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ESPEN Guideline

# ESPEN practical and partially revised guideline: Clinical nutrition in the intensive care unit

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SUMMARY

Following the new ESPEN Standard Operating Procedures, the previous 2019 guideline to provide best medical nutritional therapy to critically ill patients has been shortened and partially revised. Following this update, we propose this publication as a practical guideline based on the published scientific guideline, but shortened and illustrated by flow charts. The main goal of this practical guideline is to increase understanding and allow the practitioner to implement the Nutrition in the ICU guidelines. All the items discussed in the previous guidelines are included as well as special conditions.

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## 1. Introduction

The European Society for Clinical Nutrition and Metabolism (ESPEN) has published guidelines on nutrition in the intensive care unit (ICU) in 2006 (enteral nutrition (EN)) and 2009 (parenteral nutrition (PN)) [1,2]. Since then, the ESPEN methodology has been upgraded to the "S3 guidelines level" described elsewhere [3] resulting in rigorous evidence-based and consensus-based recommendations that were published in 2019 [4]. The present guideline is a shortening and a partial revision of the previous guideline. The determination of the effect of nutrition alone on any possible outcome is complicated by the fact that the severity of illness and the number of comorbidities encountered among adult ICU patients is increasing [5]. Furthermore, the large heterogeneity of the ICU population potentially reduces the external validity of the recommendations,

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**Abbreviations**

| | |
|---|---|
| ASPEN | American Society for Parenteral and Enteral Nutrition |
| BIA | bioelectric impedance analysis |
| BMI | body mass index |
| DHA | docosahexaenoic acid |
| ECMO | extracorporeal membrane oxygenation |
| EE | energy expenditure |
| EFI | enteral feeding intolerance |
| EN | enteral nutrition |
| EPA | eicosapentaenoic acid |
| ESICM | European Society of Intensive Care Medicine |
| ESPEN | European Society for Clinical Nutrition and Metabolism |
| FA | fatty acid |
| GIDS | Gastrointestinal Dysfunction Score |
| GLIM | Global Leadership Initiative on Malnutrition |
| GLN | glutamine |
| GRV | gastric residual volume |
| HDL | high-density lipoprotein |
| ICU | intensive care unit |
| LCT | long chain triglyceride |
| MCT | medium chain triglyceride |
| MNA | mini-nutrition assessment |
| MUST | malnutrition universal screening tool |
| NRS | nutritional risk screening |
| NUTRIC | nutritional risk in critically ill |
| PN | parenteral nutrition |
| RCT | randomized controlled trial |
| REE | resting energy expenditure |
| SCCM | Society for Critical Care Medicine |
| SGA | subjective global assessment |
| SIGN | Scottish Intercollegiate Guidelines Network |
| SOP | standard operating procedure |

which should be seen as a basis to support decisions made for each patient on an individual basis [6]. For now, a gap exists between nutritional practices and the previous guideline [7] and many available studies address only one or at most some of the specific aspects of nutritional therapy. In the current guideline, the timing, route, dose and composition of nutrition will be discussed and recommendations will be made recognizing that acute metabolic changes as well as prolonged energy and protein deficits play a major role in patient outcome. The goal is to achieve optimal nutritional support for ICU patients and to illuminate the gaps in knowledge in order to provide priorities for future clinical research.

## 2. Methodology

The present practical guideline consists of 56 recommendations and is based on the ESPEN guideline on clinical nutrition in the ICU [4]. The original guideline was shortened by focusing the commentaries on the evidence and literature on which the recommendations are based. Some of the recommendations themselves have been changed, and the presentation of the content has been transformed into graphical presentations. The original guideline was developed according to the standard operating procedure (SOP) for ESPEN guidelines and consensus papers [3].

This SOP is oriented on the methodology of the Scottish Intercollegiate Guidelines Network (SIGN). Literature was searched and graded 1–4 according to the evidence, and recommendations were created and graded into four classes (A/B/0/GPP).

All recommendations were agreed in a multistage consensus process, which resulted in a percentage of agreement (%). Six recommendations (former R21, R22, R33, R35, R36, R37), were revised and updated (R21 and R35) or merged (R36 and R37) into one within the preparation of this practical guideline according to the recent evidence. These recommendations were voted on within the working group, and the percentages of agreement for the respective recommendations are taken from this voting. One recommendation (former R26, now 30) also needs revision, but will be revised during the next revision process in the near future. The guideline process summary and dissemination were funded exclusively by ESPEN. For further details on methodology, see the full version of the ESPEN guideline [4] and the ESPEN SOP [3].

## 3. Recommendations (Fig. 1)

### 3.1. General recommendations (Fig. 2)

**1) Statement 1: Every critically ill patient staying for more than 48 h in the ICU should be considered at risk for malnutrition. (S1, strong consensus, 96%)**

No specific nutritional score for use in the ICU has been validated thus far. The existing nutritional screening tools (nutritional risk screening (NRS) 2002 [8] and the malnutrition universal screening tool (MUST) score [9]) have not been designed specifically for critically ill patients. NUTRIC (= nutritional risk in critically ill) is a novel risk assessment tool merely based on the severity of disease was proposed [10].

Rather than mortality, long-term functional tests might better reflect the benefit of a nutritional policy [11]. It appears that among all the screening tools, NRS 2002 and MUST have the strongest predictive value for mortality, and they are the easiest and quickest to calculate [12]. Validation of their utility for daily clinical practice and nutrition management has not been performed, and therefore only expert opinion can be expressed.

A pragmatic approach should be considered for patients at risk, such as those staying in the ICU for more than two days, requiring mechanical ventilation, with infection, who are underfed for more than five days, and/or presenting with a severe chronic disease.

**2) Medical nutrition therapy shall be considered for all patients staying in the ICU, mainly for more than 48 h (Fig. 2). (R1, Grade GPP, strong consensus 100%)**

**Commentary**

There are no studies directly addressing the effect of duration of starvation on outcome in critically ill patients. Such studies could be considered unethical as energy intake is a mainstay of survival. Since previous recommendations [1,2], a cut-off of 48 h for the initiation of early nutrition and contraindications to early EN has been better established [13]. Additionally, one study showed possible benefit of a further delay of PN if EN is not possible/tolerated [14]. A careful and progressive re-introduction of nutrition may limit the risk of refeeding syndrome, especially in patients who are severely malnourished or have been in a starved state before admission.

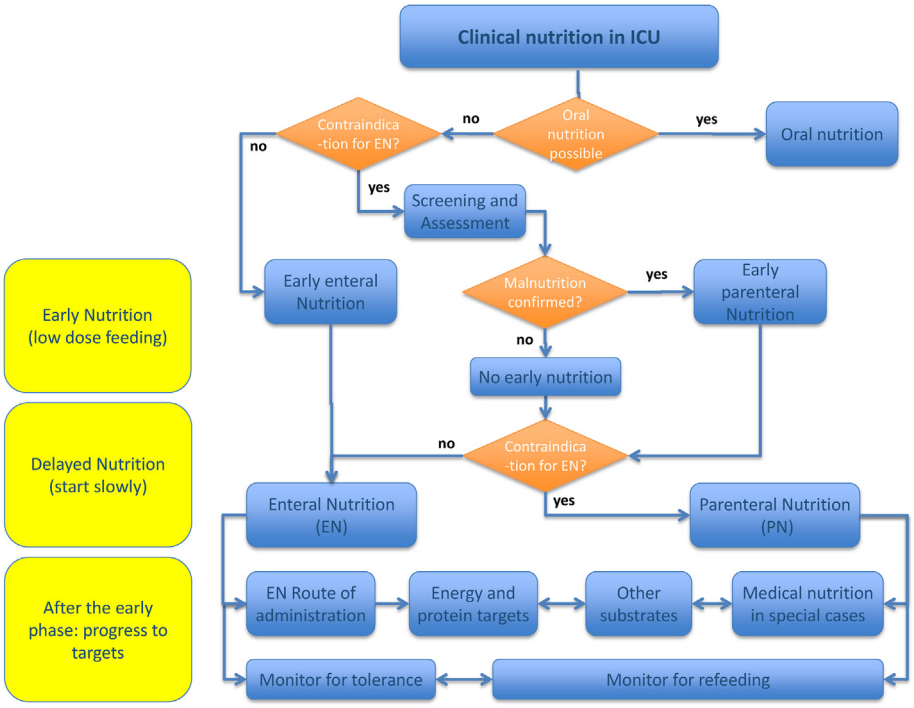


**Fig. 1.** ESPEN practical guideline: Clinical nutrition in the intensive care unit. Overview of the structure of the guideline. EN, enteral nutrition; ICU, intensive care unit; PN, parenteral nutrition.

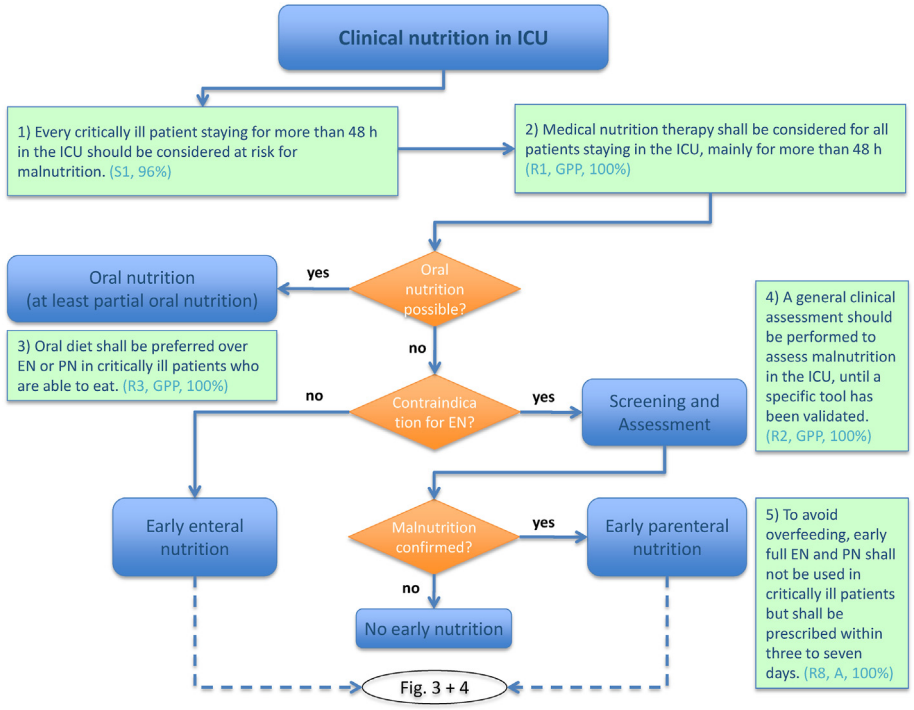


**Fig. 2.** General recommendations. Recommendations are presented in green boxes. References to other panels in ellipse. Abbreviations: see Fig. 1.

