone-specific therapy, cessation of menstrual bleeding, any ongoing therapy with insulin, oral anti-diabetic drugs, elevation of liver enzymes, eGFR <90mL/min/1.73m^2, elevation of alkaline phosphatase, systemic or inhalative glucocorticoid use, hypogonadism, any systemic inflammatory disease, 25-hydroxyvitamin D deficiency <10 ng/mL, or alcohol use >3 units/d	
Notes	**Author's Conclusion:** Based on our findings, the approach of vitamin D loading before RYGB or SG and an ongoing vitamin D, calcium, and BMI-adjusted protein supplementation in combination with aerobic physical exercise decelerates the loss of aBMD and lean body mass after bariatric surgery. Moreover, the increases of BTM are less pronounced because of vitamin D, calcium, and protein, regardless of the method of surgery. We conclude that supplementation and exercise have a positive effect on the long-term outcome in bone protection after RYGB/SG and should, therefore, be recommended for all patients undergoing bariatric surgery.		
Outcome measures/results	primary outcome: differences in serum markers of bone turnover (BTM) (loading/supplementation of vitamin D, calcium, protein, and muscle exercise) after 24 months secondary outcome: changes in areal lumbar spine, total hip and total body BMD, trabecular bone score (TBS), changes in lean body mass, body composition, and quality-of-life scores	- relative percentage changes of serum levels of sclerostin (12.1% versus 63.8%), cross-linked C-telopeptide (CTX, 82.6% versus 158.3%), 25-OH vitamin D (13.4% versus 18.2%), phosphate (23.7% versus 32%, $p < 0.001$ for all), procollagen type 1 amino-terminal propeptide (P1NP, 12% versus 41.2%), intact parathyroid hormone (iPTH, –17.3% versus –7.6%), and Dickkopf-1 (–3.9% versus –8.9%, $p < 0.05$ for all) differed - decline in lumbar spine, total hip and total body aBMD, changes in BMI, lean body mass (LBM), as well as changes in trabecular bone score (TBS) values ($p<0.005$ for all) were less, but significantly, pronounced in the intervention group	

4. Schmidt JB, Pedersen SD, Gregersen NT et al. Effects of RYGB on energy expenditure, appetite and glycaemic control: a randomized controlled clinical trial. Int J Obes (Lond) 2016; 40: 281-290. doi:10.1038/ijo.2015.162			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries:** Denmark **Centers:** n/a **Setting:** n/a **Funding Sources:** Danish Ministry of Science, Technology and Innovation **Dropout rates:** 25% **Study limitations:** small sample size, relatively healthy group of obese subjects may have limited the potential for further improvements	**Total no. Patients:** 28 **Inclusion criteria:** obese, normal glucose-tolerant white Caucasians, aged 18–65 years, with body mass index) ≥ 40 or ≥ 35 kg m^{-2} combined with obstructive sleep apnea or hypertension approved for RYGB **Exclusion criteria:** diabetes mellitus, thyroid dysfunction, hypothalamic or known genetic etiology of obesity, a current cancer diagnosis, use of drugs affecting energy metabolism, pregnancy, presence of contraindications to a low-calorie diet, substance abuse or smoking and high intake of alcohol or caffeine (> 300 mg per day)	- obese normal glucose-tolerant participants were randomized to receive RYGB after 8 or 12 weeks - participants followed a low-calorie diet from weeks 0–11, with those operated at week 12 serving as a control group for those operated at week 8
Notes	**Author's Conclusion:** Among obese non-diabetic patients scheduled for RYGB surgery, a low-calorie diet combined with surgery compared with diet alone resulted in a greater reduction in 24-h EE and basal EE. These findings, therefore, do not support the hypothesis that EE is increased after RYGB surgery in humans. More likely, RYGB promotes a negative energy balance by reducing motivation to eat, which is at least partly mediated by changes in postprandial GLP-1, PYY and ghrelin. The early improvement in insulin sensitivity after RYGB surgery was not different the improvement following a low-calorie diet.		
Outcome measures/results	energy expenditure, appetite sensation, taste preferences, nausea and vital signs, biochemical measures, weight, body composition		- compared with controls, RYGB-operated participants had lower body composition-adjusted 24-h EE and basal EE 3 weeks postoperatively (both P<0.05) but EE parameters at week 78 were not different from preoperative values (week 7) - surgery changed the postprandial response of GLP-1, peptide $YY_{3–36}$ (PYY), ghrelin, cholecystokinin, fibroblast growth factor-19 and bile acids (all P<0.05) - particularly, increases in GLP-1, PYY and decreases in ghrelin were associated with decreased appetite - none of HOMA-IR, Matsuda index, the insulinogenic index, the disposition index and fasting hepatic insulin clearance were different between the groups, but

		RYGB operated had lower fasting glucose (P<0.05) and the postprandial glucose profile was shifted to the left (P<0.01)

Empfehlung 29

Für alle weiteren Fragestellungen können die Empfehlungen für Patienten mit großen viszeralchirurgischen Eingriffen zur Anwendung kommen. (BM)

Empfehlungsgrad 0 – Starker Konsens 100 % Zustimmung

5. Ballesta C, Berindoague R, Cabrera M, Palau M, Gonzales M Management of anastomotic leaks after laparoscopic Roux-en-Y gastric bypass. Obes Surg 2008; 18:623-630.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Retrospective Study 2+	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** n/a	**Total no. patients:** 1200 • With leaks (n =59) • Without leaks (n =1141) **Inclusion criteria:** n/a **Exclusion criteria:** n/a	Of 1,200 patients who underwent laparoscopic Roux-en-Y gastric bypass with manual gastrojejunal anastomosis for morbid obesity from January 2002 to January 2007, we retrospectively analyzed 59 patients with anastomotic leak
Notes	**Author's Conclusion:** In our experience, most anastomotic leaks can be managed with conservative measures alone. In many patients, abdominal drains are effective in the management of leaks, obviating the need for reintervention. Nasoenteral nutrition was effective in the non-operative management of gastrojejunal leaks in patients without signs of systemic toxicity		
Outcome measures/results	The location of the leak, day of diagnosis, diagnostic methods, clinical manifestations, treatment modalities, associated complications, and length of hospital stay were analyzed.		Leaks were located as follows: 67.8% in the gastrojejunostomy, 10.2% in the gastric pouch, 3.4% in the excluded stomach, 5.1% in the jejunojejunal anastomosis, 3.4% in the gastrojejunostomy plus pouch, 3.4% in the pouch plus excluded stomach, and 6.8% in undetermined sites. Routine upper gastrointestinal series revealed contrast extravasation in nine patients (15.3%). Leaks were asymptomatic at diagnosis in 29 patients (49.2%). Surgical reintervention was carried out in 23 patients, and conservative treatment was provided in the remaining 36. Transfer to the intensive care unit was required in 11 patients, with five deaths (0.4%)

6. Gonzalez R, Sarr MG, Smith CD, Baghai M, Kendrick M, Szomstein S, Rosenthal R, Murr MM Diagnosis and contemporary management of anastomotic leaks after gastric bypass for obesity. J Am Coll Surg 2007; 204:47-55.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Prospective Study 2+	**Countries:** n/a	**Total no. patients:** n= 3018 **Inclusion criteria:**	The aim of this study was to review and document the spectrum of clinical presentation, the use and efficacy of diagnostic tests, and outcomes of treatment in

	Centers: University of South Florida Health Sciences Center, Tampa, FL; Mayo Clinic, Rochester, MN; Emory University School of Medicine, Atlanta GA; Cleveland Clinic Florida, Weston, FL) **Setting:** four academic, tertiary referral centers **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** Databases were not designed for detailed studies of the in-hospital clinical course. Second, although UGI series were obtained in the majority of patients, we could not ascertain whether some of the radiologic studies were done as a result of change in patient's condition or per routine care. Third, treatment protocols and criteria for nonoperative versus operative treatment were not developed a priori.	patients who underwent Roux-en-Y gastric bypass **Exclusion criteria:** n/a	patients who developed anastomotic leaks after undergoing Roux-en-Y gastric bypass (RYGB) for clinically significant obesity. Therefore, prospectively collected data on consecutive patients who underwent RYGB in 4 tertiary referral centers were reviewed.
Notes	**Author's Conclusion:** Lack of specificity in clinical presentation and imaging studies make diagnosing anastomotic leaks challenging, so operative exploration should be part of the diagnostic algorithm. Nonoperative treatment is safe and effective in a subset of patients who exhibit stable hemodynamic parameters and are known to have controlled leaks.		
Outcome measures/results	Collected data included patient demographics, previous medical history, preoperative clinical characteristics, obesity-related comorbidities, medication use; Operative data included approach (open versus laparoscopic), technique for the gastrojejunostomy,		Sixty-three patients (2.1%) developed anastomotic leaks (open, 2.1%; laparoscopic, 2.1%) at a median of 3 days (range 0 to 28 days) after Roux-en-Y gastric bypass. Symptoms and signs included tachycardia (72%), fever (63%), or abdominal pain (54%). Upper gastrointestinal series and CT demonstrated leaks in only 17 of 56

	and perioperative outcomes; clinical signs and symptoms, radiologic and biochemical findings (both routine and specific), treatment outcomes in each of these patients	(30%) and 28 of 50 (56%) patients, respectively; when done jointly, both studies were negative in 30% of patients. The 68 anastomotic leaks occurred at the gastrojejunostomy (49%), excluded stomach (25%), jejunojejunostomy (13%), gastric pouch (9%), and uncertain location (4%). Forty patients (63%) required 58 reoperations for drainage of intraabdominal collections (55%), repair of anastomotic defects (34%), or revision of the leaking anastomosis (11%), with an overall morbidity of 53% and mortality of 10%. Nonoperative treatment was successful in 23 of 26 patients, with an overall morbidity of 61% and no mortality (p = NS versus operative). Operative treatment was more common in patients with hypotension or oliguria ($p < 0.01$)

8. Organtransplantation

8.1 Wann ist eine enterale Ernährung vor Organtransplantation notwendig?

Empfehlung 30

Bei Mangelernährung soll vor Organtransplantation eine Optimierung des Ernährungsstatus erfolgen. (BM)

Empfehlungsgrad A – Starker Konsens 100 % Zustimmung

Empfehlung 31

Bei manifester Mangelernährung sollten zunächst ein strukturierter Ernährungsplan und erst danach die Supplementierung mit Trinknahrung oder eine enterale Sondenernährung erfolgen. (BM)

Empfehlungsgrad B – Starker Konsens 100 % Zustimmung

1. Langer G, Grossmann K, Fleischer S, Berg A, Grothues D, Wienke A, Behrens J, Fink A Nutritional interventions for liver-transplanted patients. Cochrane Database Syst Rev 2012; 8:CD007605.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Review 1++	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** Jiangsu Province Government Foundation **Dropout rates:** n/a **Study limitations:** -Meta-analyses were not possible due to clinical heterogeneity of the interventions -limited available data from RCTs evaluating the efficacy of parenteral or enteral nutrition and oral nutritional supplements on clinically important outcomes	**Total no. patients**: n= 417 (9 trials) **Inclusion criteria:** Randomized clinical trials of parallel or cross-over design evaluating the beneficial and harmful effects of enteral or parenteral nutrition, or oral nutritional supplements administered to patients before or after liver transplantation; for cross-over trials, only data from the first period were considered; no restrictions on date of publication, language of publication, or publication status; People of any age, sex, and ethnic group before, during, and after liver transplantation, in any care setting, irrespective of diagnosis and disease stage, post-mortem or	The aim of this review was to assess the beneficial and harmful effects of enteral and parenteral nutrition as well as oral nutritional supplements administered to patients before and after liver transplantation. Therefore, a databased search of literature dealing with the mentioned topic was performed and the extracted data analyzed.

