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ESPEN Guidelines on Clinical nutrition in surgery - Special issues to be revisited

Arved Weimann*, Maria Wobith

Department of General, Visceral and Oncological Surgery, St. George Hospital Leipzig, Germany

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ABSTRACT

The ESPEN Guidelines on Clinical nutrition in Surgery from 2017 has been also available as practical guideline with algorithms since 2021 (www.espen.org). An update will be perfomed in the near future. This review focuses on recent data with regard to special issues and topics to be revisited in the guidelines: These are nutritional assessment, sarcopenic obesity, prehabilitation, oral/enteral immunonutrition, postoperative oral supplementation in hospital and after discharge.

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1. Introduction

The increasing implementation of Enhanced Recovery after Surgery (ERAS) –

Programs as the standard of care in visceral surgery and new data on feasibility and safety of early oral food intake even after resections in the upper gastrointestinal tract, make the necessity of guidelines for perioperative nutrition therapy debatable. It has also been shown that the traditional postoperative "protection" of the gastrointestinal tract, and the anastomoses may delay recovery and hospital.length of stay. The indications for enteral and "total" parenteral nutrition therapy have been reserved for selected patients with malnutrition or severe risk.

In surgical patients, particularly those with gastrointestinal tumors, cancer and/or therapy-associated weight loss triggers malnutrition despite being overweight or even obese. The "metabolic risk" may be not clinically apparent and underestimated in an overweight society. This is why it has also been called a "silent epidemic" [1,2]. The impact of malnutrition and sarcopenia for the risk of postoperative complications and the length of hospital stay has been known for a long time [3–5], and is even relevant for an "Enhanced Recovery after Surgery Protocol" [6,7]. Screening for malnutrition should be carried out early in the trajectory and in case of severe metabolic risk, nutritional therapy or even conditioning - may be as "prehabilitation" - should be started.

Even in the ERAS protocol as plan A, there may be severe complications with subsequent catabolic deterioration of the nutritional status. From a metabolic point of view, patients with complicated course, reoperation and intensive care treatment are a special risk group requiring a nutritional plan B. Furthermore, with special regard to patients undergoing major resections in the upper gastrointestinal tract long-term insufficient calorie and protein requirement has to be expected even for months.

The current "Practical Guideline" of the European Society for Surgery Clinical Nutrition and Metabolism (ESPEN) of 2021 [8] including treatment algorithms and available as a guideline app (espen.org) refers to the evidence from 2017, This overview will focus on special issues to be revisited.

2. Nutritional assessment

Definition of malnutrition - GLIM criteria.

In 2019, an international consensus "Global Leadership Initiative on Malnutrition (GLIM)" has developed a new definition of malnutrition that has been adopted worldwide and supported by all major medical nutritional societies [9]. It is a two-step process: 1) screening and 2) assessment of malnutrition. For the screening, a validated tool of choice can be used, i.e. Nutritional Risk Score (NRS), MUST etc.

Recommendation of the guideline:

"*Therefore, as a basic requirement a systematic nutritional risk screening (NRS) has to be considered in all patients on hospital admission. The items of the NRS comprise BMI < 20.5 kg/m2,*

* Corresponding author. Delitzscher Str. 141, 04129, Leipzig, Germany.
E-mail address: Arved.Weimann@sanktgeorg.de (A. Weimann).

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weight loss > 5% within 3 months, diminished food intake, and severity of the disease. In older adults comprehensive geriatric assessment is necessary and should definitely include NRS".

The assessment incorporates etiologic (reduced food intake or absorption, inflammation, disease severity) and phenotypic (unwanted weight loss, low body mass index, reduced muscle mass) criteria. Apart from weight loss and low body mass index (BMI), which is already part of assessments used before, muscle mass measurement is included. According to the very recently published guidance by Barazzoni et al. [10] reduced muscle mass may be measured by

- Bioelectrical impedance analysis (BIA)
- Computed tomography of the abdomen (CT)
- Dual X-ray Absorptiometry (DXA)
- Ultrasound

Computed tomography (CT) in particular is a routine procedure in patients with gastrointestinal tumors and also available several times during the clinical course. Using various software, at the axial layer at the level of lumbar vertebrae L3 muscle mass and its radiodensity can be determined, and has been shown representative for the entire muscle mass of the patient. A significant association between CT-defined sarcopenia and clinical outcome in surgical patients with gastrointestinal tumors has also been observed in different tumor entities [11,12].

Muscle mass assessment gains importance, as the presence of sarcopenia is relevant in patients undergoing major abdominal surgery. In esophageal cancer patients sarcopenia is associated with overall complications, major complications, and delayed hospital discharge [13].