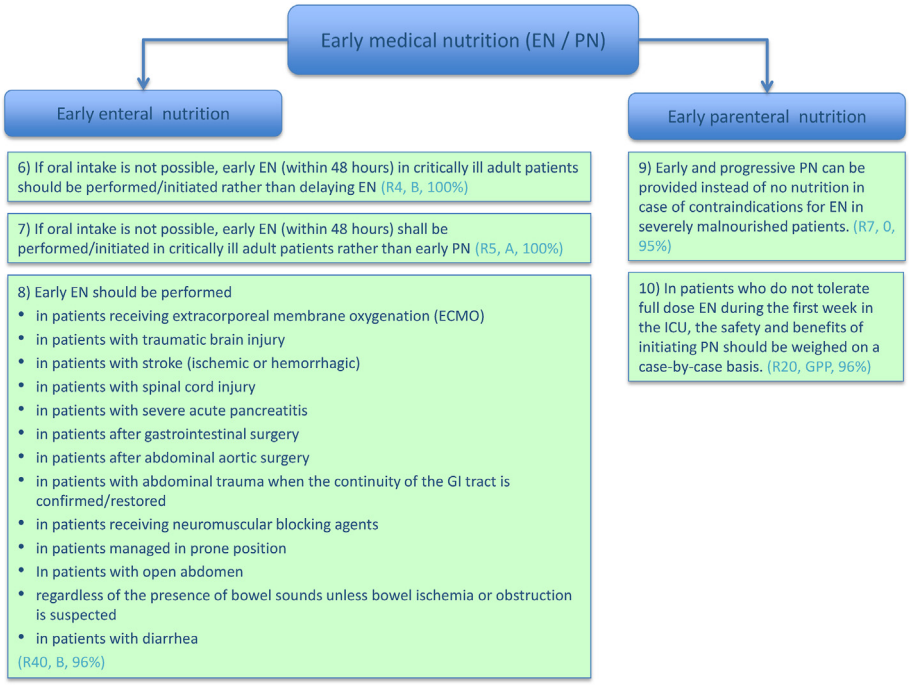


**Fig. 3.** Early medical nutrition (enteral/parenteral) in the ICU patient. Abbreviations: see Fig. 1.

**3) Oral diet shall be preferred over EN or PN in critically ill patients who are able to eat.**
**(R3, Grade GPP, strong consensus, 100%) (Fig. 2)**

**Commentary**

For patients able to eat, this route should be preferred if the patient is able to cover 70% of his needs from day 3–7, without risks of vomiting or aspiration. This amount (i.e. 70% or more of the needs) is considered as adequate.

**4) A general clinical assessment should be performed to assess malnutrition in the ICU, until a specific tool has been validated.**

**Remark:**

**General clinical assessment could include anamnesis, report of unintentional weight loss or decrease in physical performance before ICU admission, physical examination, general assessment of body composition, and muscle mass and strength, if possible.**
**(R2, Grade GPP, strong consensus 100%)**

**Commentary**

Weight and body mass index (BMI) do not accurately reflect malnutrition. Loss of muscle and sarcopenia have to be detected in the ICU, including in obese patients. Frailty has been suggested as the burden of comorbid disease, is well defined [15] and can be diagnosed by clinical observations or by complementary examinations [16]. Use of screening tools (NRS 2002) and assessment (subjective global assessment (SGA), mini-nutrition assessment (MNA)) are recommended in the daily practice. A definition of acute critical illness-associated malnutrition still needs to be developed [8]. Meanwhile, following the screening process, the malnutrition assessment requires the association of a phenotype (weight loss %, BMI, decrease in appetite, and/or low muscle mass) and an etiology e.g. critical illness [17] (GLIM (Global Leadership Initiative on Malnutrition) criteria).

Muscle mass can be evaluated by ultrasound [18], computerized tomography scan [19], or bioelectric impedance analysis (BIA) [20]. Sarcopenia, a decrease in muscle mass and/or function, is frequent in undernourished patients admitted to the ICU [21]. This loss of muscle may be considered as frailty and is associated with a prolonged hospital stay, and a decrease in quality of life and functional capacity [22]. Handgrip dynamometry can assess muscle function [23]. BIA can assess body composition in a stable patient not suffering from fluid compartment shifts and phase angle [24] is useful in the evaluation of the prognosis of critically ill patients. Patients with low muscle mass found at admission by computerized tomography have a higher length of stay and higher mortality [25].

**5) To avoid overfeeding, early full EN and PN shall not be used in critically ill patients but shall be prescribed within three to seven days (Fig. 2).**
**(R8, Grade A, strong consensus, 100%)**

**Commentary**

In a meta-analysis of studies comparing enteral and parenteral routes independent of timing, Elke et al. [26] found a reduction in ICU infections with EN as compared to PN (RR 0.64, 95% CI 0.48–0.87, $p = 0.004$, $I^2 = 47\%$). This difference did not occur when the amount of energy administered by PN and EN was similar (most recent studies), suggesting that caloric overfeeding may play a role in the infectious complications associated with PN and therefore in the decision process regarding the route, timing and the calorie target should also be taken into account. The energy/protein goal should be achieved progressively and not before the first 48–72 h to avoid over-nutrition. This progression should be ordered according to a local protocol preventing sharp and too rapid increases. Full targeted medical nutrition therapy is considered to achieve more than 70% of the resting energy expenditure (REE), but not to

exceed 100% of measured EE. Provision of excessive amounts of nutrients by any route should be avoided in the early phase of critical illness, which is associated with relevant endogenous energy production.

### 3.2. Medical nutrition therapy

#### 3.2.1. Early medical nutrition (Fig. 3)

**6) If oral intake is not possible, early EN (within 48 h) in critically ill adult patients should be performed/initiated rather than delaying EN.**
**(R4, Grade B, strong consensus, 100%)**

**Commentary**

In comparing early EN with delayed EN (six studies in ICU patients and four studies including non-ICU patients), and similar to an earlier meta-analysis [13], a reduction of infectious complications with early EN (RR 0.76, CI 0.59, 0.97, $p < 0.03$) was observed [4]. However, this was true only when including studies that also enrolled patients outside of the ICU. There were no differences in other outcomes between early and delayed EN. Excluding earlier studies (before 2000) attenuates the signal that early EN may reduce infectious complications compared to delaying EN beyond 48 h. Importantly, the dosage of EN was not taken into consideration in this meta-analysis.

**7) If oral intake is not possible, early EN (within 48 h) shall be performed/initiated in critically ill adult patients rather than early PN.**
**(R5, Grade A, strong consensus 100%)**

**Commentary**

When comparing early EN with early PN (six studies in ICU patients and seven studies with non-ICU patients included) a reduction of infectious complications with EN (RR 0.50, 95%CI 0.37–0.67, $p = 0.005$), as well as shorter ICU (RR -0.73, 95%CI -1.30 to −0.16, $p = 0.01$) and hospital stay (RR -1.23, 95%CI -2.02 to −0.45, $p = 0.002$) was observed, while mortality was not different [4]. However, recent randomized controlled trials (RCTs) do not demonstrate a clear advantage of EN over PN, and the observed benefit of EN in earlier studies may be due to the higher energy and amino acid/protein content provided by PN compared to EN.

**8) Early EN should be performed**
- in patients receiving extracorporeal membrane oxygenation (ECMO)
- in patients with traumatic brain injury
- in patients with stroke (ischemic or hemorrhagic)
- in patients with spinal cord injury
- in patients with severe acute pancreatitis
- in patients after gastrointestinal surgery
- in patients after abdominal aortic surgery
- in patients with abdominal trauma when the continuity of the gastrointestinal tract is confirmed/restored
- in patients receiving neuromuscular blocking agents
- in patients managed in prone position
- In patients with open abdomen
- regardless of the presence of bowel sounds unless bowel ischemia or obstruction is suspected
- in patients with diarrhea

**(R40, Grade B, strong consensus, 96%)**

**Commentary**

The European Society of Intensive Care Medicine (ESICM) guidelines formulated 17 recommendations favoring initiation of early EN (within 48 h of ICU admission) and seven recommendations favoring delaying EN [13], as summarized in our recommendations No. 8, 11, 12. In meta-analyses performed for the ESICM guidelines, early EN reduced infectious complications in unselected critically ill patients, in patients with severe acute pancreatitis, and after gastrointestinal surgery, whereas no evidence of superiority for early PN or delayed EN over early EN was detected in any of the sub-questions. However, all issued recommendations were weak due to the low quality of evidence, with most of them finally based on expert opinion [13].

**9) Early and progressive PN can be provided instead of no nutrition in case of contraindications for EN in severely malnourished patients.**
**(R7, Grade 0, strong consensus, 95%)**

**Commentary**

EN is not feasible when a patient is determined to be at high nutrition risk (e.g., NRS 2002 $\geq 5$) or severely malnourished, and, the initiation of low-dose PN should be carefully considered and balanced against the risks of overfeeding and refeeding, which may outweigh the expected benefits.

**10) In patients who do not tolerate full dose EN during the first week in the ICU, the safety and benefits of initiating PN should be weighed on a case-by-case basis.**
**(R20, Grade GPP, strong consensus, 96%)**

**Commentary**

There is no debate regarding the need for supplementing PN to EN in the case of prolonged nutritional deficit. However, the best timing to prescribe supplemental PN remains debated. Casaer et al. [14] observed that early (supplemental or exclusive) PN is associated with increased morbidity including prolonged ICU dependency and mechanical ventilation, and increased infection rate and need for renal replacement therapy. These findings may be related to the specific study protocol, the patients' characteristics and the large amounts of energy administered under guidance of predictive equations instead of indirect calorimetry. However, results of this study revealed the potential harm of nutritional intervention aiming at full, possibly overestimated calorie targets during the acute phase of critical illness. In addition, it is not known whether use of calorimetry would have resulted in different targets and different outcomes in the EPaNIC study. The optimal time point for supplemental PN aiming to achieve full caloric needs is not clear, but is suggested to be between days four and seven.