	- All included trials were classified as high risk of bias trials: no report on adequate generation of randomization sequence and allocation concealment, lack of blinding, incomplete outcome data, selective reporting, lack of intention-to-treat analyses, small sample sizes, high dropout rates, short follow-up times - systematic literature search may have failed to identify all of the existing trials	living donor, route of nutritional supplementation, or prescribed medication; trials describing the use of parenteral nutrition, enteral nutrition, or nutritional supplements which are compared with placebo, no intervention, or standard care; Comparisons between different types and dosages of nutritional supplements and comparisons between different types of enteral and parenteral nutrition were only considered if comparisons of interventions with an untreated group were not available **Exclusion criteria:** objects of investigation were pharmaceutical drugs; trails including other interventions as exercise , dietary counselling only, synbiotic/prebiotics therapy	
Notes	**Author's Conclusion:** We were unable to identify nutritional interventions for liver transplanted patients that seemed to offer convincing benefits. Further randomized clinical trials with low risk of bias and powerful sample sizes are needed.		
Outcome measures/results	**Primary outcome measures:** Number of infections and other complications, Number of biopsy-proven rejection episodes, Patient and graft survival time after transplantation, Mortality, Length of Hospitalization after transplantation including rehospitalization **Secondary outcome measures:** Acceptability of nutritional intervention, Side effects of nutritional support, Costs, Health-related quality of life, Adverse events.	Thirteen trials met the inclusion criteria. Four publications did not report outcomes pre-defined in the review protocol, or other clinically relevant outcomes and additional data could not be obtained. Nine trials could provide data for the review. Most of the 13 included trials were small and at high risk of bias. Meta-analyses were not possible due to clinical heterogeneity of the interventions. No interventions that were likely to be beneficial were identified. For interventions of unknown effectiveness, postoperative enteral nutrition compared with postoperative parenteral nutrition seemed to have no beneficial or harmful effects on clinical outcomes. Parenteral nutrition containing protein, fat, carbohydrates, and branched-chain amino acids with or without alanyl-glutamine seemed to have no beneficial effect on the outcomes of one- and three-years survival when	

		compared with a solution of 5% dextrose and normal saline. Enteral immunonutrition with Supportan® seemed to have no effect on occurrence of immunological rejection when compared with enteral nutrition with Fresubin. There is weak evidence that, compared with standard dietary advice, adding a nutritional supplement to usual diet for patients during the waiting time for liver transplantation had an effect on clinical outcomes after liver transplantation. The combination of enteral nutrition plus parenteral nutrition plus glutamine-dipeptide seemed to be beneficial in reducing length of hospital stay after liver transplantation compared with standard parenteral nutrition (mean difference (MD) -12.20 days; 95% CI -20.20 to -4.00). There is weak evidence that the use of parenteral nutrition plus branched-chain amino acids had an effect on clinical outcomes compared with standard parenteral nutrition, but each was beneficial in reducing length of stay in intensive care unit compared to a standard glucose solution (MD -2.40; 95% CI -4.29 to -0.51 and MD -2.20 days; 95% CI -3.79 to -0.61). There is weak evidence that adding omega-3 fish oil to parenteral nutrition reduced the length of hospital stay after liver transplantation (mean difference -7.1 days; 95% CI -13.02 to -1.18) and the length of stay in intensive care unit after liver transplantation (MD -1.9 days; 95% CI -1.9 to -0.22).For interventions unlikely to be beneficial, there is a significant increased risk in acute rejections in malnourished patients with a history of encephalopathy and treated with the nutritional supplement Ensure® compared with usual diet only (MD 0.70 events per patient; 95% CI 0.08 to 1.32).

2. Reilly J, Mehta R, Teperman L, Cemaj S, Tzakis A, Yanaga K, Ritter P, Rezak A, Makowka L Nutritional support after liver transplantation: a randomized prospective study. JPEN J Parenter Enteral Nutr 1990; 14:386-391.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries:** n/a **Centers:** University of Pittburgh **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** n/a	**Total no. patients**: n= 30 • Group 1 (no nutritional support) n= 10 • Group 2 (standard TPN) n= 10 • Group 3 (TPN supplemented with BCAA) n= 10	Group 1 -no specific nutritional therapy, standard isotonic intravenous glucose solution as dictated by their clinical hydration status Group 2 -standard parenteral nutrition (TPN) supplying non-protein caloric intake at 35kcal/kg/day and 1,5g/kg/day of protein; dextrose was limited to 5mg/kg/min; the balance of energy intake was administered as intravenous fat emulsion; crystalline amino acids (5%) in the standard formulation were administered in a 25% dextrose solution

		Inclusion criteria: patients undergoing liver transplantation **Exclusion criteria:** n/a	Group 3 -isocaloric, isonitrogenous TPN supplemented with a branched-chain amino acid (BCAA)-enriched formula (3,5% amino acid base solution identical to that of group 2 to achieve a final protein concentration of 5%, total protein intake was 1,5g/kg/day); Nutritional support started on postoperative day 1 for 7 days(once hemodynamic stability was achieved) with one-half of the total estimated nutritional regimen. From day 2 to 7 full nutritional regimen was given. Clear liquid diet was allowed in all groups.
Notes	All patients were hypoalbuminemic prior to the transplant (mean serum albumin 2,52 ± 0,39g %). **Author's Conclusion:** Nutritional support may improve respiratory muscle function, allowing earlier weaning from ventilatory support. A shortened length of ICU stay justifies the expense of TPN.		
Outcome measures/results	Standard liver function tests, electrolytes, glucose, calcium, phosphorus, magnesium, plasma amino acids, nitrogen balance, presence of encephalopathy, intubated days, Days in ICU, length of hospital stay, hospital costs		Jaundice resolution was unaffected by nutritional support. Nitrogen balance favored both TPN groups. Branched-chain amino acid (BCAA) aromatic amino acid ratios were highest in group 3. Coma scores and serum ammonia levels were similar in all groups. Both TPN groups achieved respirator independence earlier; this difference was not statistically significant. Group 1 patients stayed longest in ICU; the difference was statistically significant. TPN with either standard or BCAA- enriched amino acids is tolerated well immediately after successful liver transplant. Positive nitrogen balance is achieved; large protein loads do not worsen encephalopathy.

3. Wicks C, Somasundaram S, Bjarnason I, Menzies IS, Routley D, Potter D, Tan KC, Williams R Comparison of enteral feeding and total parenteral nutrition after liver transplantation. Lancet 1994; 344:837-840.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** n/a	**Total no. patients**: n= 24 • TPN group n= 10 • Enteral nutrition group n= 14 **Inclusion criteria:** patients undergoing primary orthotopic liver transplantation **Exclusion criteria:** patients requiring gut surgery during	Total parenteral nutrition group -TPN starting within 24h after transplant; formula composition: crystalline L-amino acids Carbohydrate in the form of dextrose, fat emulsion vitamins, and minerals; TPN was stopped if 70% of the estimated requirements were achieved orally Enteral nutrition group -enteral nutrition via nasojejunal access starting within 18 h after transplant;

		transplant-e.g., formation of Roux loop in patients with primary sclerosing cholangitis	formula composition: 1 kcal/mL (4-2kJ/mL), whole protein (4-2 g/100 mL), nutritionally complete, isotonic ; energy distribution: 16,6% protein, 30,8% fat (50% of the fat were medium- chain triglyceride, the remainder long-chain triglycerides) , 52,6% carbohydrates; enteral nutrition was stopped if 70% of the estimated requirements were achieved orally
Notes	**Author's Conclusion:** We conclude that the practical aspects of enteral feeding after liver transplantation are surmountable and that enteral feeding is as effective at maintaining nutritional status as total parenteral nutrition, and has potential benefits in terms of reduced complications and costs.		
Outcome measures/results	intestinal absorptive capacity and intestinal permeability before transplant (within 1 month of surgery), and at 14 h, 3 days, and 10 days after transplant; mid-arm circumference, triceps skinfold thickness, biceps skinfold thickness (pretransplant and on days 1, 3, 5, 7, and 10 post-transplant), weight		24 patients were studied: 14 received enteral feeding and 10 total parenteral nutrition. A double-lumen enteral tube was used to deliver the feed directly into the jejunum with the second lumen of the tube being used for gastric aspiration. Enteral feeding was started post-operatively within 18h, was well-tolerated, and of comparable efficacy to total parenteral nutrition. The median number of days for patients to start eating (4) and to achieve 70% of estimated requirements orally (5) did not differ significantly between the two groups. Mid-arm circumference, triceps skinfold thickness, and biceps skinfold thickness were, by comparison with pre-operative values, maintained on the tenth postoperative day in both groups. Early postoperative absorptive capacity, as assessed by a combined carbohydrate test, was reduced significantly in both groups but insufficiently to be of nutritional concern. Intestinal mucosal integrity, as assessed by an intestinal permeability test, was maintained throughout.