Comparisons between existing malnutrition assessments were made, especially with the Subjective Global assessment (SGA), patient generated (PG)-SGA, and ESPEN definition, but also with screening tools. In several studies, the prevalence of malnutrition was higher when using GLIM [14]. GLIM criteria are predictive for the risk of developing complications in patients undergoing major abdominal surgery [15]. Patients with malnutrition according to GLIM criteria had a 4.4-fold higher mortality risk [16].

Recommendation of the guideline:

"*It is recommended to assess the nutritional status before and after major surgery. Grade of recommendation GPP,strong consensus (100% agreement)*"

The assessment of malnutrition should always be done before major abdominal surgery, in particular in cancer patients. Several studies support the influence of malnutrition on the postoperative long- and short-term outcome. Yin et al. recently showed that GLIM criteria predicted postoperative complications in patients undergoing esophagectomy for cancer as the best method [17]. In cancer patients undergoing major abdominal surgery, GLIM criteria predicted postoperative pulmonary complications as well as 90-day mortality [18]. Additionally, malnutrition according to GLIM criteria were associated with postoperative complications in patients with abdominal resections in the Norwegian registry study [19].

So far, the GLIM give recommendations on the muscle mass measurements without giving specific cut-off values, especially regarding the differentiation between moderate and severe reduced muscle mass. Validation of muscle mass assessment is needed, as preferred tools like DXA, MRI, CT, or BIA are not frequently used and cut-off values are not validated yet. The GLIM will soon publish further recommendations regarding this topic.

3. Sarcopenic obesity

The guideline states:

"*Disease related weight loss in patients who are overweight is not necessarily associated with a low BMI.*"

In a primarily overweight society, malnutrition may be underestimated. In order to differentiate muscle and fat mass, body composition measurement is needed, especially for sarcopenic obesity, defined as adiposity combined with low muscle mass/function [20]. While sarcopenic obesity is shown to be an independent risk factor for the development of complications in patients undergoing major abdominal surgery [2,21]. More attention has to be attributed in the future. It is also called a "double burden" as those people have a higher risk of developing frailty and disability and are generally present with poorer quality of life [22].

As it is not appropriately discussed yet in the guidelines, this topic needs to be addressed in the future. Donini et al. recently published recommendations on the diagnostic procedure of sarcopenic obesity, which consists of two steps. The screening contains a high BMI or waist circumference (according to ethnic cut-off points) as well the suspicion to be sarcopenic by clinical symptoms or a questionnaire. To diagnose sarcopenic obesity there needs to be altered skeletal muscle function parameters and altered body composition with increased fat mass plus reduced muscle mass. A staging for the severity is based on the presence of complications with stage I as having no complications and stage II as having complications like metabolic diseases, functional disabilities, and cardiovascular or respiratory diseases.

In order to avoid missing of sarcopenic obesity again exploitation of CT scan for body composition analysis may be recommended. Furthermore, measurement of muscle function like hand grip strength should be implemented in clinical routine before surgery.

4. Prehabilitation

The guideline states:

"The premise of the multimodal prehabilitation approach with a nutrition and physical exercise component rests on their synergy …. Patients with low functional and physiological reserve such as the elderly, frail, sarcopenic and cancer patients could benefit more from prehabilitation than other patient populations. This possibility needs to be studied."

In the meantime prehabilitation has continued to be a very promising strategy for risk patients undergoing major abdominal surgery especially for those at high risk for developing complications. "Making the patient fit for ERAS" includes trimodal nutrition, endurance and resistance training, and psychological intervention for 4–6 weeks. Neoadjuvant therapy opens a regular time window before surgery. Despite plenty of studies and meta-analyses, only a few randomized controlled studies really focused on high-risk patients for an intervention in a prehabilitation program. Barberan-Garcia et al. included 125 blinded, randomized controlled high-risk patients undergoing major elective abdominal surgery aged >70 years and/or with an ASA score III/IV. The prehabilitation was individualized for four weeks. Significantly fewer patients with severe postoperative complications were found in the prehabilitation group. The number of complications per patient and

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non-surgical complications (p = 0.001) were also significantly lower [23].

Berkel et al. defined high-risk as patients with an oxygen uptake at the ventilatory anaerobic threshold <11 mL/kg/min at the baseline cardiopulmonary exercise test, who underwent colorectal surgery. Patients in the intervention group participated in a 3-week personalized exercise program and had significant lower postoperative complications [24]. Carli et al. defined high-risk as patients older than 65 years and a Fried Frailty Index ≥2. With a multimodal prehabilitation program of 4 weeks, there were no significant differences between intervention and control group [25].