#### 3.2.2. Delayed medical nutrition (Fig. 4)

**11) EN should be delayed in several conditions displayed on Fig. 4**
- if shock is uncontrolled and hemodynamic and tissue perfusion goals are not reached, whereas low dose EN can be started as soon as shock is controlled with fluids and

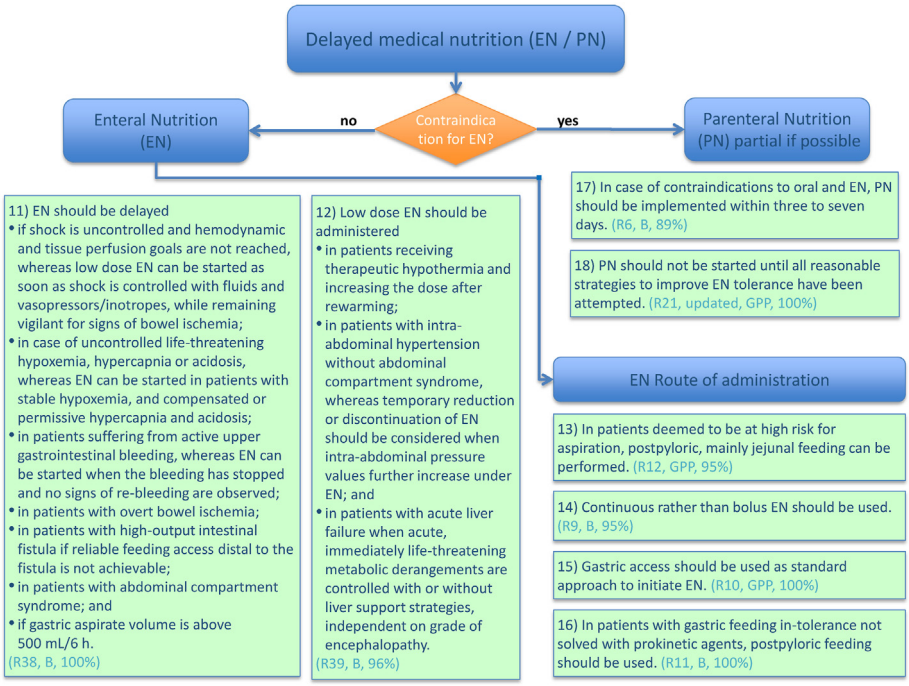


**Fig. 4.** Delayed medical nutrition (enteral/parenteral) in the ICU patient. Abbreviations: see Fig. 1.

vasopressors/inotropes, while remaining vigilant for signs of bowel ischemia;
- in case of uncontrolled life-threatening hypoxemia, hypercapnia or acidosis, whereas EN can be started in patients with stable hypoxemia, and compensated or permissive hypercapnia and acidosis;
- in patients suffering from active upper gastrointestinal bleeding, whereas EN can be started when the bleeding has stopped and no signs of re-bleeding are observed;
- in patients with overt bowel ischemia;
- in patients with high-output intestinal fistula if reliable feeding access distal to the fistula is not achievable;
- in patients with abdominal compartment syndrome; and
- if gastric aspirate volume is above 500 mL/6 h.

**(R38, Grade B, strong consensus, 100%%)**

**Commentary**

This recommendation is based on a previous recommendation published by the ESCIM [13]. See commentary to No. 8.

**12) Low dose EN should be administered**
- in patients receiving therapeutic hypothermia and increasing the dose after rewarming;
- in patients with intra-abdominal hypertension without abdominal compartment syndrome, whereas temporary reduction or discontinuation of EN should be considered when intra-abdominal pressure values further increase under EN; and
- in patients with acute liver failure when acute, immediately life-threatening metabolic derangements are controlled with or without liver support strategies, independent on grade of encephalopathy.

**(R39, Grade B, strong consensus, 96%)**

**Commentary**

This recommendation is based on a previous recommendation published by the ESCIM [13]. See commentary to No. 8.

### 3.2.3. *Enteral nutrition — route of administration (Fig. 4)*

**13) In patients deemed to be at high risk for aspiration, postpyloric, mainly jejunal feeding can be performed.**
**(R12, Grade GPP, strong consensus, 95%)**

**Commentary**

Patients with a very high risk of aspiration may benefit from early postpyloric EN. We recommend postpyloric feeding in patients with a high risk for aspiration. According to the American Society for Parenteral and Enteral Nutrition (ASPEN) recommendations [27], patients at increased risk for aspiration may be identified by a number of factors, including inability to protect the airways, support with mechanical ventilation, age >70 years, reduced level of consciousness, poor oral care, inadequate nurse:patient ratio, supine positioning, neurologic deficits, gastroesophageal reflux, transport out of the ICU, and use of bolus intermittent EN [28]. The Canadian Critical Care Practice Guideline guidelines [29] confirm this approach: "Strategies to Optimize Delivery and Minimize Risks of EN: Small Bowel Feeding vs. Gastric. Based on eleven level 2 studies, small bowel feeding compared to gastric feeding may be associated with a reduction in pneumonia in critically ill patients."

**14) Continuous rather than bolus EN should be used (Fig. 4).**
**(R9, Grade B, strong consensus, 95%)**

**Commentary**

Five studies were identified and meta-analysis found a significant reduction in diarrhea with continuous versus bolus administration (RR 0.42, 95%CI 0.19–0.91, p = 0.03), whereas no difference was identified in other outcomes [4]. Despite the fact that bolus administration is significantly different from continuous feeding in healthy individuals, it significantly increases gastric volume and superior mesenteric artery blood volume in critically ill patients [30], although these differences are not always translated into clinical advantages. This limited amount of data suggests that bolus and continuous enteral feeding can achieve the same target without an increase in side effects in any of these routes. Finally, bolus feeding could provide a greater stimulus for protein synthesis [31].

15) **Gastric access should be used as the standard approach to initiate EN.**
**(R10, Grade GPP, strong consensus, 100%) (Fig. 4)**

**Commentary**

Our meta-analysis [4] shows that feeding intolerance was more prevalent in the case of gastric feeding in five studies (RR 0.16, 95% CI 0.06–0.45, p = 0.0005). We observed a trend for less pneumonia (eleven studies) (RR 0.75, 95%CI 0.55–1.03, p = 0.07) in patients treated with postpyloric feeding with no differences in mortality (twelve studies), diarrhea (seven studies) or ICU length of stay. As postpyloric tube placement requires expertise, is commonly associated with some time delay, and is considered less physiological compared to gastric EN, the routine use of the postpyloric route is currently not justified. Moreover, postpyloric feeding could possibly be harmful in cases of gastrointestinal motility problems distal to the stomach. Taken together, we suggest using gastric access as a standard and implementing postpyloric access in the case of intolerance to gastric feeding due to gastroparesis.

16) **In patients with gastric feeding intolerance not solved with prokinetic agents, postpyloric feeding should be used (Fig. 4).**
**(R11, Grade B, strong consensus, 100%)**

**Commentary**

Postpyloric EN has been associated with a decrease in ventilator acquired pneumonia in several earlier meta-analyses, but this benefit did not translate into decreases in length of ventilation, ICU or hospital stay, or mortality [4]. It should be considered that postpyloric tube placement requires expertise, is probably less physiologic compared to gastric EN, and could possibly be harmful in cases of GI motility problems distal to the stomach.

*3.2.4. Parenteral nutrition (Fig. 4)*

17) **In case of contraindications to oral and EN, PN should be implemented within three to seven days.**
**(R6, Grade B, consensus 89%)**

**Commentary**

When to start, which route to prefer and how to progress PN have been a matter of debate for years., Recent guidelines written by ESPEN [1,2], ASPEN/SCCM [32], the Canadian Critical Care Practice Guideline group [29] and the most recent clinical practice guidelines on early EN in critically ill patients by the ESICM working group on gastrointestinal function [13] were considered when formulating the updated ESPEN recommendations [4]. The latter performed an extensive review of the literature, multiple meta-analyses, six web-seminars and utilized the GRADE methodology, evidence to decision framework and Delphi methodology. Since many of the authors of the current guidelines are also co-authors of the ESICM guidelines, a decision was made to endorse the respective recommendations related to early enteral feeding. Following the literature search we could agree with other guideline statements such as the ASPEN/SCCM guidelines [27] suggesting the "use of EN over PN in critically ill patients who require nutrition support therapy" (Evidence low to very low). The Canadian Critical Care Practice Guideline guidelines [29] recommend similarly stating "when considering nutrition support for critically ill patients, we recommend the use of EN over PN in patients with an intact gastrointestinal tract."

18) **PN should not be started until all reasonable strategies to improve EN tolerance have been attempted.**
**(R 21, updated, Grade GPP, consensus, 100%)**

**Commentary**

1. Revised indications/contraindications of PN considering dosage: Early full feeding independent of the route may be associated with impaired outcomes [33]. In fact, early full EN may even be more detrimental than early full PN [34].
2. Complications of EN and evidence on enteral feeding intolerance (EFI): EFI is defined as worsening gastrointestinal function in response to feeding attempts. Full EN may be associated with severe complications in shock patients [33,35]. Enhancing EN tolerance and reducing complications lacks a definitive strategy. Proposed interventions include:
   a) Using adequate indications and contraindications for EN (according to recommendation 38)
   b) Using postpyloric feeding in patients with gastric feeding intolerance/high risk for aspiration (according to recommendations 11 and 12), while being aware of the risk of bowel distension and mesenteric ischemia (very low evidence) [36]. Vomiting/gastric residual volume (GRV) monitoring may be needed to achieve safety.
   c) Using prokinetic drugs as indicated to prevent complications, rather than for maximizing EN provision. Energy-dense feed delivery is associated with increased prokinetic use, but does not affect other outcomes [37]. A better survival was observed in patients in whom EFI was resolved within 72 h, more likely in patients receiving prokinetics [38].
   d) Using adequate definitions for EN-associated complications to define EFI: abdominal distention, gastric overfilling, vomiting, diet regurgitation, bowel distension up to Ogilvie's syndrome and/or intestinal ischemia, diarrhea. Definition of EFI should not be limited solely to gastric function [39].
   e) Considering intra-abdominal pressure to initiate and maintain, or not, EN [40].
   f) Monitoring of gastrointestinal function with the use of scores such as the Gastrointestinal Dysfunction Score (GIDS) (not yet validated) [41].