4. Hasse JM, Blue LS, Liepa GU, Goldstein RM, Jennings LW, Mor E, Husberg BS, Levy MF, Gonwa TA, Klintmalm GB Early enteral nutrition support in patients undergoing liver transplantation. JPEN J Parenter Enteral Nutr 1995; 19:437-443.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1-	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** Dietitians in Nutrition Support Practice Group	**Total no. patients**: n= 50 • Tube feeding group n= 14 • Control group n= 17 **Inclusion criteria:** patients undergoing liver transplantation	control group - conventional IV electrolyte solutions as determined by hydration status until oral diets were initiated tube feeding (TF) group -postoperative enteral nutrition via nasojejunal (NJ) feeding tube starting 12h after surgery until at least 66% of the nutritional needs could be achieved by oral intake

	Member Research Award, Elan Pharma, Dallas Transplant Surgeons Associates **Dropout rates:** n= 19 (38%) **Study limitations:** n/a	**Exclusion criteria:** patients requiring dialysis or if a choleochojejunostomy was performed at the time of transplant	
Notes	**Author's Conclusion:** Early posttransplant tube feeding was tolerated and promoted improvements in some outcomes and should be considered for all liver transplant patients.		
Outcome measures/results	calculated calorie and protein intakes of the 12 days posttransplant; Resting energy expenditure (REE), respiratory quotient (RQ), urinary urea nitrogen (UUN, nitrogen balance, grip strength (postoperative days 2,4,7, and 12); septic complications, rejection episodes, number of hours on the ventilator, length of ICU stay, length of hospital stay, rehospitalizations, overall cost during the first 21 days after liver surgery	Tube feeding was tolerated in the TF group (n= 14). The TF patients had greater cumulative 12-day nutrient intakes (22,464 ± 3554 kcal, 927 ± 122g protein) than did the control patients (15,474 ± 5265, 637 ± 248g protein) ($p < .002$). Nitrogen balance was better in the TF group on posttransplant day 4 than in the control group ($p < .03$). There was a rise in the overall mean resting energy expenditure in the first two posttransplant weeks from 1487 ± 228 to 1990 ± 367 kcal ($p = .0002$). Viral infections occurred in 17,7% of control patients compared with 0% of TF patients ($p = .05$). Although other infections tended to occur more frequently in the control group vs the TF group (bacterial, 29,4% vs 14,3%; overall infections, 47,1% vs 21,4%), these differences were not statistically significant. Early posttransplant tube feeding did not influence hospitalization costs, hours on the ventilator, lengths of stay in the intensive care unit and hospital, rehospitalizations, or rejection during the first 21 posttransplant days.	

5. Delafosse B, Viale JP, Pachiaudi C, Normand S, Goudable J, Bouffard Y, Annat G, Bertrand O Long- and medium-chain triglycerides during parenteral nutrition in critically ill patients. Am J Physiol 1997; 272:E550-555.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Prospective, randomized, cross-over trial 1+	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates: Study limitations:**	**Total no. patients**: n= 20 • Esophageal carcinoma resection n= 12 • Orthotopic liver transplantation n= 8 **Inclusion criteria:** n/a **Exclusion criteria:** patients suffering from diabetes, sepsis,	Orthotopic liver transplantation patients -parenteral nutrition containing a total caloric intake of 1,0 of the measured resting energy expenditure (MREE); Nitrogen intake represented 17,2% of total intake, Nonprotein caloric intake provided 70%glucose-30% lipid Esophageal carcinoma resection patients -parenteral nutrition containing a total caloric intake of 1.5 of the MREE; Nitrogen intake represented 17,2% of total intake, Nonprotein caloric intake 50% glucose-50% lipid

		renal insufficiency, or major hepatic dysfunction	Patients in both groups randomly received lipids either as a Long-chain triglyceride (LCT) or a Medium-chain triglycerides – long chain triglycerides (MCT-LCT; 50-50%) emulsion for 24 hours.
Notes	**Author's Conclusion:** In conclusion, in critically ill patients experiencing hyperglycemia and hyperinsulinemia, shifting a part of 24- LCT administration to MCT did not modify lipid or glucose oxidation rate or the nitrogen balance.		
Outcome measures/results	Oxygen consumption (VO_2); carbon dioxide elimination (VCO_2); respiratory quotient; nitrogen excretion; contraction of blood glucose, free fatty acid, ketone bodies, Plasma insulin and [^{13}C]glucose		The metabolic measurements were performed simultaneously by two methods, namely indirect calorimetry and isotopic methods based on natural abundance of nutrients. Although both groups of patients were hyperglycemic and hyperinsulinemic, the measured carbohydrate and lipid oxidation rates were not different with whatever type of lipid was administered. The MCT-LCT emulsions did not offer clear-cut advantages over LCT emulsions in critically ill patients when lipid energetic fate was considered.

6. Rayes N, Seehofer D, Hansen S, Boucsein K, Muller AR, Serke S, Bengmark S, Neuhaus P Early enteral supply of lactobacillus and fiber versus selective bowel decontamination: a controlled trial in liver transplant recipients. Transplantation 2002; 74:123-127.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries:** n/a **Centers:** Samsung Medical Center **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n=10 (9,5%) **Study limitations:** n/a	**Total no. patients**: n=105 • SBD n=32 • Lactobacillus & fiber n=31 • Placebo n=32 **Inclusion criteria:** adult patients undergoing orthotopic liver transplantation with side-to-side anastomosis of the bile duct **Exclusion criteria:** severe renal insufficiency (creatinine clearance <50 ml/min), intestinal obstruction (ileus), cerebral disorders with danger of aspiration, Roux-en-Y reconstruction of the bile duct	selective bowel decontamination (SBD) group - standard enteral nutrition (starting on second postoperative day on until postoperative day 12) enriched with 5ml of SBD containing 80 mg of tobramycin, 500 mg of amphotericin B, and 100 mg colistin sulfate (orally four times a day for 6 weeks postoperatively) enteral group with Lactobacillus and fibers -supplemented enteral nutrition (15 g/L fiber, divided into 0.6 g/L soluble and 14.4 g/L non-soluble fibers; starting 24 hr. after operation), administration of L plantarum 299 in a dose of 10^9 and oat fiber twice day via feeding tube for the first 12 days placebo - supplemented enteral nutrition (15 g/L fiber, divided into 0.6 g/L soluble and 14.4 g/L non-soluble fibers; starting 24 hr. after operation); administration of heat-killed L plantarum 299 (AB Probi) and oat fiber twice a day

Notes	Patients were stratified using the classification of the American Society of Anesthesiologists (ASA): ASA 1: healthy patient ASA 2: patient with mild, controlled, functionally nonlimiting systemic disease, ASA 3: patient with severe or poorly controlled systemic disease that is functionally limiting, ASA 4: patient with severe systemic disease that is a constant threat to life, ASA 5: moribund patient not expected to survive 24 hr. with or without surgery **Author's Conclusion:** Early enteral nutrition with fiber-containing solutions and living L plantarum 299 was well tolerated. It decreases markedly the rate of postoperative infections both in comparison with inactivated L plantarum 299 and significantly with SBD and a standard enteral nutrition formula. As it is a cheap and feasible alternative to SBD, further studies should evaluate whether this ecoimmunonutrition should be already started while patients are on the waiting list for transplantation.	
Outcome measures/results	Length of hospital stay, length of surgical procedure, length of stay in the intensive care unit, the first day of bowel movement, side effects of enteral and parenteral nutrition, kind and amount of antibiotic treatment	The groups were comparable regarding preoperative American Society of Anesthesiologists classification, Child-Pugh classification of cirrhosis, operative data, and degree of immunosuppression. The patients who received living lactobacilli plus fiber developed significantly fewer bacterial infections (13%) than the patients with SBD (48%). The incidence of infections was 34% in the group with inactivated lactobacilli and fiber. Cholangitis and pneumonia were the leading infections and enterococci the most commonly isolated bacteria. In the living Lactobacillus group, the mean duration of antibiotic therapy, the mean total hospital stay, and the stay on the intensive care unit were also shorter than in the groups with inactivated lactobacilli and fiber as well as with SBD. However, these differences did not reach statistical significance.

7. Rayes N, Seehofer D, Theruvath T, Schiller RA, Langrehr JM, Jonas S, Bengmark S, Neuhaus P Supply of pre- and probiotics reduces bacterial infection rates after liver transplantation--a randomized, double-blind trial. Am J Transplant 5:125-130.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** n/a	**Total no. patients**: n=66 • Intervention group n=33 • Control group n=33 **Inclusion criteria:** patients scheduled for liver transplantation **Exclusion criteria:** *d*ecompensated renal insufficiencies (creatinine clearance <50 mL/min), cerebral disorders	Intervention group: -composition of 10^{10}*Pediacoccus pentosaceus* 5-33:3, *Leuconostoc mesenteroides* 77:), *Lactobacillus paracasei* ssp. paracasei F19 and *L. plantarum* 2362; fibers: 2.5 g of each betaglucan, inulin, pectin and resistant starch, totally 10 g/dose, or 20 g/day twice a day via the feeding tube or orally starting on the day of the operation and continued for the first 14 days after the operation. Control group: - fibers: 2.5 g of each betaglucan, inulin, pectin and resistant starch, totally 10 g/dose, or 20 g/day twice a day via the feeding tube or orally starting on the day of the operation and continued for the first 14 days after the operation

		with danger of aspiration, patients with roux and Y-anastomosis (assumed danger of anastomotic leak due to early enteral nutrition)	Both groups received enteral nutrition with a low-fiber formula starting within the first hour after operation for at least 8 days
Notes	**Author's Conclusion:** Early enteral nutrition supplemented with a mixture of LAB and fibers reduces bacterial infection rates following liver transplantation. Treatment with only fibers led to a low incidence of severe infections.		
Outcome measures/results	**Primary outcome measures:** occurrence of post-operative bacterial infection during the first 30 post-operative days **Secondary outcome measures:** total hospital stay, days on intensive care unit, side effects of enteral nutrition, duration of antibiotic therapy, **non-infectious complications**		The incidence of post-operative bacterial infections was significantly reduced; being 48% with only fibers and 3% with LAB and fibers. In addition, the duration of antibiotic therapy was significantly shorter in the latter group. In both groups, mainly mild or moderate infections occurred. Fibers and LAB were well tolerated.