Although there is evidence for the benefit of nutritional prehabilitation only in a meta-analysis of 33 studies in the elderly [26] a recently published umbrella-review which analysed 55 systematic reviews and meta-analysis revealed the considerable heterogeneity. While moderate evidence was found for the functionally relevant improvement of the 6 Minutes Walking Distance (6MWD), there were just low to very low certainty evidence that supports reductions in complications, non-home discharge, and length of hospital stay [27]. Because it may be possible that colorectal cancer patients benefit less [28,29]. The focus might be directed on upper gastrointestinal resections [30].

The challenge remains the heterogeneity of current data with different kind of study populations, program duration, and program contents which makes them hard to be compared. Currently there cannot be a specific prehabilitation program recommended. In future studies it might be the purpose to identify modifiable risk factors by specific screenings and assessments. In a prospective cohort study, six modifiable risk factors were evaluated (physical fitness, malnutrition, anaemia, frailty, substance use (smoking, alcohol), psychological resilience). About 50% of the patients compiled with 100% with the tailor made prehabilitation program [31].

From a metabolic point of view the type of the nutritional intervention is a matter of debate and has to be elucidated for a period of 4–6 weeks. In comparison with standard oral supplements preoperative immunonutrition and synbiotics have proven benefits regarding the significant decrease of complications just for the administration of 5–7 days before surgery [32]. An innovative concept including a preconditioning supplement containing glucose, glutamine, antioxidants and green tea was investigated in a small double-blind placebo controlled randomized trial [33]. The administration one day and 3 h before surgery led to a significant increase in the total endogenous capacity. In conclusion, there is no data for enriched nutritional supplements for a longer period, and randomized trials have to be encouraged.

5. Oral/enteral immunonutrition

The ESPEN guideline states:

"*Preoperatively, oral nutritional supplements shall be given to all malnourished cancer and high-risk patients undergoing major abdominal surgery.A special risk group are the elderly people with sarcopenia. (A) Immune modulating oral nutritional supplements including arginine, omega-3-fatty acids and nucleotides can be preferred (0)and administered for five to seven days preoperatively (GPP)*"

It has been open whether the combination of arginine, omega-3-fatty acids, and ribonucleotides in an enriched oral drink supplement may be also beneficial regarding a decrease of infectious complications in an ERAS program. So far, only one PRCT investigated immunonutrition in the framework of an ERAS program. In the SONVI study a total of 264 patients were randomized. The intervention group received immunonutrition and the control group a hypercaloric hypernitrogenous supplement for 7 days before colorectal resection and 5 days postoperatively. The median length of the postoperative hospital stay was 5 days with no differences between the groups. A decrease in the total number of complications was observed in the immunonutrition group compared with the control group, primarily due to a significant decrease in infectious complications (23.8% vs. 10.7%, p = 0.0007). Of the infectious complications, wound infection differed significantly between the groups (16.4% vs. 5.7%, p = 0.0008) [34].

The pre-, post- or perioperative timing of immunonutrition has also been a matter of debate. Furthermore, the comparison with a standard enteral diet is of importance. This has not been appropriately considered in many meta-analyses showing benefits of immunonutrition. From a clinical point of view the question arises whether the exclusively preoperative administration of immunonutrition without postoperative continuation is even beneficial in comparison with a standard oral nutritional supplement. Very recently, again a significant increase in the immune parameters CD4/CD8 ratio, the killer cell rate (NK), and the IgA serum level has been shown for patients undergoing esophageal resections compared to standard enteral nutrition, but without any impact on the clinical outcome [35].

Unrelated to the nutritional status in a randomized trial 176 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. No difference was observed for the rates of infectious (17.7% vs. 15.9%, p = 0.751) and total (31.6% vs. 29.3%, p = 0.743) complications. 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). While no difference was observed for the length of hospital stay (7.6 ± 2.5 vs. 7.4 ± 2.3 days, p = 0.635) and the overall change in body weight (p = 0.379), it is noteworthy that only the immunonutrition group showed weight recovery after discharge (+0.4 ± 2.1 vs. −0.7 ± 2.3 kg, p = 0.002) [36].

In a meta-analysis from 16 randomized trials with 1387 surgical patients with gastrointestinal cancer (immunonutrition n = 715, controls n = 672) the exclusive preoperative use led to a significant decrease in the incidence of infectious complications in comparison with a normal and an isonitrogenous standard enteral diet (OR 0.52; 95% CI 0.71, p < 0.0001). The heterogeneity was low (I^2 = 16%). There was also a significant reduction of the length of hospital stay in comparison with the normal diet (−1.57 days, 95%CI, −2.48-0.66, p = 0.0007, I^2 = 34%), and a tendency in comparison with the standard diet. The rate of non-infectious complications and mortality were without difference [37].