*3.2.5. Energy and protein targets (Fig. 5)*

19) **In critically ill mechanically ventilated patients, energy expenditure (EE) should be determined by using indirect calorimetry.**
**(R15, Grade B, strong consensus, 95%)**

### Commentary

The weakness of predictive equations and the use of indirect calorimetry have been subject to multiple evaluations and recommendations from ESPEN [2] and ASPEN [27], both preferring the use of indirect calorimetry to evaluate ICU patient actual energy expenditure The predictive equations are associated with significant inaccuracy (up to 60%), leading to over or under evaluation of the needs and inducing over or underfeeding [42]. Numerous meta-analyses have demonstrated the poor value of predictive equations [43,44], variability that is increased because body weight remains difficult to accurately assess [45].

**20) If indirect calorimetry is used, isocaloric nutrition rather than hypocaloric nutrition can be progressively implemented after the early phase of acute illness.**
**(R16, Grade 0, strong consensus, 95%) (Fig. 5)**

### Commentary

Our meta-analysis focused only on studies using indirect calorimetry found a trend (RR 1.28, 95%CI 0.98–1.67, p = 0.07) to improved short-term mortality when using indirect calorimetry to identify the energy target, compared to hypocaloric regimens but there were no significant differences in long term mortality, infection or length of stay [4]. Four RCTs have based their energy targets on indirect calorimetry. The pilot TICACOS study [46] showed that such a strategy was associated with an improvement in 60 day survival in the per protocol study, but also to an increase in length of ventilation, infections and length of stay related to the calorie overload and positive energy balance due to non-nutritional energy intakes. Petros et al. [47] showed a reduction in infection rate in the study group. Heidegger et al. [48] measured EE at day 3 and adapted the energy intake accordingly, comparing supplemental PN from day four to an EN only group. The intervention group had a lower late nosocomial infection rate after day 9. The recent EAT-ICU study compared the goal-directed group, receiving the EE measured with indirect calorimetry as a caloric target to reach within 24 h to patients receiving standard therapy. The study group also received protein according to urinary nitrogen loss. No advantages or harm were observed in terms of functional outcome, morbidity, or mortality in this RCT [49].

**21) Statement: If calorimetry is not available, using $VO_2$ (oxygen consumption) from pulmonary arterial catheter or $VCO_2$ (carbon dioxide production) derived from the ventilator will give a better evaluation on EE than predictive equations.**
**(S2, consensus, 82%)**

### Commentary

If indirect calorimetry is not available, calculation of REE from $VCO_2$ only obtained from ventilators (REE = $VCO_2$ x 8.19) has been demonstrated to be more accurate than equations [50] but less accurate than indirect calorimetry [51]. $VO_2$ calculated from pulmonary artery catheter can also be used. In the absence of indirect calorimetry, $VO_2$ or $VCO_2$ measurements, the use of simple weight-based equations (such as 20–25 kcal/kg/d) may be preferred [1,2,27].

**22) If predictive equations are used to estimate the energy need, hypocaloric nutrition (below 70% estimated needs) should be preferred over isocaloric nutrition for the first week of ICU stay.**
**(R19, Grade B, strong consensus, 95%)**

### Commentary

Studies using predictive equations and observational studies were analyzed [4]. If predictive equations are used, we suggest using hypocaloric nutrition (up to 70% estimated needs), over isocaloric nutrition (70% or greater of estimated needs), in the early phase of acute illness (RR 0.92, 95%CI 0.86–0.99, p = 0.02). Various studies have compared energy intake based on predictive equations

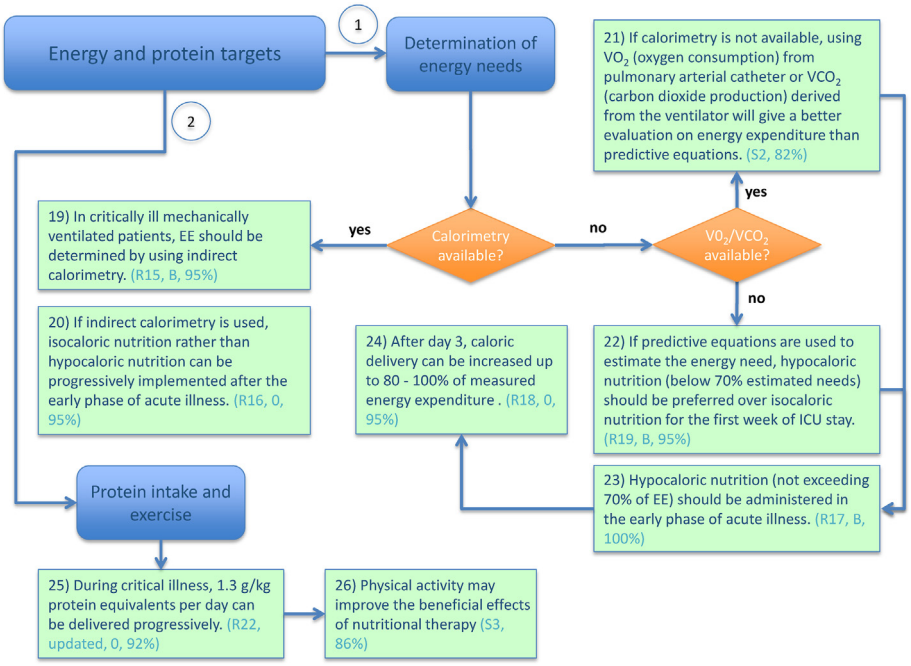


**Fig. 5.** Energy and protein targets for ICU patients. EE, energy expenditure.

to reduced calorie intake achieving even trophic enteral feeding concluding that there was no difference between normocaloric versus hypocaloric diets in critically ill patients [4]. Berger & Pichard observe an increase in mortality in the group of patients receiving energy close to the prescribed recommended energy intake [52]. Conversely, Reignier et al. observed a better outcome in patients receiving low energy and proteins over 7 days (Nutrirea 3 = ref 33). Large observational series including hundreds to thousands of patients have observed that the optimal calorie load associated with the best survival is around 80% of predicted energy needs [53], whereas others suggested no relation between intake and outcome or better outcome with lower energy intakes [54]. However, in all these studies, calorie delivery was lower than recommended/prescribed or the studies were not targeted to this parameter.

**23) Hypocaloric nutrition (not exceeding 70% of EE) should be administered in the early phase of acute illness (Fig. 5).**
**(R17, Grade B, strong consensus, 100%)**

**Commentary**

A larger database analysis suggested that energy intake is associated with significantly improved survival when it is close to measured EE [55] or between 70 and 100% of the repeatedly measured resting EE [56]. Undernutrition or over-nutrition is deleterious to outcome according to these large observational studies. If there is consensus stating that overfeeding should be avoided, it remains difficult to define which calorie targets should be proposed in the different phases of critical illness. Actual EE should not be the target during the first 72 h of acute critical illness. Early full feeding causes overfeeding as it adds to the endogenous energy production which amounts to 500–1400 kcal/d and can lead to. deleterious effects such as increased length of stay, ventilation duration and infection rates [57]. Early full feeding also increases the risk of refeeding (see No. 60). On the other hand, a too low intake, below 50%, was associated in retrospective studies with a worse clinical outcome. may lead to severe calorie debt and empty the energy reserves, reduce lean body mass and may increase infectious complications [58,59]. However, prospective studies (Nutrirea-3 Permit EPANIC) comparing two levels of energy intake found a benefit associated with early provision of lower amounts.

**24) After day three, energy delivery can be increased up to 80–100% of measured EE.**
**(R18, Grade 0, strong consensus, 95%)**

**Commentary**

Recently the analysis of a large data base including 1171 patients with indirect calorimetry data [56] confirmed that under- and overfeeding were both deleterious, and that the optimal amount appeared to be between 70 and 100% of measured EE. Prospective randomized studies comparing the delivery of 70–80% of the measured EE to another regimen may improve our knowledge.

**25) During critical illness, 1.3 g/kg protein equivalents per day can be delivered progressively.**
**(R22, updated, Grade 0, strong consensus, 92%)**

**Commentary**

Numerous observational studies showed associations between high-dose protein delivery and improved outcomes (morbidity or mortality). However, RCTs did not confirm the expected benefit of higher protein intakes alone, or combined with physical activity or energy [37,54,58]. Recently [60], a comparison between 1.6 ± 0.5 g/kg/d compared with 0.9 ± 0.3 g/kg/d administered protein did not find any significant difference in outcomes, but an increased mortality in patients with acute kidney injury randomized to high protein intakes. The recruited patients' energy intake was very variable, although similar in the groups (around 14 kcal/kg/d) receiving high and low-dose proteins. In accordance with the Lee et al. meta-analysis, there is no support to recommend higher doses than 1.3 g/kg/d, except for increased muscle mass in individual patients. Medium doses (not low and not high) are associated with the best outcomes [61]. The timing of administration has been mainly studied retrospectively or in post hoc analysis [62]. Recent stable isotope studies [63,64] demonstrate that amino acid conversion is improved with time, allowing an increase in whole body protein production only after the early period of the acute phase, even increasing further in the post-acute phase. This supports the progressive increase of protein intakes. There is a need for well-conducted RCTs to answer the question of the best timing and dose of protein administration in the ICU.

**26) Statement 3: Physical activity may improve the beneficial effects of nutritional therapy.**
**(S 3, consensus, 86%)**

**Commentary**

Exercise has been suggested in several studies [65,66] to be effective in preventing anabolic resistance, reducing morbidity and improving the level of activity. Administration of increased protein intake together with increased physical activity during the late phase of critical illness should be further explored.