8. Kim JM, Joh JW, Kim HJ, Kim SH, Rha M, Sinn DH, Choi GS, Kwon CH, Cho YY, Suh JM, Lee SK Early Enteral Feeding After Living Donor Liver Transplantation Prevents Infectious Complications: A Prospective Pilot Study. Medicine (Baltimore) 2015; 94: e1771. [423]			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Pilot study 1+	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** -missing comparison of calorie intake between the two groups -small number of malnourished patients -inadequate selection bias due to the small number of patients -small number of events related to graft or patient	**Total no. patients**: n= 36 • EN group n= 17 • Control group n= 19 **Inclusion criteria:** patients who underwent elective living donor liver transplantation (LDLT) **Exclusion criteria:**	Enteral feeding group -EN via nasogastric tube starting within 12 hours of tube replacement; Enteral feeding was discontinued once a patient could eat more than 50% of the provided regular diet Control group - initiation of intravenous fluid until oral diets

	survival could have obscured the effect of nutritional status on these parameters		
Notes	**Author's Conclusion:** Early enteral feeding after LDLT prevents posttransplant bacterial infection, suggesting the possibility of a reduction of in-hospital mortality as a result of decreased infectious complications.		
Outcome measures/results	**Primary outcome measure:** occurrence of infectious complications **Secondary outcome measures:** length of stay in the hospital, improvement in nutritional status, episodes of acute rejection, bile duct complications, graft failure, mortality (All outcomes were evaluated during the first 3 months after LDLT)	The pretransplant and perioperative characteristics of patients did not differ between the 2 groups. The incidence of bacterial infection was significantly lower in the EN group (29.4%) than in the control group (63.2%) ($P = 0.043$). In addition, the incidence of bile duct complications in the EN group was lower than in the control group (5.9% versus 31.6%, $P = 0.041$). Multivariate analysis showed that early enteral feeding was closely associated with bacterial infections (odds ratio, 0.178; $P = 0.041$). There was no statistically significant difference in nutritional status between the 2 groups. There were no cases of in-hospital mortality.	

9. Lei Q, Wang X, Zheng H, Bi J, Tan S, Li N Perioperative immunonutrition in patients undergoing liver transplantation: a meta-analysis of randomized controlled trials. Asia Pac J Clin Nutr 2015; 24: 583-590.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-analysis 1+	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Dropout rates:** n/a **Study limitations:** -small sample sizes in most of the included trials -lack of blinding (except 1 trials) -possible heterogeneities in the peri-operative care (surgeons with varying technical proficiency were	**Total no. patients**: n= 501 (7 RCTs) **Inclusion criteria:** Patients involved were females or males aged 18 or over, with liver transplantation on enteral or parenteral nutrition therapy; Comparing perioperative immunonutrition support with standard enteral or parenteral nutrition, and immunonutrition supplemented one or more of nutrients including ω-3 FAs, Gln, Arg and RNA; Studies re-porting at least one of the following outcome measures; When some studies	The purpose of this present meta-analysis was to examine the high-level evidence of safety and efficacy in liver transplantation comparing perioperative immunonutrition (including one or more of Arg, Gln, ω-3FAs and RNA) with standard nutrition.

	from different clinical centers) -absence of accurate data about antibiotic treatment which may influence the outcomes, specifically the rate of infectious complications	were reported by the same institution and/or authors, they were selected only if there was no overlap between the results of their researches; RCTs Two of the studies were published in Chinese. **Exclusion criteria:** Reviews and case reports; Non-comparative articles; Studies reporting the same patient cohorts evaluated in the published literature.	
Notes	**Author's Conclusion:** Peri-operative nutrition support adding immunonutrients like glutamine, ω-3 polyunsaturated fatty acids, arginine and ribonucleic acids may improve outcomes in patients undergoing liver transplantation. Due to the limited sample size of the included trials, further large-scale and rigorously designed RCTs are needed.		
Outcome measures/results	infection complication, postoperative hospital stay, 1- year mortality, rejection reaction, liver function (serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB) and direct bilirubin (DB))		A total of 7 randomized controlled trials (RCTs) involving 501 patients were included. Peri-operative immunonutrition significantly reduced the risk of infectious complications (RR: 0.51; 95% CI:0.27 to 0.98, p=0.04) and shortened the postoperative hospital stay [weighted mean difference (WMD):-3.89; 95% CI:-7.42 to -0.36; p=0.03]. Furthermore, peri-operative immunonutrition improved liver function by decreasing the levels of aspartate aminotransferase (AST) in the blood (WMD:-25.4; 95% CI:-39.9 to -10.9, p=0.0006). However, we did not find statistically significant differences in serum alanine aminotransferase (ALT), total bilirubin (TB) and direct bilirubin (DB) levels. There were no statistically significant differences in mortality and rejection reaction.

10. Plank LD, Mathur S, Gane EJ, Peng SL, Gillanders L, McIllroy K, Chavez CP, Calder PC, McCall JL. Perioperative immunonutrition in patients undergoing liver transplantation - a randomized double blind trial. Hepatology 2015; 61: 639-647.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	**Countries:** New Zealand **Centers:** Auckland City Hospital	**Total no. patients**: n= 120 • IMN group n= 52 • CON group n= 49	Immunonutrition group (IMN) -Intake of 74 g sachets per day of an immunonutrition-supplemented, powdered Oral formula until the day of transplant; formula composition: reconstituted with

	Setting: n/a **Funding Sources:** n/a **Dropout rates:** n= 19 (15.8%) **Study limitations:** - Compliance with the supplements was not 100% - Consenting patients were not placed on the supplement as soon as they were listed in most cases since this would have extended considerably the time on supplementation for many patients	**Inclusion criteria:** patients (16 years of age or older) listed for orthotopic liver transplantation (OLT) **Exclusion criteria:** Patients with acute liver failure and patients listed for retransplant	water yields 600 mL (1 kcal/mL) containing 7.5 g arginine, 2 g ω-3 fatty acids, 0.8 g ribonucleic acid Control group (CON) -Intake of equivalent amount of an isocaloric, but not isonitrogenous control product until the day of transplant Enteral IMN or CON was resumed postoperatively (starting as soon as tolerated, usually within 12 hours of surgery at 20 mL/h) and continued for at least 5 days.
Notes	**Author's Conclusion:** In patients undergoing LT, perioperative IMN did not provide significant benefits in terms of preoperative nutritional status or postoperative outcome.		
Outcome measures/results	**Primary outcome measures:** total body protein (TBP) immediately pretransplant **Secondary outcome measures:** pre- and postoperative complications, body composition up to day 360, muscle function		Fifty-two IMN and 49 CON patients received supplemental nutrition for a median (range) 56 (0-480) and 65 (0-348) days, respectively. Preoperative changes in TBP were not significant (IMN: 0.06 ± 0.15 [SEM]; CON: 0.12 ± 0.10 kg). Compared to baseline, a 0.7 ± 0.2 kg loss of TBP was seen in both groups at 30 days after LT ($P < 0.0001$) and, at 360 days, TBP had not increased significantly (IMN: 0.08 ± 0.19 kg; CON: 0.26 ± 0.23 kg). Infectious complications occurred in 31 (60%) IMN and 28 (57%) CON patients ($P = 0.84$). The median (range) postoperative hospital stay was 10 (5-105) days for IMN and 10 (6-27) days for CON patients ($P = 0.68$)

11. Zhu XH, Wu YF, iu YD, Jiang CP, Ding YT Liver protecting effects of omega-3 fish oil lipid emulsion in liver transplantation. World J Gastroenterol 2012; 18: 6141-6147.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 2+	**Countries:** n/a **Centers:** Department of Hepatobiliary Surgery of the Affiliated Drum Tower Hospital of Medical School of Nanjing University	**Total no. patients*:*** n= 66 • PN group n= 33 • PUFA group n= 33 **Inclusion criteria:** patients undergoing orthotopic liver transplantation; age < 50 years,	parenteral nutrition (PN) group -source of lipids: standard lipid emulsion (20% emulsion, with a ratio of long-chain triglycerides to medium-chain triglycerides of 1:1 PUFA group - source of lipids: omega-3 fish oil lipid emulsion Both groups:

	Setting: n/a **Funding Sources:** Jiangsu Provincial Government, China **Dropout rates:** n/a **Study limitations:** n/a	matched ABO blood group and no history of chronic liver disease; no evidence of malignant tumor, viral hepatitis or other viral infections; no cirrhosis, mass or severe fatty degeneration of the donor liver seen during organ harvesting; and liver biopsies of each donor liver taken before transplantation were reviewed by two pathologists. Donor livers with normal pathology or mild fatty change (10%-30%) **Exclusion criteria:** patients with manifest metabolic diseases (e.g., diabetes mellitus and hyperthyroidism) or severe renal abnormality	PN starting on postoperative day 2 for seven days; formula composition: isonitrogenous and isocaloric, Nitrogen intake 0.16 g/kg body weight per day, caloric intake 104.5 kJ/kg per day, nonprotein calories provided with dextrose (4.0 g/kg per day) , 1.0 g amino acid/kg per day (branched-chain amino acid solution), lipid intake 1.0 g/kg per day, fat emulsion ratio of 2:1
Notes	Liver function was tested on days 2 and 9 after surgery. Pathological examination was performed after reperfusion of the donor liver and on day 9. **Author's Conclusion:** Post-transplant parenteral nutritional support combined with omega-3 fatty acids can significantly improve the liver injury, reduce the infectious morbidities, and shorten the post-transplant hospital stay.		
Outcome measures/results	post-transplant mechanical ventilation; total hospital stay; infectious morbidities (pneumonia, intra-abdominal abscess, central line sepsis, wound infection, urinary tract infection); acute and chronic rejection; mortality (intensive care unit mortality, hospital mortality, 28-d mortality, survival at one-year post-transplant surveillance period)	On days 2 and 9 after operation, a significant decrease of alanine aminotransferase (299.16 U/L ± 189.17 U/L *vs* 246.16 U/L ± 175.21 U/L, *P* = 0.024) and prothrombin time (5.64 s ± 2.06 s *vs* 2.54 s ± 1.15 s, *P* = 0.035) was seen in PUFA group compared with PN group. The pathological results showed that omega-3 fatty acid supplement improved the injury of hepatic cells. Compared with PN group, there was a significant decrease of post-transplant hospital stay in PUFA group (18.7 d ± 4.0 d *vs* 20.6 d ± 4.6 d, *P* = 0.041). Complications of infection occurred in 6 cases of PN group (2 cases of pneumonia, 3 cases of intra-abdominal abscess and 1 case of urinary tract infection), and in 3 cases of PUFA group (2 cases of pneumonia and 1 case of intra-abdominal abscess). No acute or chronic rejection and hospital mortality were found in both groups. The one-year mortality in PN group was 9.1% (3/33), one died of pulmonary infection, one died of severe intra-hepatic cholangitis and hepatic dysfunction and the other died of hepatic cell carcinoma recurrence. Only one patient in PUFA group (1/33, 3.1%) died of biliary complication and hepatic dysfunction during follow-up.	