For preoperative nutrition in patients with esophageal cancer in a meta-analysis a total of 15 studies enrolling 1864 participants were included [38]. The overall meta-analysis found that preoperative nutrition could reduce infectious complications (odds ratio [OR] = 0.51, 95% confidence interval [CI] 0.26, 0.98; I^2 = 48%) and length of hospital stay (mean difference = −2.10 day, 95% CI -3.72, −0.47; I^2 = 78%) after esophagectomy. No significant difference was found for the incidence of overall complications (OR = 0.76, 95% CI 0.52, 1.11; I^2 = 32%), in-hospital mortality (OR = 1.03, 95% CI 0.41, 2.61; I^2 = 12%), and anastomotic leak (OR = 1.05, 95% CI 0.69, 1.58; I^2 = 0%). Patients in the subgroup with preoperative immunonutrition had more benefits. The complication rate of feeding tube access was low (1.6–16%).

An umbrella review included 20 meta-analyses (eleven on

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abdominal surgery, one twice and eight on pancreatic, esophageal, liver or colorectal surgery). Overall, with considerable heterogeneity, immunonutrition was associated with a significantly lower rate of infectious complications (OR 0.60 [0.54–0.65] (random effect model) (heterogeneity (I^2 = 64%) and lower postoperative morbidity (OR 0.78 [0.74–0.81], I^2 = 30.3%).The exclusion of three studies with significant heterogeneity did not change the results. There was no significant difference in the timing of the intervention (pre, peri-, or just postoperative) [39].

In conclusion, there is growing evidence that preoperative immunonutrition may be beneficial which might upgrade the guideline recommendation. Further randomized studies focusing on the preoperative period including prehabilitation and patient management in ERAS programs are warranted. A multicentric randomized trial (POINT) regarding the effects of preoperative enteral immunonutrition in patients with esophageal cancer undergoing neoadjuvant chemoradiotherapy was recently started [40].

study including 230 patients undergoing abdominal surgery was performed. [40]. The E-SPN group received a higher mean (SD) energy intake between days 3 and 7 compared to the L-SPN group (26.5 + 7.4 vs. 15.1 + 4.8 kcal/kg daily; p < 0.001). The E-SPN group had significantly fewer nosocomial infections compared to the L-SPN group (10/115 [8.7%] vs. 21/114 [18.4%]; risk difference 9.7%; 95% CI 0.9%–18.5%, p = 0.04). No significant differences were observed between the E-SPN group and the L-SPN group in the number of non-infectious complications, adverse events, and other secondary endpoints. A significant difference was also found in the mean number of antibiotic therapy 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 = 0.01).

From a nutritional point of view, early oral feeding is “feasible” within ERAS. However, the energy requirement may be not adequately covered for a longer period of time even after discharge. This is an indication for supplementing oral nutrition with sip feed or even via a fine-needle catheter jejunostomy (FNCJ) placed during surgery.

The guideline recommendation for supplementing oral nutrition has to be revisited and clarified. The following scheme may be proposed [42].

Oral intake in percentage of caloric requirement expected for more than five days	Nutritional strategy
None	Start enteral feeding
<30%	Start enteral - if oral/enteral is <30% on pod 3 start parenteral
<50%	Start enteral - if oral/enteral is expected to be <50% for seven days start parenteral
>50%	Monitoring the increase of oral intake

6. Postoperative oral nutrition

The ESPEN guideline states:

“*In most instances, oral nutritional intake shall be continued after surgery without interruption (A). It is recommended to adapt oral intake according to individual tolerance and to the type of surgery carried out with special caution to elderly patients. (GPP).*

Perioperative nutritional therapy should also be initiated, if it is anticipated that the patient will be unable to eat for more than five days perioperatively. It is also indicated in patients expected to have low oral intake and who cannot maintain above 50% of

recommended intake for more than seven days. In these situations, it is recommended to initiate nutritional support therapy (preferably by the enteral route − ONS-TF)

without delay (GPP)”.

Early oral feeding - the plan A.