*3.2.6. Other substrates (Fig. 6)*

**27) The amount of glucose (PN) or carbohydrates (EN) administered to ICU patients should not exceed 5 mg/kg/min.**
**(R23, Grade GPP, strong consensus, 100%)**

**Commentary**

The optimal nutritional composition of macronutrients is defined by minimal requirements and upper limits. Carbohydrates are the preferential substrate for production of energy, but in critical illness, insulin resistance and hyperglycemia are common secondary to stress. A minimal requirement has been proposed in previous guidelines [2] based on a society recommendation [67]. This evaluation is weak as has been stated: “carbohydrate could be theoretically eliminated from the diet, but it is probably safe® to give 150 g/d: This may be explained by organ dependence on glucose such as the brain (1–0 - 120 g/d), red blood cells, immune cells, renal medulla and all the transparent tissues of the eyes” [2] and the risks associated with hypoglycemia. The exact optimal carbohydrate amount to administer is difficult to determine. Endogenous glucose production is increased and does not decrease when nutrients and insulin are administered as compared with healthy conditions [68]. Excessive glucose based energy provision is associated with hyperglycemia, enhanced $CO_2$ production, enhanced lipogenesis, increased insulin requirements and no advantage in protein sparing in comparison with lipid based energy provision [69]. The use of diabetic-specific enteral

formula in ICU patients suffering from Type 2 Diabetes Mellitus decrease the requirement for insulin [70,71] and. The recommended glucose administration should not exceed 5 mg/kg/min [2].

**28) The administration of intravenous lipid emulsions should be generally a part of PN.**
**(R24, Grade GPP, strong consensus, 100%) (Fig. 6)**

**Commentary**

Essential fatty acids (FA) were previously recommended at a dose of 8 g/d, but recent studies have shown that pediatric patients receiving pure fish oil lipid emulsions did not develop essential FA deficiency even after months. Lipid metabolism is modified in critical illness and low plasma triglyceride levels and high-density lipoprotein (HDL) cholesterol levels are associated with improved survival [72]. Administration of marked amounts of carbohydrates and lipids can lead to hyperglycemia and liver function test abnormalities while high fat administration can lead to lipid overload, and especially unsaturated fat to impaired lung function and immune suppression [73]. Close monitoring of triglycerides and liver function tests may guide the clinician [74].

**29) Intravenous lipid (including non-nutritional lipid sources) should not exceed 1.5 g lipids/kg/d and should be adapted to individual tolerance.**
**(R25, Grade GPP, strong consensus, 100%) (Fig. 6)**

**Commentary**

For intravenous lipids, the upper recommendation is 1 g/kg body weight/d with a tolerance up to 1.5 g/kg/d. Administration in excess can lead to waste, storage or even toxicity.

Special attention should be paid if propofol is administered, since it is a source of FAs. This lipid solution contains 1.1 kcal/mL and can provide a large energy load exceeding nutritional support [75]. Electronic patient data management systems help to recognize this calorie overload. Citrate use in continuous veno-venous hemo-diafiltration is also associated with increased carbohydrate load and should be taken into account as a non-nutritional calorie intake [75].

Regarding the FA composition of the lipid emulsions, recent expert recommendations indicated that a blend of FAs should be considered, including medium chain triglycerides (MCTs), omega-9 monounsaturated FAs, and omega-3 polyunsaturated FAs. At this stage, the evidence for omega-3 FA-enriched emulsions in non-surgical ICU patients is not sufficient to recommend it as a standalone [76].

**30) In patients with burns >20% body surface area, additional enteral doses of glutamine (GLN) (0.3–0.5 g/kg/d) should be administered for 10–15 days as soon as EN is commenced.**
**(R26, Grade B, strong consensus, 95%)**

**Commentary**

The amino acid GLN is a normal component of proteins, representing around 8% of all amino acids, and is present in standard

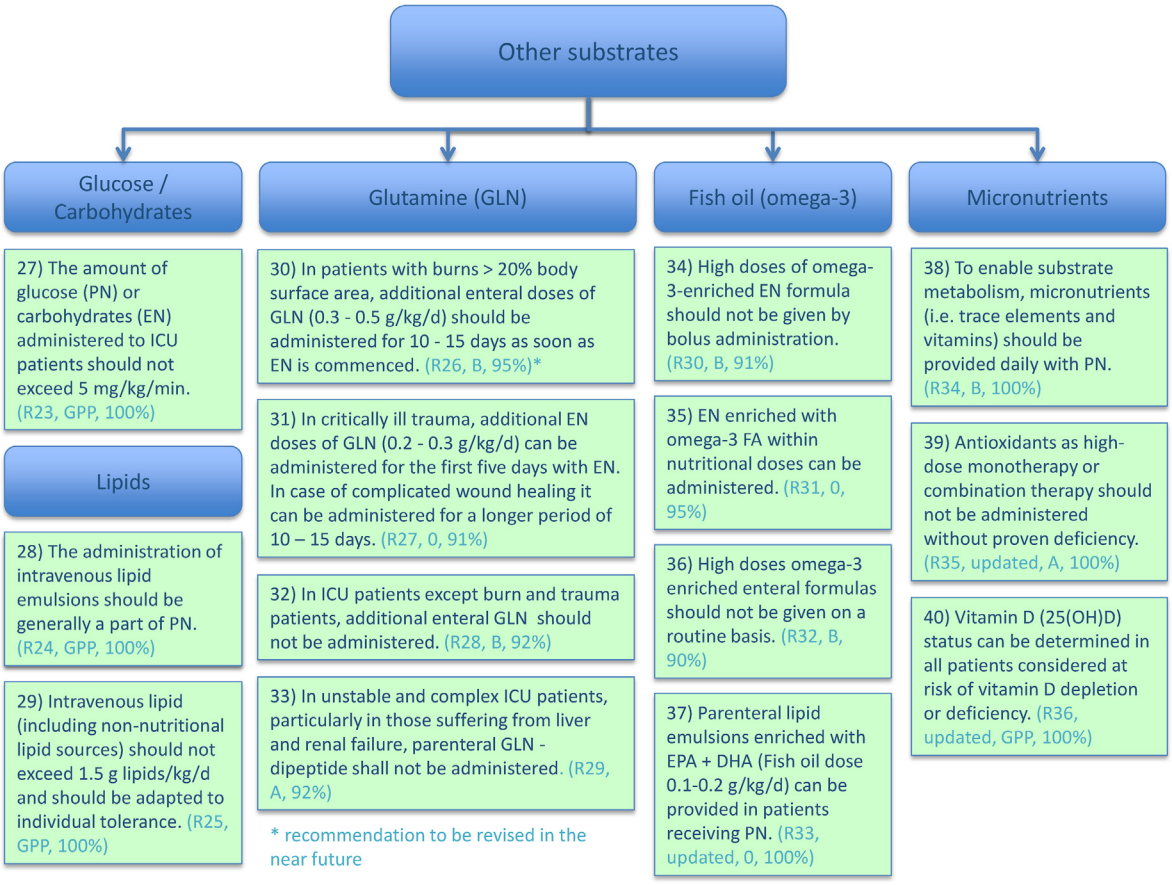


**Fig. 6.** Nutritional substrates other than protein needed for treatment of ICU patients.

commercial enteral feeds. GLN for parenteral use has been available since 1994, after its synthesis by Fürst and Stehle [77]. For stability reasons, it was not present in standard PN.

In major burns, studies include a limited number of patients: nevertheless, the existing randomized trials have repeatedly demonstrated that GLN (and its precursor ornithine α-ketoglutarate) has beneficial effects in major burn injuries, reducing infectious complications (mainly gram negative infections) and also mortality [4]. This has been confirmed in the latest meta-analysis [4], and is included in the specific ESPEN burn guidelines [78], but is challenged by the largest RCT revealing no benefit from GLN supplementation in burns [79]. A higher GLN requirement in burn patients is explained by exudative losses: analysis of burn exudates shows that GLN is lost in larger amounts than any other amino acid [80].

**31) In critically ill trauma, additional EN doses of GLN (0.2–0.3 g/kg/d) can be administered for the first five days with EN. In case of complicated wound healing, it can be administered for a longer period of ten to 15 days (Fig. 6). (R27, Grade 0, strong consensus, 91%)**

**Commentary**

The efficiency of enteral GLN on infection reduction was also suggested in major trauma. A RCT in 20 trauma patients with delayed wound healing, showed that oral antioxidant and GLN containing supplements reduced time to wound closure (22 days versus 35: $p = 0.01$). In the control patients a decline of plasma GLN was observed, while it was modestly increased in those having received 20 g GLN per day for 14 days. Finally, enteral GLN was shown to improve body composition and in particular lean body mass in a group of 44 head and neck cancer patients randomized to receive a GLN supplement (30 g daily) for four weeks [81]. The authors observed a significant improvement of fat-free mass, serum albumin, and quality of life scores post-operatively [81].

**32) In ICU patients except burn and trauma patients, additional enteral GLN should not be administered (Fig. 6). (R28, Grade B, strong consensus, 92%)**

**Commentary**

Rodas et al. [82] showed a U-shaped association between plasma GLN levels and outcome.

In other critically ill patients, the MetaPlus trial [83] showed no advantage in terms of infection of a feeding solution containing additional enteral GLN. Of note, none of the groups received the planned high dose protein resulting in a mean delivery of 0.9 g/kg/d.

**33) In unstable and complex ICU patients, particularly in those suffering from liver and renal failure, parenteral GLN-dipeptide shall not be administered (Fig. 6). (R29, Grade A, strong consensus, 92%)**

**Commentary**

Since the 1990s, many studies have shown benefits in terms of infectious complication reduction, lower mortality and reduction of hospital costs recently confirmed in an analysis including RCTs performed after 2000, using GLN as part of nutrition support [84].

When analyzed together [84] most single center studies observed improved survival while some multicenter studies did not confirm this finding, The positive trials used GLN as part of global nutrition in stabilized patients. The REDOXS study [85], designed as a 2 x 2 factorial trial, generated concerns for several reasons, including the fact that the randomization was associated with higher severity with more organ failures in the GLN groups upon enrollment, largely explaining the higher mortality. Finally, Stehle et al. [86] in a meta-analysis including only stable patients showed an advantage to administering GLN.