12. Lim AK, Manley KJ, Roberts MA, Fraenkel MB. Fish oil for kidney transplant recipients. Cochrane Database Syst Rev 2016; Aug 18: (8); CD005282 doi: 10. 1002/14651858: CD 005282 pub 3.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic review 1++	**Countries:** n/a **Centers:** n/a **Setting:** n/a **Funding Sources:** n/a **Study limitations:** - poor or average quality due to small patient numbers, inadequate randomization or allocation concealment, and lack of blinding - Some data from one group publishing several studies were expressed in a way that could not be incorporated in the analysis - several potential sources of heterogeneity, including differing doses of fish oils, duration of treatment, timing of initiation of treatment - differences between cyclosporin A (CSA) and tacrolimus could not be examined (majority of studies were conducted in the early to mid-1990s, prior to the common use of tacrolimus)	*Total no. patient:* n= 733 (15 RCTs) **Inclusion criteria:** All randomized controlled trials (RCTs) and quasi-RCTs of fish oils in kidney transplant recipients on a calcineurin inhibitor-based immunosuppressive regimen; first period of randomized cross-over studies; All recipients of cadaveric or living kidney transplants on a CNI based immunosuppressive protocol; types of interventions; Fish oil versus control oil, Fish oil versus statin; Early versus late introduction (> three months); Short-course versus long-course (> three months); Types of outcome measures: Patient survival/death: yes/no, Graft failure, defined as creatinine clearance (CrCl)/GFR <15 mL/min OR dialysis: yes/no, Acute rejection (biopsy proven) present: yes/no, CNI toxicity (biopsy proven) present: yes/no, Cardiovascular events (stroke, myocardial infarction and cardiovascular death): yes/no, Adverse effects (gastrointestinal upset, taste, breath): yes/no, Compliance (percentage drop-out rate during study period)and satisfaction	This review aimed to look at the benefits and harms of fish oil treatment in ameliorating the kidney and cardiovascular adverse effects of CNI-based immunosuppressive therapy in kidney transplant recipients.

		(quality of life assessment by standard validated method e.g. the SF-36), Kidney function (GFR, CrCl, serum creatinine (SCr)), Blood pressure (systolic, diastolic, mean arterial pressure (MAP)), Serum lipid levels (total cholesterol, LDL, HDL, triglycerides) **Exclusion criteria:** patients with CNI-free transplant immunosuppression protocol; Multi-organ combined transplants, e.g. liver-kidney, pancreas-kidney;	
Notes	**Author's Conclusion:** There is insufficient evidence from currently available RCTs to recommend fish oil therapy to improve kidney function, rejection rates, patient survival or graft survival. The improvements in HDL cholesterol and diastolic blood pressure were too modest to recommend routine use. To determine a benefit in clinical outcomes, future RCTs will need to be adequately powered with these outcomes in mind.		
Outcome measures/results	All-cause mortality, graft loss, acute rejection, calcineurin inhibitor toxicity and Calcineurin inhibitor levels, Cardiovascular events, rates of adverse effects, kidney function (GFR, CrCl, serum creatinine (SCr))); Blood pressure (systolic, diastolic, mean arterial pressure (MAP)), serum lipid levels (total cholesterol, LDL, HDL, triglycerides), compliance	Fifteen studies (733 patients) were suitable for analysis. All studies were small and had variable methodology. Fish oil did not significantly affect patient or graft survival, acute rejection rates, or calcineurin inhibitor toxicity when compared to placebo. Overall SCr was significantly lower in the fish oil group compared to placebo (5 studies, 237 participants: MD -30.63 µmol/L, 95% CI -59.74 to -1.53; I^2 = 88%). In the subgroup analysis, this was only significant in the long-course (six months or more) group (4 studies, 157 participants: MD -37.41 µmol/L, 95% CI -69.89 to -4.94; I^2 = 82%). Fish oil treatment was associated with a lower diastolic blood pressure (4 studies, 200 participants: MD -4.53 mm Hg, 95% CI -7.60 to -1.45) compared to placebo. Patients receiving fish oil for more than six months had a modest increase in HDL (5 studies, 178 participants: MD 0.12 mmol/L, 95% CI 0.03 to 0.21; I^2 = 47%) compared to placebo. Fish oil effects on lipids were not significantly different from low-dose statins. There was insufficient data to analyze cardiovascular outcomes. Fishy aftertaste and gastrointestinal upset were common but did not result in significant patient drop-out.

13.	Ribeiro HS, Coury NC, de Vasconcelos Generoso S et al. Energy Balance and Nutrition Status: A Prospective Assessment of Patients Undergoing Liver Transplantation. Nutr Clin Pract 2020; 35: 126-132. doi:10.1002/ncp.10323		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Prospective observational study 2- NOS 6/9	**Countries:** Brazil **Centers:** n/a **Setting:** n/a **Funding Sources:** FAPEMIG (APQ-01582-14; APQ-02216-14) and CNPq **Dropout rates:** n/a **Study limitations:** Risk of Bias: moderate Inconsistency: n/a Indirectness: moderate Impreciseness: high Publication bias: n/a energy balance is based on dietary surveys, suboptimal method for TEE analysis, wide preoperative assessment time variation, small number of patients	**Total no. Patients:** 29 **Inclusion criteria:** > 20 years old undergoing LTx, according to the adopted criteria in the country, who were under regular follow-up at a liver transplantation clinic **Exclusion criteria:** patients with dual transplant, retransplantation, or fulminant hepatitis as the indication for transplantation	patients undergoing liver transplantation (LTx), who were assessed before and after the operation
Notes	**Author's Conclusion:** Negative EB was overwhelmingly present throughout the perioperative LTx period. Low food consumption and high prevalence of malnutrition suggest the importance of individualized nutrition interventions, including dietary intake assessment and nutrition therapy both before and after LTx in order to avoid poor clinical outcomes and nutrition status deterioration as indicated. Finally, SPA might be useful in detecting and monitoring the nutrition status of these patients for whom commonly used parameters are influenced by water retention.		
Outcome measures/results	resting energy expenditure (REE), total energy expenditure (TEE), dietary intake, and energy balance, anthropometry, handgrip strength, and standard phase angle (SPA)		- REE and TEE were not different in the pretransplant and posttransplant phases - energy and protein intake (in grams) was significantly decreased in relation to the pretransplant phase, in the first postoperative assessment ($P < 0.05$) - EB in the pretransplant and posttransplant periods was similar ($P > 0.05$), and the majority of the patients presented with negative EB, inadequate energy intake compared with the requirements (71.4% pretransplant and 77.8% posttransplant)

		- prevalence of malnutrition ranged from 17.2% to 57.7% (according to MAC and SPA, respectively) in the pretransplant phase and 30.8% to 86.4% (according to TSF and SPA, respectively) in the post transplantation

8.2 Wann ist eine künstliche Ernährung nach Organtransplantation indiziert?

<u>Empfehlung 33</u>

Nach Organtransplantationen sollte ein früher oraler Kostaufbau bzw. eine enterale Ernährung gemäß individueller Toleranz innerhalb von 24 Stunden erfolgen. (BM)

Empfehlungsgrad B – Starker Konsens 100 % Zustimmung

<u>Empfehlung 34</u>

Nach Dünndarmtransplantationen kann frühzeitig mit der oralen/enteralen Zufuhr begonnen werden, wobei innerhalb der ersten Woche auf eine vorsichtige Steigerung zu achten ist. (BM)

Empfehlungsgrad 0 – Starker Konsens 100 % Zustimmung

<u>Empfehlung 35</u>

Wenn vor oder nach Organtransplantation die enterale Ernährung nicht ausreicht, sollte eine supplementierende parenterale Ernährung erfolgen. (BM)

Empfehlungsgrad B – Starker Konsens 100 % Zustimmung

14.	**European Association for the Study of the Liver. EASL Clinical Practice Guidelines on nutrition in chronic liver disease. J Hepatol 2019; 70: 172-193. doi:10.1016/j.jhep.2018.06.024**
Guideline **Relevant recommendations/ statements**	- After liver transplantation initiate normal food and/or enteral tube feeding preferably within 12–24 hours postoperatively, or as soon as possible, to reduce infection rates. (Grade II-2, B1) - When oral or enteral nutrition are not possible or impracticable, prefer parenteral nutrition to no feeding in order to reduce complication rates and time on mechanical ventilation and ICU stay. (Grade II-2, B1) - Consider PN in patients with unprotected airways and hepatic encephalopathy (HE) when cough and swallow reflexes are compromised, or enteral nutrition is contraindicated or impractical. (Grade II-2, C1) - Utilize enteral tube feeding and/or PN with a reduced target energy intake (25 kcal/kg.BW/d) and an increased target protein intake (2.0 g/kg.BW/d) in obese patients. (Grade III, C2)

9. Besondere Aspekte in der Kinderchirurgie

Empfehlung 37

Ein frühzeitiger postoperativer oraler Kostaufbau kann bei Kindern und Jugendlichen erfolgen. (BM, QL)

Empfehlungsgrad 0 – Starker Konsens 100 % Zustimmung

1. Peng Y, Xiao D, Xiao S et al. Early enteral feeding versus traditional feeding in neonatal congenital gastrointestinal malformation undergoing intestinal anastomosis: A randomized multicenter controlled trial of an enhanced recovery after surgery (ERAS) component. J Pediatr Surg 2021; 56: 1479-1484. doi:10.1016/j.jpedsurg.2021.02.067			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+ ROB 12/14	**Countries:** China **Centers:** n/a **Setting:** newborns with congenital malformation **Funding Sources: n/a** **Dropout rates:** 0% **Study limitations:** Risk of Bias: moderate Inconsistency: n/a Indirectness: low Impreciseness: moderate Publication bias: n/a Firstly, the study included various congenital gastrointestinal malformation with a diverse range of pathologies and operation technique which might lead to lack of specificity to a single disease. Secondly, thought the staffs involved in the operation were blind to the allocation, it was not possible to blind the	**Total no. patients:** 156 **Inclusion criteria**: intestinal anastomosis because of gastrointestinal malformation, birth weight greater than 1500 g, gestational age greater than 32 weeks **Exclusion criteria:** preoperative septic shock, intestinal perforations, chromosomal malformation, parents' refusal to sign the written informed consent form	Early enteral feeding (EEN, n = 78) vs. control (C, n = 78)

	assessment of outcome which might lead to bias. Finally, nutritional and growth data on long-term follow-up were lacking.		
Notes	**Author's Conclusion:** In conclusion, early enteral feeding following intestinal anastomosis in neonates with congenital gastrointestinal malformation is safe. Post-operative outcomes demonstrated a trend to- ward improvement thought these improvements did not reach statistical significance. More randomized controlled trials are required to assess the true impact on early enteral feeding following intestinal in neonates congenital gastrointestinal malformation.		
Outcome measures/results	Primary outcomes: length of postoperative stay, time to full feeds Secondary outcomes: morbidity of complications, parenteral nutrition duration, feeding intolerance, 30 day mortality rate, 30 day readmission rate		The average time to first enteral feed (postoperative days) in the EEN group was 2.0 (1.0–2.0) days and was 6.0 (4.0–14.0) days in the C group; the difference was statistically significant ($p < 0.05$). The mean time to full feeds and : length of postoperative stay in the EEN group were 15.0 (9.8–22.8) days and 17.6 (12.0–29.8) days, while that were 18.0 (12.0–24.0) days and 20.0 (15.0–30.3) days in C groups respectively. There were no significant difference in time to full feeds and length of postoperative stay between two groups ($P > 0.05$). No significant intergroup difference was found with respect to postoperative morbidity, including anastomotic leakage, peritonitis, gastrointestinal hemorrhage, postoperative neonatal necrotizing enterocolitis and sepsis. The weight for age Z score at discharge in both two groups were lower than that at operation, however there was no statistically significant difference between the two groups. During postoperative follow-up, abdominal distention was the most common observation, followed by repeated vomiting. However, there was no significant difference in the incidence of abdominal distension (35.9 vs 23.1%, $P > 0.05$) or repeated vomiting (30.0 vs 23.1%, $P > 0.05$) between the two groups. There were no statistically significant differences in the incidence of re- peated decompressive nasogastric tube (21.8 vs. 21.1%, $P > 0.05$) or repeated nil per os (25.6 vs. 32.9%, $P > 0.05$) because of feeding intolerance be- tween the two groups.