In general, even after operations on the lower gastrointestinal tract, oral diet can be started within hours. Is early oral nutrition even after gastrectomy and esophageal resection feasible? In a randomized multicentre Dutch study feasibility and safety of early oral feeding were investigated after minimally invasive esophagectomy with intrathoracic anastomosis. In the intervention group (/n = 65) oral feeding was started without delay, while the control group for 5 days exclusively was fed enterally by tube (n = 67). A difference in the primary endpoint

the postoperative recovery (7 vs. 8 days) and the secondary endpoints complications, anastomotic leak (18.5% vs. 16.4%) and pneumonia rate (24.6% vs. 34.3%) was not observed [41].

With the aim of comparing the effect of early parenteral (E-SPN day 3) with late supplementation (L-SPN day 8) in the case of inadequate oral/enteral energy intake a multicentre, randomized

7. Oral/enteral supplementation after intensive care treatment and after discharge

The guideline states:

“*Regular reassessment of nutritional status during the stay in hospital and, if necessary, continuation of nutritional support therapy including qualified dietary counselling after discharge, is advised for patients who have received nutritional support therapy perioperatively and still do not cover appropriately their energy requirements via the oral route (GPP).*”

While the need for postoperative nutrition therapy after referral from the intensive care unit to the normal ward and finally after discharge from the hospital seems to be obvious, evidence is sparse.

It has been shown that after referral from the intensive care unit to the normal ward, exclusively oral nutrition is feasible, but spontaneous oral food intake is often inadequate and will not cover energy requirement according to indirect calorimetry. Therefore, at least enteral supplementation may be required [43].

Our own data show that 40% of the patients who underwent upper gastrointestinal surgery for esophageal, gastric, or pancreatic cancer lost >10% of their body weight 6 months after surgery, despite postoperative continuation of nutritional therapy via feeding jejunostomy [44]. This may be considered the “bariatric effect” of upper GI resections. A decrease in skeletal muscle mass from the baseline to 4 weeks after esophagectomy measured by CT was an independent risk factor for lower overall survival and recurrence-free survival [45]. Postoperative loss of body weight and lean body mass additionally increases the risk of toxicity of adjuvant chemotherapy in patients with gastric cancer, which may lead

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to early termination of adjuvant therapy, bearing the risk of tumor recurrence and a worse overall survival [46].

Within the past two years several randomized studies have been published. In a randomized study involving 353 patients undergoing gastrectomy, dietary counseling with oral nutritional supplements (ONS) for 3 months significantly reduced weight loss with a higher body mass index and skeletal muscle mass index (SMI) than dietary counseling alone. Furthermore, the prevalence of sarcopenia was significantly lower in the dietary counselling and ONS groups, as were fatigue and appetite [47]. Chen et al. demonstrated significant benefits from home enteral nutrition for at least 8 weeks for BMI, Patient-Generated Subjective Global assessment scores, serum albumin, and immune parameters in patients undergoing esophagectomy [48]. In patients receiving postoperative chemotherapy, there were also significantly fewer modifications due to delayed or limited tolerance. In a meta-analysis, 15 randomized controlled trials involving 1.059 patients undergoing upper gastrointestinal resection for malignancy were compared for home enteral nutrition versus ONS [49]. Home enteral nutrition seemed to be superior by significantly diminished weight loss (−3.95 kg vs. −5.82 kg; standardized mean difference: 1.98 kg; 95% CI 1.24–2.73) and the reduction in the incidence of malnutrition or latent malnutrition (risk ratio = 0.54; $p < 0.01$). Interestingly, no significant difference could be observed between the ONS subgroup and the control group. Physical function (weighted mean difference [WMD]: 5.29; 95% CI 1.86–8.73) and fatigue (WMD: −8.59; 95% CI −12.61 to −4.58) as dimensions in the quality of life were significantly better in the home enteral group. The possible impact of night home enteral nutrition after gastrectomy has been recently emphasized with regard to the tolerance of adjuvant chemotherapy [50]. A recent multicentric randomized trial involving 1.003 patients undergoing gastrectomy compared the impact of ONS 400 kcal/day on weight loss 1 year after gastrectomy. In the ONS group, 50.4% of the patients had an intake of >200 kcal/day (average 301 mL) and significantly less body weight loss after 1 year (8.2% ± 7.2%) [51]. Therefore, patients undergoing major upper gastrointestinal surgery are at high risk of not fulfilling their energy and protein requirements. Next to dietary counseling, ONS supplementation should be considered, and in patients with severe metabolic risk, if available, feeding jejunostomy may be maintained and used even after discharge.

In conclusion, there is plenty of new data available for the evaluation of evidence. Next to the evidence based recommendations, the guideline update should raise again the awareness that perioperative nutrition therapy may create “marginal gains with cumulative effects” which may turn out in “clinically significant improvements of outcome” [52].

Declaration of competing interest

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