**34) High doses of omega-3-enriched EN formula should not be given by bolus administration. (R30, Grade B, strong consensus, 91%)**

**Commentary**

Aggregating all the studies in ICU patients without taking into account the amount of omega-3 FAs or whether they are given as bolus or continuous administration, does not yield any advantage for any formula [87]. Glenn and Wischmeyer [88] analyzed separately the studies administering omega-3 FAs as a bolus or in a continuous manner and found that continuous administration improved length of stay and length of ventilation; in contrast, bolus administration had no advantage. The pre-emptive administration of the same formula administered in three studies in severe, ventilated, multiple trauma patients did not find any advantage [89]. In at least one study, the membrane content of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) was very low at baseline and was hardly corrected with omega-3 and borage oil administration, suggesting that we do not know the exact amount of omega-3 FAs to administer to this category of patients.

**35) EN enriched with omega-3 FA within nutritional doses can be administered. (R31, Grade 0, strong consensus, 95%)**

**Commentary**

Eight studies addressing this question were identified; in four of them antioxidants were also given. A meta-analysis did not reveal any benefit of omega-3 FA, but there was a trend towards increase in $PO_2/FiO_2$ with intervention (RR 22.59, 95%CI -0.88 - 46.05, $p = 0.06$). However, because it may change quickly and is dependent on ventilator settings, fluid status, body position etc. $PO_2/FiO_2$ is probably not the best outcome variable [4].

Enteral formulae enriched in borage oil and/or omega-3 FAs have been administered in patients suffering from adult respiratory distress syndrome, acute lung injury and sepsis with positive effects regarding length of stay, length of ventilation and even mortality [4]. Our meta-analysis found no significant advantage in oxygenation for enteral formulae enriched in omega-3 FAs (mainly EPA), gamma-linolenic acid and antioxidants over control groups receiving lipid-rich formulas [4].

**36) High doses omega-3 enriched enteral formulas should not be given on a routine basis. (R32, Grade B, consensus, 90%)**

**Commentary**

In the post-hoc analysis of the MetaPlus study [90], administrating GLN, EPA/DHA and antioxidants to critically ill patients, only the change from baseline to day 4 of EPA + DHA/long chain triglyceride (LCT) ratio was statistically significantly associated with six month mortality (hazard ratio 1.18, 95%CI 1.02–1.35, $p = 0.021$) suggesting a harmful effect of these nutrients in medical ICU patients. It has to be noted that this harmful effect was not observed in

the previous studies on patients in acute lung injury or adult respiratory distress syndrome.

**37) Parenteral lipid emulsions enriched with EPA + DHA (Fish oil dose 0.1–0.2 g/kg/d) can be provided in patients receiving PN (Fig. 6).**
**(R33, updated, Grade 0, strong consensus, 100%)**

**Commentary**

Recently, several studies have shown the biological effects, clinical benefits, and safety of lipid emulsions with reduced content of 18-carbon omega-6 FA. The use of intravenous fat emulsions based solely on soybean oil (rich in 18-carbon omega-6 FA) should be avoided due to their likely pro-inflammatory effects [2]. Alternative lipid emulsions including sources incorporating olive oil, fish oil, and coconut oil (MCTs) in various combinations [76] are available. Mechanistic understandings of the action of omega-3 FA from fish oil have advanced [91], and positive effects of fish oil on organ function (kidney, liver, muscle) have been reported [92]. New trials and meta-analyses of fish oil containing PN in critically ill and surgical patients have been published [93]. Some meta-analyses combine trials of enteral and parenteral fish oil in critically ill patients [94,95]. Each of these meta-analyses favors fish oil for clinical benefit. Pradelli et al. [96] conducted a meta-analysis of 24 RCTs comparing fish oil-enriched PN with standard (non-fish oil-enriched) PN in adult patients in the ICU. In critically ill ICU patients, fish oil was associated with reductions in infections (RR 0.65, 95% CI 0.46–0.94), ICU LOS (−2.14 days, 95% CI -3.89 to −0.40), and hospital length of stay (−3.98 days, 95% CI -6.90 to −1.06), but with a non-significant reduction in 30-day mortality in all ICU patients (RR 0.90, 95% CI 0.69–1.16). It was estimated in cost-effectiveness analyses that parenteral fish oil would lower overall hospital costs (compared with standard PN) in all six countries considered.

**38) To enable substrate metabolism, micronutrients (i.e. trace elements and vitamins) should be provided daily with PN (Fig. 6).**
**(R34, Grade B, strong consensus, 100%)**

**Commentary**

Providing micronutrients to include the full range of trace elements and vitamins is an integral part of nutritional support as stated in the 2009 guidelines [2]. Parenteral and enteral feeding preparations differ in that commercially available PN solutions contain no micronutrients for stability reasons: this requires their separate prescription [2]. There are no PN studies with or without micronutrients.

The blood levels of several micronutrients are below normal ranges during the inflammatory response, and hence the impact of their provision is difficult to interpret. Recent evidence tends to show that persistently low zinc concentrations might become an important biomarker of adverse outcomes in sepsis [97].

We recommend the repletion of micronutrients in conditions of chronic and acute deficiency. Continuous renal replacement therapy for more than two weeks is a new cause of acute micronutrient deficiencies and particularly of severe copper deficiency that may explain life-threatening complications in patients requiring this therapy [98].

**39) Antioxidants as high-dose monotherapy or combination therapy should not be administered without proven deficiency (Fig. 6).**
**(R35, updated, Grade A, strong consensus 100%)**

**Commentary**

High-quality RCTs evaluating high doses of selenium [99], vitamin D [100,101], vitamin C [102–108], and combinations of vitamin C and thiamine [109], revealed no hard clinical benefit of such interventions.

**40) Vitamin D (25(OH)D) status can be determined in all patients considered at risk of vitamin D depletion or deficiency (Fig. 6).**
**(R36, updated, Grade GPP, strong consensus 100%)**

**Commentary**

Vitamin D3 can be synthesized in sufficient amounts by the human body so long as there is exposure to sunlight and good liver and renal function. Vitamin D3 has a nuclear receptor and a large number of genes are under direct or indirect control of this vitamin. Hypovitaminosis D is common in the general population, with a seasonal occurrence, while low plasma concentrations of vitamin D have been repeatedly shown in critically ill patients. In the latter patients, deficiency has been associated with poor outcome including excess mortality, longer length of stay, higher sepsis incidence, and longer mechanical ventilation [110]. There is an uncertainty regarding dosing and timing of vitamin D administration. Therefore, this recommendation replaces the 2 recommendations (R36 and R37) related to dosage in the previous guidelines.

### *3.3. Medical nutrition in special cases (Fig. 7)*

#### *3.3.1. The non-intubated patient*

**41) In non-intubated patients not reaching the energy target with an oral diet, oral nutritional supplements should be considered first and then EN.**
**(R4 1, Grade GPP, strong consensus, 96%)**

**Commentary**

Reeves et al. [111] described the energy and protein intakes of patients with adult respiratory distress syndrome receiving non-invasive ventilation. From this small observational study, it is concluded that oral intake was inadequate, mainly with increasing time on non-invasive ventilation, and earlier during their hospital admission. In total, 78% of the patients met less than 80% of the requirements. The authors recommended referring the patients recognized to have swallowing issues for swallowing evaluation, to prevent oral nutrition complications.

**42) In non-intubated patients with dysphagia, texture-adapted food can be considered. If swallowing is proven unsafe, EN should be administered.**
**(R4 2, Grade GPP, strong consensus, 94%)**

**Commentary**

Oral intake is impaired **after extubation** and a high incidence of swallowing dysfunction has been described (between 10 and 67.5%, with a mean around 50%, despite different timing and methods used for assessing the dysphagia) [112]. This post-

extubation swallowing disorder could be prolonged for to up to 21 days mainly in the elderly and after prolonged intubation. Thus, at 21 days post-extubation, 24% of older patients were feeding tube dependent [113]. Recently, 29% of 446 ICU patients had prolonged post-extubation swallowing disorder at discharge and some post-extubation swallowing disorder has been shown four months after discharge [114]. The same authors who described the tools to diagnose post-extubation swallowing disorder, also suggest the use of thickening food to increase oral intake.

**43) In non-intubated patients with dysphagia and a very high aspiration risk, postpyloric EN or, if not possible, temporary PN during swallowing training with removed nasoenteral tube can be performed.**
**(R4 3, Grade GPP, strong consensus, 92%)**

**Commentary**

Oral intake is frequently prescribed in the intensive care setting varying from 25 to 45% of the patients in the first four days, but does not reach the energy or protein requirements according to the Nutrition Day ICU survey [6]. This population includes patients admitted for monitoring, patients receiving non-invasive ventilation and post intubation/tracheostomy patients.

**After tracheostomy**, a cohort study showed that the majority of the patients returned to oral intake, but the time to commencement of oral intake was correlated with increased time to decannulation and increased time to decannulation correlated with increased hospital length of stay [115]. Supplemental PN has not been extensively studied in this population.

### 3.3.2. The surgical patient (Fig. 7)

**44) In patients after abdominal or esophageal surgery, early EN can be preferred over delayed EN.**
**(R4 5, Grade 0, strong consensus, 96%)**

**Commentary**

We performed a meta-analysis of EN vs no nutrition within the first 48 h, which did not reveal clear benefit of EN in this subgroup of patients, but a trend towards fewer infectious complications was observed (RR 0.47, 95%CI 0.20–1.07, p = 0.07) [4]. Importantly, the presence of an intestinal anastomosis or re-anastomosis without leakage should not delay EN.