2. Tian Y, Zhu H, Gulack BC et al. Early enteral feeding after intestinal anastomosis in children: a systematic review and meta-analysis of randomized controlled trials. Pediatr Surg Int 2021; 37: 403-410. doi:10.1007/s00383-02004830-w			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic Review 1+	**Countries:** n/a **Centers:** n/a	**Total no. patients:** 186 patients (4 studies)	EEF (n = 97) vs. DEF (n = 89)

AMSTAR II 10/16	**Setting:** children undergoing intestinal surgery **Funding Sources:** Canadian Institutes of Health Research (CHIR) Foundation Grant (353857). **Dropout rates:** n/a **Study limitations:** Risk of bias of single studies: moderate Inconsistency: moderate Indirectness: low Impreciseness: moderate Publication bias: n/a The findings of this review are limited by the quantity of included studies and patients, as there were only four included RCTs and had an overall moderate risk of bias. In particular, as there is only one neonatal RCT, it is inappropriate to perform subgroup analysis based on patients' ages in more detail. The diversity in the studied populations, ranging from premature neonates to adolescents, also makes generalizability difficult.	**Inclusion criteria**: main focus early enteral feeding (EEF) and delayed enteral feeding (DEF) in pediatric patients aged 0–18 years undergoing intestinal anastomosis operations for different etiologies **Exclusion criteria:** languages other than English, publication before 2000, animal studies, patients older, than 18 years, studies combining children and adults without differentiation of results according to age groups, retrospective studies, case reports and review articles	
Notes	**Author's Conclusion:** Across the pediatric gastrointestinal surgery spectrum, early enteral feeding after intestinal anastomosis in children does not increase the risk of postoperative anastomotic leak, fever, emesis, and abdominal distention. However, early enteral feeding is beneficial and safe as it promotes return of bowel function, reduces the length of hospital stay and reduces the incidence of surgical infection in comparison to delayed enteral feeding.		

Outcome measures/results	Primary outcome: postoperative anastomotic leak Secondary outcomes: fever, vomiting, abdominal distention, surgical infection, length of hospital stay, time to bowel movement return, time to full enteral feeding	The pooled results indicated no evidence of a significant difference in the number of anastomotic leaks between the two groups (OR = 0.86; 95% CI 0.17–4.46; p = 0.86). There was no heterogeneity among the studies (p = 0.90, I^2 = 0%). The pooled incidence of fever was similar between both groups based on a fixed effects model analysis (OR = 0.37; 95% CI 0.10–1.31; p = 0.12), and there was no heterogeneity between the two studies (p = 0.98, I^2 = 0%). There were no differences regarding vomiting between the two groups. The incidence of abdominal distension showed no difference among three studies (OR = 0.63; 95% CI 0.13–3.16; p = 0.58). There was a lower incidence of surgical infections in the EEF group (OR = 0.27; 95% CI 0.08–0.90; p = 0.03) and no heterogeneity among studies (p = 0.86, I^2 = 0%). The pooled results showed a statistically significant decrease in LOS in the EEN group (MD = − 3.38; 95% CI − 4.29 to − 2.48; p < 0.00001). Time to first stool was significantly shorter in the EEF group than the DEF group after anastomosis surgery (MD = − 0.57; 95% CI − 0.79 to − 0.35; p < 0.00001).

3. Chen X, Zhang M, Song Y et al. Early high-energy feeding in infants following cardiac surgery: a randomized controlled trial. Translational Pediatrics 2021; 10: 2439-2448. doi:10.21037/tp-21-360			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1- ROB 9/12	**Countries:** China **Centers:** Tertiary pediatric cardiology center **Setting:** open heart surgery in infants **Funding Sources:** Key Subject Program for Clinical Nutrition from Shanghai Municipal Health Commission for Li HONG (No. 2019ZB0103) **Dropout rates:** 0% **Study limitations:** Risk of Bias: moderate Inconsistency: n/a Indirectness: low Impreciseness: moderate	**Total no. patients:** 244 **Inclusion criteria**: age less than 6 months, undergoing surgery for congenital heart disease (CHD), moderate or severe malnutrition according to World Health Organization (WHO) standards **Exclusion criteria:** genetic diseases, no or mild malnutrition, no consent provided by the guardians	Intervention group: Postoperative early high-energy feeding; n=124 vs. Control group: no intervention; n=120

	Publication bias: n/a The intervention was only implemented during hospitalization. Thus, growth in the follow-up period was affected by a number of factors		
Notes	**Author's Conclusion:** Early high-energy feeding is associated with improved growth, shorter cardiac ICU stay, decreased ventilator support time, and reduced infection during the early postoperative period in infants who have undergone congenital heart surgery.		
Outcome measures/results	Primary outcome: energy delivery and Z-scores (weight-for-height (WHZ), weight-for-age (WAZ), height-for-age (HAZ)) Secondary outcomes: malnutrition recovery, ventilator support time, infection rate, and cardiac ICU stay length		The initial feeding time of the intervention group was earlier than that of the control group (12 vs. 22 h; P<0.001). Additionally, the actual daily energy delivery of the intervention group was higher than that of the control group (44.5±10.7 vs. 34.7±9.5 kcal/kg; P<0.001). However, the difference in the accumulated liquid volume between the 2 groups was not statistically significant (P=0.285). Infants in the intervention group had a higher WHZ (−2.29 vs. −2.76; P<0.001) and WAZ (−3.08 vs. −3.43; P=0.005) than those of the control group. However, the difference in the HAZs (−1.92 vs. −1.96; P=0.446) between the 2 groups was not statistically significant. With median recovery times of 93 and 91 days, respectively, the intervention group exhibited a higher incidence of recovery from malnutrition than the control group (P=0.015). The difference in the postoperative nutrient recovery rates at 1 month (7.3% vs. 0.2%; P=0.003) and 3 months (19.4% vs. 6.5%; P=0.002) was statistically significant. Differences in the ventilator support times (25.7 vs. 31.6 h; P=0.116), length of hospital stay (17 vs. 20 days; P=0.233) and length of CICU stay (7 vs. 8 days; P=0.503) between the 2 groups was not statistically significant.

4. Fivez T, Kerklaan D, Mesotten D et al. Early versus Late Parenteral Nutrition in Critically Ill Children. N Engl J Med 2016; 374: 1111-1122. doi:10.1056/nejmoa1514762			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+ ROB 12/14	**Countries:** The Netherlands **Centers:** Multicentric **Setting:** pediatric intensive care unit **Funding Sources:** Grant from the Flemish Agency for Innovation through Science	**Total no. patients:** 1,440 **Inclusion criteria**: children (from term newborns to children 17 years of age) who were admitted to one of the participating pediatric ICUs were eligible for inclusion if a stay of 24 hours or more in the ICU	withholding parenteral nutrition for 1 week (late parenteral nutrition, n = 717) vs. early parenteral nutrition (initiation within 24 hours after ICU admission, n = 723)

	and Technology and other non-industrial funding sources **Dropout rates:** 0% **Study limitations:** Risk of Bias: low Inconsistency: n/a Indirectness: high Impreciseness: low Publication bias: n/a A limitation of this study is that the patients, their parents, and the staff providing intensive care were aware of the treatment assignments.	was expected, if they had a score on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) of 2 or more (with a score of 0 indicating low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk) **Exclusion criteria:** Not critically ill enough to necessitate nutritional support, STRONGkids score lower than 2 on pediatric ICU admission, non-pediatric patients (aged 17 or older), premature newborns (<37 weeks gestational age upon admission in the pediatric ICU), 'Do not resuscitate' code at the time of pediatric ICU admission, Expected death within 12 hours, readmission to pediatric ICU after already having been randomized, enrollment in another intervention trial, transfer from another PICU or neonatal ICU after a stay of more than 7 days, ketoacidotic or hyperosmolar coma, inborn metabolic diseases requiring specific diet, short bowel syndrome or other conditions requiring PN for more than 7 days prior to pediatric ICU admission	
Notes	**Author's Conclusion:** In conclusion, in critically ill children, withholding parenteral nutrition for 1 week while administering micronutrients intravenously was clinically superior to providing early parenteral nutrition to supplement insufficient enteral nutrition.		
Outcome measures/results	Primary outcomes: new infection acquired during the ICU stay and the adjusted duration of ICU dependency, as assessed by the number of days in the ICU and as time to discharge alive from ICU	The rate of acquisition of a new infection was 7.8 percentage points lower (95% confidence interval [CI], 4.2 to 11.4) among children receiving late parenteral nutrition than among children receiving early parenteral nutrition (adjusted odds	

	Secondary safety outcomes: death during the first 7 days in the pediatric ICU, during the total stay in the pediatric ICU, during the stay in the index hospital, and at 90 days after admission to the pediatric ICU and randomization; the number of patients with hypoglycemia (glucose level <40 mg per deciliter [2.2 mmol per liter]); and the number of readmissions to the pediatric ICU within 48 hours after discharge Secondary efficacy outcomes: time to final (live) weaning from mechanical ventilatory support, the duration of pharmacologic or mechanical hemodynamic support, the proportion of patients receiving renal replacement therapy, markers of liver dysfunction and inflammation, and the time to (live) discharge from the hospital	ratio, 0.48; 95% CI, 0.35 to 0.66). Late parenteral nutrition was also associated with a shorter stay in the pediatric ICU by a mean of 2.7 days (95% CI, 1.3 to 4.3), with a higher likelihood of an earlier discharge alive from the pediatric ICU at any time (adjusted hazard ratio, 1.23; 95% CI, 1.11 o 1.37). Mortality was similar in the two groups at all prespecified time points. The percentage of patients with an episode of hypoglycemia (glucose level <40 mg per deciliter) was higher in the group receiving late parenteral nutrition than in the group receiving early parenteral nutrition. Rates of readmission to the pediatric ICU within 48 hours after discharge and of the occurrence of serious adverse events were similar in the two study groups. The duration of mechanical ventilatory support was shorter and the likelihood of being weaned alive earlier from mechanical ventilation was higher among patients receiving late parenteral nutrition than among those receiving early parenteral nutrition whereas there was no significant between-group difference in the duration of hemodynamic support. The peak plasma total bilirubin levels were higher in the late-parenteral-nutrition group than in the early-parenteral-nutrition group during the first 7 days in the pediatric ICU and during the duration of the pediatric ICU stay, whereas the peak plasma γ-glutamyltransferase and alkaline phosphatase levels were higher with early parenteral nutrition. Although there were fewer new infections with late parenteral nutrition than with early parenteral nutrition, the peak plasma levels of C-reactive protein were higher with late parenteral nutrition during the first 7 days in the pediatric ICU. The mean duration of stay in the index hospital was 4.1 days shorter (95% CI, 1.4 to 6.6), and the likelihood of an earlier discharge alive from the hospital was higher (adjusted hazard ratio, 1.19; 95% CI, 1.07 to 1.33) in the late parenteral-nutrition group than in the early parenteral-nutrition group

10. Besonderheiten in der Wundheilung

10.1 Wird eine Supplementierung bei Wundheilungsstörungen und chronischen Wunden empfohlen?

Empfehlung 38

Bei chronischen Wunden sollte frühzeitig eine orale / enterale eiweißreiche Ernährung ggfs. mit Substitution von Spurenelementen verabreicht werden. (BM)

Empfehlungsgrad B – Starker Konsens 100 % Zustimmung

1. Cereda E, Gini A, Pedrolli C et al. Disease-specific, versus standard, nutritional support for the treatment of pressure ulcers in institutionalized older adults: a randomized controlled trial. J Am Geriatr Soc 2009; 57: 1395-1402. doi:10.1111/j.1532-5415.2009.02351.x								
level of evidence	**Study design**	**Intervention**		**Participants**	**Eligibility criteria**	**Outcome**	**Results**	**Rating**
		Type	**Period**					
Ib	randomized controlled trial	Two arms: – Study-group: 30 kcal/kg disease-specific nutrition treatment consisting of the standard diet plus a 400-mL oral supplement or specific enteral formula enriched with protein (20% of the total calories), arginine, zinc, and vitamin C (p<0.001 for all nutrients vs. control). – Control-group: 30 kcal/kg per day standard nutrition (hospital diet or standard enteral formula; 16% calories from protein),	12-week follow-up	Total n=28 – Study-group: n=13 – Control-group: n=15	Eligible: Residents of long-term care aged 65 and older, patients with Stage II, III, or IV lesions as assessed according to the revised (2007) National Pressure Ulcer Advisory Panel staging system. Exclusion: cute illness (e.g. infection) or chronic disease (e.g. diabetes mellitus, peripheral vascular disease, autoimmune or neoplastic disorders)	To investigate whether a disease-specific nutritional approach is more beneficial than a standard dietary approach to the healing of pressure ulcers (PUs) in institutionalized elderly patients.	both groups showed significant improvement (p<0.001). The treatment produced a higher rate of healing, the PUSH score revealing a significant difference at week 12 (-6.1±2.7 vs. -3.3±2.4; p<0.05) and the reduction in ulcer surface area is significantly higher in the treated patients already by week 8 (-1,140.9±669.2 mm^2 vs. -571.7±391.3 mm^2; p<0.05 and ~57% vs. ~33%; p< 0.02).	+

2. Theilla M, Singer P, Cohen J et al. A diet enriched in eicosapentanoic acid, gamma-linolenic acid and antioxidants in the prevention of new pressure ulcer formation in critically ill patients with acute lung injury: A randomized, prospective, controlled study. Clin Nutr 2007; 26: 752-757. doi:10.1016/j.clnu.2007.06.015								
level of evidence	Study design	Intervention		Participants	Eligibility criteria	Outcome	Results	Rating
		Type	Period					
Ib	prospective randomized controlled trial	Two arms: – Study-group: Formula with same macronutrient composition as Control-group with additions of EPA, GLA and vitamins A, C, E – Control-group: ready to feed, high fat, low carbohydrate, enteral formula	not given	Total n=95 – Study-group: n=46 – Control-group: n=49	Eligible: acute lung injury. Exclusion: head trauma, cerebral bleeding, coagulation disorders, those receiving steroids in a dose 40.25 mg/kg/day methylprednisolone or non-steroidal anti-inflammatory agents, diarrhea, patients less than 18 years and pregnant patients.	to evaluate the preventive and healing effects of an enteral diet enriched in eicosapentanoic acid (EPA) and gamma-linolenic acid (GLA) and vitamins (vitamins A, C and E) on pressure ulcers.	A significantly lower rate of occurrence of new pressure ulcers in the study group compared to the control group ($p<0.05$). No difference in the healing of existing pressure ulcers and nutritional parameters between the two groups.	±

3. Berger MM, Binnert C, Chiolero RL et al. Trace element supplementation after major burns increases burned skin trace element concentrations and modulates local protein metabolism but not whole-body substrate metabolism. Am J Clin Nutr 2007; 85: 1301-1306. doi:10.1093/ajcn/85.5.1301x								
level of evidence	Study design	Intervention		Participants	Eligibility criteria	Outcome	Results	Rating
		Type	Period					
Ib	prospective, randomized controlled trial	Two arms: – TE-Group: daily a 250-mL 0.9% saline solution over 12 h intravenously containing 59 µmol Cu, 4.8 µmol Se, and 574 µmol Zn and for 14 days if their burns covered 20–60% BSA or for 21 days if the burns exceeded 60% BSA – Vehicle (V)-group: daily a 250-mL 0.9% saline solution for the	not given	Total n=21 – TE-group: n=11 – V-group: n=10	Eligible: admission within 6 h of injury, age 16–65 years, burns covering >20% BSA, including ≥10% BSA assessed as surgical on admission.	to assess the effects of TE supplements on systemic substrate turnover and local protein metabolism during wound healing after major burns.	Plasma TE concentrations were significantly higher in the TE group. In the burned areas, the skin contents of selenium ($p=0.02$) and zinc ($p=0.03$) increased by day 20. The supernatantto-plasma 13C enrichment ratio in burned skin was 0.363±0.094 (TE group) and 0.286±0.130 (V group) after 1 h (n.s.) and 0.592±0.153 (TE group)	+

		same time as TE group containing					and 0.262±0.171 (V group) after 6 h, which reflected lower catabolism in the TE group (p=0.03). No significant differences in whole-body substrate turnover were found between the groups.	

4. Collins CE, Kershaw J, Brockington S. Effect of nutritional supplements on wound healing in home-nursed elderly: a randomized trial. Nutrition 2005; 21: 147-155. doi:10.1016/j.nut.2004.10.006								
level of evidence	**Study design**	**Intervention**		**Participants**	**Eligibility criteria**	**Outcome**	**Results**	**Rating**
		Type	**Period**					
Ib	randomized controlled trial	Two arms: – Supplement group 1: 4 week supply of 1-kcal supplement provided 1 kcal/mL, 25% micronutrients, 1050 kJ (~12% total energy expenditure), 8.8 g of protein, 3.8 mg of zinc, 4.7 mg of iron, and 34 mg of vitamin C – Supplement group 2: 4 week supply of 2-kcal supplement provided approximately 50% micronutrients, 1995 kJ (~25% of total energy expenditure), 19.8 g of protein, 5.7 mg of zinc, 4.5 mg of iron, and 75 mg of vitamin C.	not given	Total n=38 – Supplement group 1: n=20 – Supplement group 2: n=18	Eligible: Subjects with all types of wounds including skin grafts, lacerations, skin tears, ulcers, pressure ulcers, and postsurgical wounds if they were older than 60 y and able to give informed consent. Exclusion: Subjects with an allergy or intolerance to milk-based products.	to determine whether provision of oral nutritional supplements, delivered by community nurses, could improve nutritional status and wound healing in home-nursed elderly	In both groups, there was significantly greater improvement in Mini-Mental State Examination scores at week 4 (95% CI -2.0-0.001, p=0.04) and a greater decrease in the wound effusion score (95% CI -2.0-0.0, p=0.045). Median length of stay did not differ between groups (p>0.05).	±

5. Houwing RH, Rozendaal M, Wouters-Wesseling W et al. A randomised, double-blind assessment of the effect of nutritional supplementation on the prevention of pressure ulcers in hip-fracture patients. Clin Nutr 2003; 22: 401-405. doi:10.1016/s0261-5614(03)00039-6								
level of evi-dence	**Study design**	**Intervention**		**Participants**	**Eligibility criteria**	**Outcome**	**Results**	**Rating**
		Type	**Period**					
Ib	randomized, controlled trial	Two arms: – Study-group: 400 mL daily of a supplement enriched with protein, arginine, zinc and antioxidants – Control-group: 400 mL daily of a non-caloric, water-based placebo supplement	21 months	Total n=103 – Study-group: n=51 – Control-group: n=52	Eligible: hip fracture. Exclusion: terminal care, metastatic hip fracture, insulin-dependent diabetes, renal disease (creatinine 4176 mmol/L), hepatic disease, morbid obesity, need for therapeutic diet incompatible with supplementation and pregnancy or lactation.	to investigate the effect of a high-protein supplement enriched with arginine, zinc and antioxidants on the development of PU in patients with a hip fracture	No difference in incidence of PU between supplement (55%) and placebo (59%), but incidence of PU stage II showed a 9% difference (difference: 0.091; 95% CI: 0.07-0.25) between supplement (18%) and placebo (28%). Time of onset showed a trend (p=0.090) towards later onset of PU with supplement than placebo	±

6. Ohura T, Nakajo T, Okada S et al. Evaluation of effects of nutrition intervention on healing of pressure ulcers and nutritional states (randomized controlled trial). Wound repair and regeneration : official publication of the Wound Healing Society [and] the European Tissue Repair Society 2011; 19: 330-336. doi:10.1111/j.1524-475X.2011.00691.x								
level of evi-dence	**Study design**	**Intervention**		**Participants**	**Eligibility criteria**	**Outcome**	**Results**	**Rating**
		Type	**Period**					
Ib	randomized controlled trial	Two arms: – Study-group: daily calories in the range of Basal Energy Expenditure BEEx1.1x1.3 to 1.5 – Control-group: same nutrition management as before participating	not given	Total n=60 – Study-group: n=30 – Control-group: n=30	Eligible: Tube-fed patients with Stage III–IV pressure ulcers with albumin 2.5–3.5 g/dL, OH scale 8.5 or lower, and Braden scale 9–17. Exclusion: current condition or history of serious liver or renal disorder, severe diabetes mellitus, arteriosclerosis obliterans,	to evaluate the effects of nutrition intervention on nutritional states and healing of pressure ulcers by standardizing or unified factors including nursing, care and treatment	Significant interactions between the presence or absence of the intervention and the intervention period were noted for nutritional states ($p < 0.001$ for body weight, $p<0.05$ for prealbumin). Significant difference in size of ulcers	+

					or a malignant tumor (within the past 5 years), patients with unmanageable severe general condition or unavailable pressure ulcer wounds.		between subjects in the intervention group and in the control group ($p<0.001$).	