**45) In critically ill patients with surgical complications after abdominal or esophageal surgery and unable to eat orally, EN (rather than PN) should be preferred unless discontinuity or obstruction of gastrointestinal tract, or abdominal compartment syndrome is present (Fig. 7).**
**(R4 6, Grade GPP, strong consensus, 96%)**

**Commentary**

Esophageal surgery commonly results in the loss of the lower esophageal sphincter function and is therefore associated with a

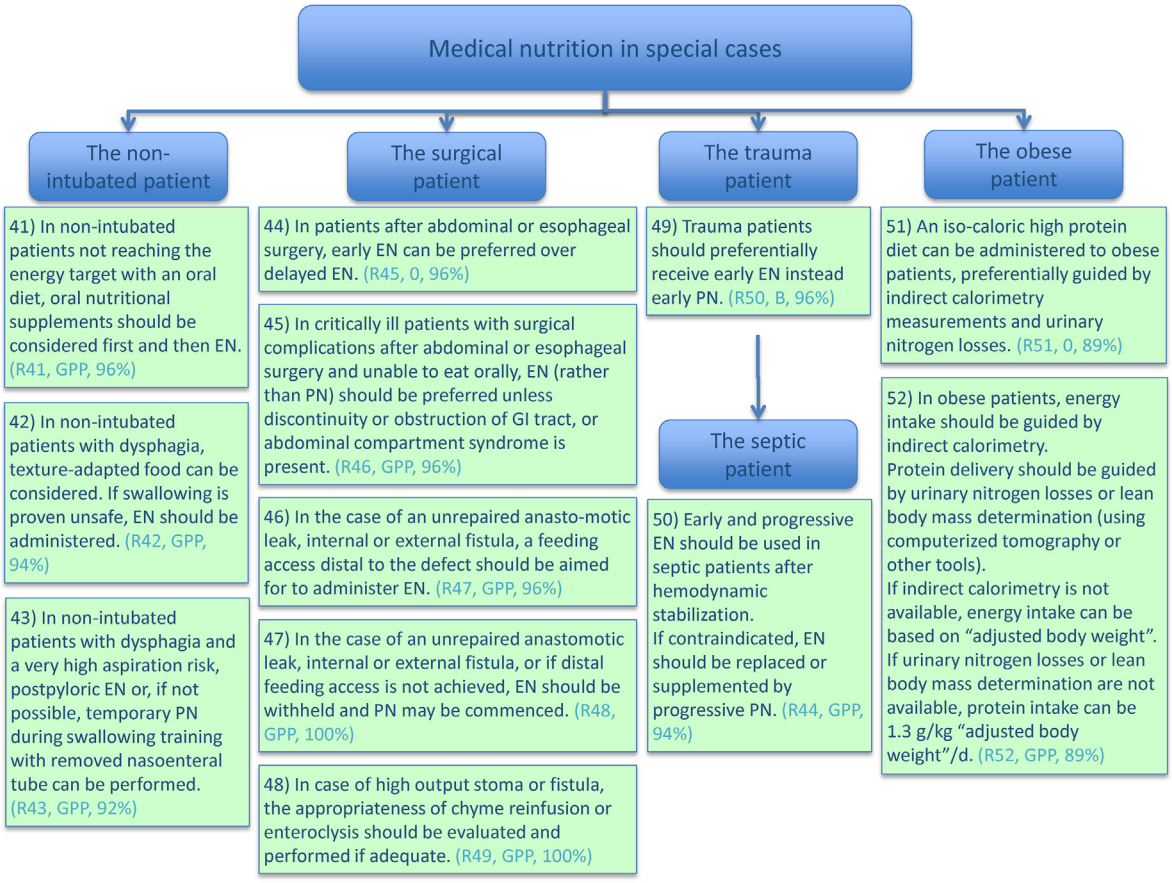


**Fig. 7.** Medical nutrition in special cases. Abbreviations: see Fig. 1.

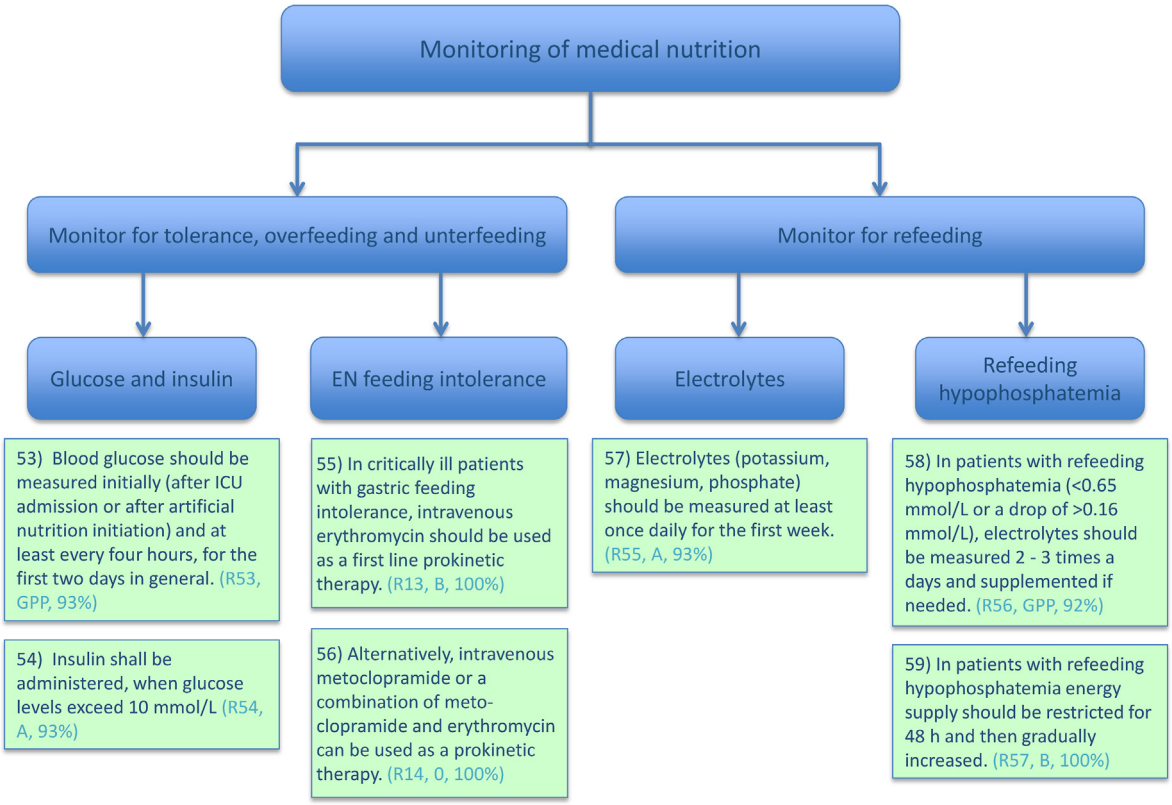


**Fig. 8.** Monitoring of medical nutrition in the ICU. Abbreviations: see Fig. 1.

significantly increased risk of aspiration. Therefore, many centers use "nil per mouth" strategy with EN via a surgical jejunostomy. We identified two RCTs addressing early EN via surgical jejunostomy in patients after esophageal surgery (in one case, the study group included other upper gastrointestinal surgery patients, not limited to esophageal surgery), suggesting potentially beneficial effects on the inflammatory state when compared with early PN and lower infection rates when compared with delayed EN. One larger retrospective study comparing early EN via surgical jejunostomy with early PN resulted in less life-threatening complications and a shorter postoperative hospital stay [116].

**46) In the case of an unrepaired anastomotic leak, internal or external fistula, a feeding access distal to the defect should be aimed for to administer EN.**
**(R4 7, Grade GPP, strong consensus, 96%)**

Without evidence, but based on common reasoning and pathophysiological considerations, surgical complications leading to gastrointestinal contents leaking into the abdominal cavity should always lead to withholding/stopping EN. At the time of developing such complications, patients usually have developed considerable energy deficits. Therefore, PN should be considered early after re-surgery if such a problem clearly cannot be solved within the next days, but started at a slow infusion rate. Enteral feeding access distal to the leak should be aimed for in these cases. Small bowel ischemia associated with early (in some cases aggressive) EN via surgical jejunostomy has been reported in several case reports [117,118]. In these cases, close monitoring of abdominal symptoms is required, and only continuous administration and slow build-up of EN via jejunostomy is advocated.

**47) In the case of an unrepaired anastomotic leak, internal or external fistula, or if distal feeding access is not achieved, EN should be withheld and PN may be commenced.**
**(R4 8, Grade GPP, strong consensus, 100%)**

**Commentary**

Two studies addressing early EN vs early PN in elective upper gastrointestinal surgery were identified [119–121]. In a sub-group analysis of the EPaNIC study, early and late PN were compared in complicated pulmonary/esophageal and abdomino-pelvic surgery patients. Reduced infection rates in late vs early PN were observed (29.9% vs. 40.2%, $p = 0.01$) with no difference in any mortality outcomes, whereas all these patients received virtually no EN during the seven study days [14]. The latter finding should most likely be interpreted as a harmful effect of early full feeding, also demonstrated in several other recent studies.

**48) In case of high output stoma or fistula, the appropriateness of chyme reinfusion or enteroclysis should be evaluated and performed if adequate (Fig. 7).**
**(R 49, Grade GPP, strong consensus, 100%)**

**Commentary**

In many cases of complicated abdominal surgery, patient tolerance to EN is impaired. Furthermore, depending on surgery, maldigestion and/or malabsorption may occur. Therefore (supplemental), PN should be considered timely to avoid prolonged nutritional deficits. In specific situations with high-output stoma or fistula, chyme reinfusion or entero/fistuloclysis should be considered [122].

### 3.3.3. The trauma patient (Fig. 7)

**49) Trauma patients should preferentially receive early EN instead of early PN.**
**(R 50, Grade B, strong consensus, 96%)**

**Commentary**

Our meta-analysis including three studies showed a decrease in length of stay (RR -0.47, 95%CI -7.57 to −1.71, p = 0.002), and a trend for decrease in mortality (RR 0.69, 95%CI 0.39–1.23, p = 0.21), but no difference in incidence of pneumonia when early EN was administered rather than early PN [4].

Most trauma patients are not malnourished on admission (6% SGA C), but may become malnourished during ICU stay (increase in SGA B) [123]. Kompan et al. [124] compared early EN to early PN followed by EN in multiple trauma patients and found a significant decrease in pneumonia and length of stay, but not in hospital stay and mortality. Fan et al. [125] compared three groups: early EN, early PN and EN followed by supplemental PN. Complications and mortality were significantly decreased and nutritional status and clinical outcomes were improved in the early EN + supplemental PN group. An earlier meta-analysis [126] showed that early EN was associated with reduced mortality. Higher protein intake reaching 1.5–2 g/kg/d may be considered in this population, since there are large protein losses (20–30 g/L of abdominal fluid) [127].