7. van Anholt RD, Sobotka L, Meijer EP et al. Specific nutritional support accelerates pressure ulcer healing and reduces wound care intensity in non-malnourished patients. Nutrition 2010; 26: 867-872. doi:10.1016/j.nut.2010.05.009								
level of evi-dence	**Study design**	**Intervention**		**Participants**	**Eligibility criteria**	**Outcome**	**Results**	**Rating**
		Type	**Period**					
Ib	randomized controlled trial	Two arms: – ONS-group: 3 times a day 200 mL of ONS in addition to the regular diet and standard wound care for a maximum of 8 weeks. – Control-group: 3 times a day 200 mL of a non-caloric control product in addition for a maximum of 8 weeks	15 months	Total n=43 – ONS-group: n=22 – Control-group: n=21	Eligible: age 18 to 90 years, at least one stage III to IV pressure ulcer according to the revised European Pressure Ulcer Advisory Panel classification system and receiving standard care and a standard (institutional) diet without nutritional supplements for at least 2 weeks before the study. Exclusion: malnourished patients, as indicated by a BMI below 18.5 kg/m^2 for patients 18 to 70 years old or a BMI below 21 kg/m^2 for those older than 70 years, severe medical conditions, non–pressure-related ulcers (e.g., diabetic ulcers), life	to investigate the potential of a high-protein, arginine- and micronutrient-enriched ONS and to improve healing of pressure ulcers in non–malnourished patients who would usually not be considered for extra nutritional support.	Supplementation with the specific ONS accelerated pressure ulcer healing, indicated by a significantly different decrease in ulcer size compared with the control, over the period of 8 week ($p\leq0.016$). The decrease in severity score (Pressure Ulcer Scale for Healing) in the supplemented group differed significantly ($p\leq0.033$) from the control. Significantly fewer dressings were required per week in the ONS group compared with the control ($p\leq 0.045$) and less time was	+

					expectancy shorter than 6 month, receiving palliative care, use of corticosteroids, and/or dietary restrictions, i.e., a protein-restricted diet.		spent per week on changing the dressings (p≤ 0.022).	

8. Frías Soriano L, Lage Vázquez MA, Maristany CP et al. The effectiveness of oral nutritional supplementation in the healing of pressure ulcers. J Wound Care 2004; 13: 319-322. doi:10.12968/jowc.2004.13.8.26654								
level of evi-dence	**Study design**	**Intervention**		**Participants**	**Eligibility criteria**	**Outcome**	**Results**	**Rating**
		Type	**Period**					
IIa	quasi-experimental trial	daily ONS	3 weeks	Total n=39	Eligible: patients with grade III or IV pressure ulcers	to investigate the effectiveness of an oral nutritional supplement that is rich in protein and enriched with arginine, vitamin C and zinc on the healing of pressure ulcers.	median wound area reduced significantly ($p<0.001$) from 23.6 cm^2 to 19.2 cm^2, a reduction of 29%. Median healing of wound area was 0.34 cm^2 per day, taking approximately two days to heal 1 cm^2. Within three weeks the amount of exudates in infected ulcers (p=0.012) and the incidence of necrotic tissue (p=0.001) reduced significantly.	+

9. Song YP, Wang L, Yu HR et al. Zinc Therapy Is a Reasonable Choice for Patients With Pressure Injuries: A Systematic Review and Meta-Analysis. Nutr Clin Pract 2020; 35: 1001-1009. doi:10.1002/ncp.10485			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic Review 1+	**Countries:** n/a **Centers:** n/a	**Total no. patients:** 473	Zinc therapy vs. any kind of standard care

AMSTAR II 12/16	**Setting:** pressure injuries (PI) **Funding Sources:** Social and People's Livelihood Technology in Nantong city–General Project (MS12019038). **Dropout rates:** n/a **Study limitations:** Overall confidence in the results of the review: moderate Risk of bias of single studies: high Inconsistency: low Indirectness: moderate Impreciseness: low Publication bias: n/a High or unknown risk of bias of the single studies, and other flaws	**Inclusion criteria**: (1) population: patients met the PI diagnostic criteria according to the European Pressure Ulcer Advisory Panel and National Pressure Ulcer Advisory Panel; (2) intervention: zinc therapy; (3) comparison: any type of standard care (such as nutrition intervention enabling the satisfaction of treatment requirements) regardless of the use of placebo or not; (4) outcome: full-text studies reporting the outcome and/or safety of zinc therapy (primarily the healing rate of PI during treatment followed by the improvement of PI area and pressure ulcer scale for healing (PUSH) score); and (5) study design: randomized or nonrandomized clinical trials (non-RCTs) addressing the efficacy of zinc therapy compared with a control nutrition invention on PI outcomes, regardless of the use of a placebo or not **Exclusion criteria:** (1) studies without a clear description of data regarding intervention details; (2) studies that did not report the outcomes of zinc therapy or that lacked sufficient data to assess the outcomes; and (3) studies with a sample size of <20 people to ensure the accuracy of our results.	

Notes	**Author's Conclusion:** Our systematic reviews and meta-analysis from clinical research confirmed that zinc therapy can promote wound healing. Nakamura et al22 also confirmed from animal research that zinc therapymight be a reasonable therapeutic choice for patients with PIs. Medical staff may want to consider providing zinc to patients during PI treatment. In uture studies, the effects of different dose levels of zinc on PIs can be explored.	
Outcome measures/results	Primary outcome: Healing rate: "cured"- "effective" – "ineffective" Secondary outcome: Indicator of healing area	The intervention group had a significantly more rapid improvement than that of the control group (relative risk, 1.44; 95% CI, 1.01 −2.06; P = 0.043, I2 = 19.3%). All the studies included had a significant improvement in the area of PI with favors to the control group.

10. Heyland DK, Wibbenmeyer L, Pollack JA et al. A Randomized Trial of Enteral Glutamine for Treatment of Burn Injuries. N Engl J Med 2022; 387: 1001-1010. doi:10.1056/NEJMoa2203364			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1++ ROB 6/7	**Countries:** Canada, USA, Germany, UK, Sweden, Italy **Centers:** Multicenter **Setting:** ICU **Funding Sources:** U.S. Department of Defense (award number, W81XWH-09-2-0194 for the pilot phase) and the Canadian Institutes of Health Research (funding reference numbers, MCT-94834 for the pilot phase and 14238 for the definitive phase). **Dropout rates:** 23.6% **Study limitations:** Risk of Bias: low Inconsistency: n/a Indirectness: low Impreciseness: moderate	**Total no. patients:** 1,209 **Inclusion criteria:** Inclusion criteria consist of: deep second- and/ or third-degree burns requiring skin grafting. For patients aged 18–39 years, we require a TBSA (total burn surface area) ⩾ 20% or a minimum of 15% TBSA when concomitant inhalation injury is present. For patients aged 40–59 years, we require a TBSA ⩾ 15%. For patients aged 60 years or older, we require a TBSA ⩾ 10%. Outside these limits we believe that the risk of death is too small, increasing the risk of beta error. **Exclusion criteria:** 72 h from admission to ICU or burn unit to time of consent; patients aged less than 18 years; in patients without known renal disease,renal	0.5 g per kilogram of body weight per day of enterally delivered glutamine or placebo

	Publication bias: n/a low accrual that led to the alteration of the sample size and primary outcome, low completion rate of 6-month survivor questionnaires	dysfunction defined as a serum creatinine > 171 mmol/L or a urine output < 500 mL in the last 24 h (or 80 mL in the last 4 h if a 24-h period of observation is not available). In patients with acute on chronic renal failure (pre-dialysis), an absolute increase of > 80 mmol/L from baseline or pre-admission creatinine or a urine output of < 500 mL in the last 24 h (or 80 mL in last 4 h) will be required. Patients with chronic renal failure on dialysis will be excluded; liver cirrhosis - Child's class C liver disease; pregnancy (urine/blood tests for pregnancy will be done on all women of childbearing age by each site as part of standard ICU practice); contra-indication for EN: intestinal occlusion or perforation, intra-abdominal injury; patients with injuries from high voltage electrical contact; patients who are moribund (not expected to survive the next 72 h); patients with extreme body sizes: BMI < 18 or > 50; enrolment in another industry sponsored ICU intervention study (co-enrolment in academic studies will be considered on a case-by-case basis); received glutamine supplement for > 24 h before randomisation; known allergy to maltodextrin, cornstarch, corn, corn products or glutamine.	

Notes	**Author's Conclusion:** In patients with severe burns, supplemental glutamine did not reduce the time to discharge alive from the hospital.	
Outcome measures/results	Primary outcome: six-month mortaliy Secondary outcomes: time to discharge alive (TTDA) from hospital Tertiary outcomes: health related quality of life, physical function domain of SF-36, activities of daily living, incidence of acquired bacteraemia, hospital mortality, duration of mechanical ventilation, iCU stay, hospital stay.	We found no evidence of a significant difference in the time to discharge alive between the trial groups. The median time to discharge alive from the hospital was 40 days in the glutamine group and 38 days in the placebo group (subdistribution hazard ratio for discharge alive, 0.91; 95% confidence interval [CI], 0.80 to 1.04; P = 0.17). The 6-month mortality was 17.2% in the glutamine group and 16.2% in the placebo group (hazard ratio for death, 1.06; 95% CI, 0.80 to 1.41). In-hospital mortality, length-of-stay variables, and the incidence of bacteremia due to gramnegative organisms were similar in the two groups. At 6-month outcome assessments, we found no evidence of clinically significant between-group differences in health-related qualityof-life scores, activities of daily living, or instrumental activities of daily living

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