### 3.3.4. The septic patient (Fig. 7)

**50) Early and progressive EN should be used in septic patients after hemodynamic stabilization.**

**If contraindicated, EN should be replaced or supplemented by progressive PN.**
**(R4 4, Grade GPP, strong consensus 94%)**

**Commentary**

Elke et al. [128] showed that not receiving nutrition support is deleterious in 2270 patients with sepsis, pneumonia and with an ICU stay of more than three days. Increased amounts of calories and protein per day were associated with a decrease in 60-day mortality and an increase in ventilation-free days. Early versus late EN initiation were not different [129]. Hypocaloric or trophic EN versus full EN showed no survival differences either [130]. To prevent a full provision of energy, a pragmatic approach remains to consider EN as the first choice for nutrition support during the first three to four days after ICU admission. If this is not feasible or is insufficient after three days, PN should be prescribed up to approximatively half of the predicted or measured energy needs and EN prescribed as soon as the clinical condition permits. Weijs et al. reported that septic patients did not improve outcome when receiving increased (1.2 g/kg/d) protein intake compared to non-septic patients [55].

**Septic shock:** Impaired splanchnic perfusion can potentially be further aggravated by EN administration and lead to bowel ischemia [131]. EN should be started after successful resuscitation [132]. In patients with sepsis, a fraction (20–50%) of full nutrition support should be initiated as early as possible to "open" the enteral route; then the amounts of feeds should be progressively increased according to the gastrointestinal tolerance in order to achieve optimal nutrition support once patients improved. If not feasible for prolonged periods, PN should be prescribed.

### 3.3.5. The obese patient (Fig. 7)

**51) An iso-caloric high protein diet can be administered to obese patients, preferentially guided by indirect calorimetry measurements and urinary nitrogen losses.**
**(R5 1, Grade 0, consensus, 89%)**

**Commentary**

**O**verweight and obese patients have become more prevalent in ICUs. Reported recommendations [27] are summarized by Dickerson et al. [127]. There is a large variability in the prevalence between countries based on data from the Nutrition Day project [7]. If hypocaloric medical nutrition therapy appears to be the rule on many ICUs [7], we recommend the measurement of energy expenditure with indirect calorimetry and urinary nitrogen loss to guide energy requirements and protein needs, since predictive equations are inaccurate. Obese patients defined on the basis of BMI are a heterogeneous group. High BMI may be associated with an extremely trained muscle mass as in body builder at one end of the spectrum and sarcopenic obesity with an even lower muscle mass than would be expected from height at the other end. The muscle mass of obese patients will be highly dependent on their level of activity. Age is a further factor to be considered. Muscle mass typically is maximal between 25 and 35 years of age and decreases thereafter. Thus, in an older person with the same body weight, a lower muscle mass is likely to be present (see statement #4 for further details).

**52) In obese patients, energy intake should be guided by indirect calorimetry.**

**Protein delivery should be guided by urinary nitrogen losses or lean body mass determination (using computerized tomography or other tools).**

**If indirect calorimetry is not available, energy intake can be based on "adjusted body weight".**

**If urinary nitrogen losses or lean body mass determination are not available, protein intake can be 1.3 g/kg "adjusted body weight"/d.**
**(R5 2, Grade GPP, consensus, 89%)**

**Commentary**

If indirect calorimetry is not available and nitrogen excretion not measured, we suggest the use of ideal body weight as reference weight in overweight and obese patients. We propose to decrease energy provision where BMI indicates overweight or obesity. The reference (adjusted) body weight should then change from actual body weight to ideal body weight at a BMI >25 kg/m2. Probably using as ideal body weight: 0.9 x height in cm −100 (male) (or −106 (female)) is sufficiently precise giving the overall uncertainties. Such an approach would completely ignore the metabolic demand of adipose tissue and muscle. Adipose tissue utilizes 4.5 kcal/kg/d and muscle 13 kcal/kg/d [133]. The proportion of muscle within the excess weight of an obese individual might be roughly 10%. A pragmatic approach is to add 20–25% of the excess weight (actual body weight-ideal body weight) to ideal body weight for all calculations of energy requirements.

Several authors advocate a controlled undernutrition of obese subjects while providing a relatively larger dose of protein between 2 and 2.5 g/kg/d (ideal body weight as reference) [134].

Additional metabolic derangements such as decreased glucose tolerance, altered lipid metabolism, lack of micronutrients and decreased gut motility will need specific attention [135]. Recommendations on early EN, gastrointestinal tolerance and progressive

increase in nutrition over several days apply similarly to overweight and obese patients as to all other ICU patients.

### 3.4. Monitoring of medical nutrition (Fig. 8)

#### 3.4.1. Monitor for tolerance, overfeeding and underfeeding (see also rec. 5)

**53) Blood glucose should be measured initially (after ICU admission or after artificial nutrition initiation) and at least every 4 h, for the first two days in general.**
**(R5 3, Grade GPP, strong consensus, 93%)**

**Commentary**

A number of observational studies confirmed a strong association between severe hyperglycemia (>180 mg/dL, 10 mmol/L) [136], marked glycemic variability (coefficient of variation >20%) [137], mild hypoglycemia (<70 mg/dL, 3.9 mmol/L) [138] and increased mortality. However, the prospective trials remain inconclusive, owing to differences in practices and to the difficulties in achieving safe and effective glycemic control. The glycemic target associated with the best adjusted outcome ranges from 80 to 150 to 140–180 mg/dL (7.8–10 mmol/L), which is different from the blood glucose levels actually achieved [139].

**54) Insulin shall be administered, when glucose levels exceed 10 mmol/L.**
**(R5 4, Grade A, strong consensus, 93%)**

**Commentary**

Blood glucose control is essential and should be targeted. Current recommendations suggest starting insulin therapy when blood glucose exceeds 150 [43] or 180 mg/dL (10 mmol/L) [140].

In unstable patients even more frequent measurements may be required, whereas frequency can usually be decreased when a stable phase is reached, usually after 48 h.

The assessment and control of glycemia encompasses multiple steps [141]: Blood draw, use of blood gas analyzer or central laboratory analyzers (hexokinase-based) is essential, insulin: intravenous and continuous in case of ongoing nutrition support (enteral or parenteral) using an electric syringe and insulin algorithm.

**55) In critically ill patients with gastric feeding intolerance, intravenous erythromycin should be used as a first line prokinetic therapy.**
**(R13, Grade B, strong consensus, 100%)**

**Commentary**

According to our meta-analysis [4] prokinetic use is associated with a trend towards better enteral feeding tolerance (RR 0.65, 95% CI 0.37–1.14, p = 0.14). This is significant for intravenous erythromycin (usually at dosages of 100–250 mg three times a day) (RR 0.58, 95%CI 0.34–0.98, p = 0.04) for two to four days but not for other prokinetics like metoclopramide (at usual doses of 10 mg two to three times a day). Effectiveness of erythromycin or other prokinetics is decreased to one third after 72 h [142] and they should be discontinued after three days. Our meta-analysis based on six studies finds a significant advantage to erythromycin and its use should be encouraged for 24–48 h, since it promotes gastric motility, and if a large (>500 mL) GRV still persists, the use of post-pyloric feeding should be considered over withholding EN, unless a new abdominal complication (obstruction, perforation, severe distension …) is suspected [4].

**56) Alternatively, intravenous metoclopramide or a combination of metoclopramide and erythromycin can be used as a prokinetic therapy.**
**(R14, Grade 0, strong consensus, 100%)**

**Commentary**

The measurement of GRV for the **assessment** of gastrointestinal dysfunction is common and may help to identify intolerance to EN during initiation and progression of EN. However, **monitoring** of established EN with continued measurements of GRV may not be necessary [143]. We suggest that enteral feeding should be delayed when GRV is > 500 mL/6 h. In this situation, and if examination of the abdomen does not suggest an acute abdominal complication, application of prokinetics should be considered. ASPEN/SCCM [27] and the Surviving Sepsis initiative [144] recommend the use of prokinetics metoclopramide (10 mg three times a day) and erythromycin (3–7 mg/kg/d) in the case of feeding intolerance (weak recommendation, low quality of evidence for the surviving sepsis initiative, and for ASPEN/SCCM) [27].

#### 3.4.2. Monitor for refeeding

**57) Electrolytes (potassium, magnesium, phosphate) should be measured at least once daily for the first week.**
**(R5 5, Grade GPP, strong consensus, 92%).**

**Commentary**

Refeeding syndrome can be defined as the potentially fatal shifts in fluids and electrolytes that may occur in malnourished patients receiving artificial refeeding. Each case of refeeding syndrome – a potentially lethal state [145] - has to be detected early to prevent complications [146]. Therefore, assessment of nutritional status at admission is needed with a schedule for the measurement of electrolytes, including phosphate. Laboratory parameters (electrolytes monitoring, glycemia, liver function tests) are important to prevent or detect severe complications like refeeding syndrome or liver dysfunction related to nutrition, as well as to assist in the achievement of normoglycemia and normal electrolyte values.

**58) In patients with refeeding hypophosphatemia (<0.65 mmol/L or a drop of >0.16 mmol/L), electrolytes should be measured 2–3 times a day and supplemented if needed.**
**(R56, Grade GPP, strong consensus, 100%)**

**Commentary**

Repeated measurements of P, K and Mg during initiation of feeding in critically ill patients are important to detect development of refeeding syndrome, especially because among critically ill patients' electrolyte disturbances upon refeeding are not limited to patients with overt malnutrition.

**59) In patients with refeeding hypophosphatemia energy supply should be restricted for 48 h and then gradually increased.**
**(R57, Grade B, strong consensus, 100%)**

## Commentary

The occurrence of refeeding hypophosphatemia may be perceived as a warning signal. In a RCT, Doig et al. showed that protocoled caloric restriction for 48 h in patients developing hypophosphatemia upon refeeding improved survival despite similar phosphate supplementation in both groups [147]. Slow progressions to energy target during the first 72 h, also called caloric restriction, should be considered to facilitate control of electrolyte disturbances if refeeding syndrome is anticipated or detected [148]. Importantly, whereas potassium is commonly measured in critically ill patients, measurements of phosphate are less common. Undetected rapid development of severe hypophosphatemia may lead to death after initiation of feeding as patients admitted to ICU are often malnourished either before or during admission to the hospital. A recent early calorie restriction study showed that electrolyte alterations were less likely to occur with a cautious introduction of feeding and this was confirmed by a retrospective study [149].

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