Clinical Nutrition in Critical Care Medicine – Guideline of the German Society for Nutritional Medicine (DGEM)

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This guideline is the translation of the German S2k guideline entitled "Klinische Ernährung in der Intensivmedizin" and published in Aktuel Ernaehrungsmed (Thieme Publisher) 2018 [1]. This guideline was produced by the German Society for Nutritional Medicine (DGEM) in collaboration with the German Society of Anaesthesiology and Intensive Care Medicine (DGAI), the German Society of Surgery (DGCH), the German Society for Thoracic and Cardiovascular Surgery (DGTHG), the German Interdisciplinary Association of Intensive Care and Emergency Medicine (DIVI), the German Society of Medical Intensive Care and Emergency Medicine (DGIIN), the German Cardiac Society (DGK), and the German Sepsis Society (DSG) During the translation process a few language errors and misleading sentences were corrected, otherwise the text and in particular the recommendations and the consensus rates were not changed.

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List of abbreviations

AKE	Austrian Society for Clinical Nutrition
APACHE	Acute Physiology and Chronic Health Evaluation
ARDS	Acute Respiratory Distress Syndrome
AA	Amino acid
A.S.P.E.N.	American Society for Parenteral and Enteral Nutrition
AWMF	Association of the Scientific Medical Societies in Germany
BiVAD	Biventricular Assist Device
BMI	Body Mass Index
CH	Carbohydrates
CT	Computerized tomography
DGEM	German Society for Nutritional Medicine
E−%	Energy Percent
ECMO	Extracorporeal Membrane Oxygenation
ECLS	Extracorporeal Life Support
EN	Enteral Nutrition
ESPEN	European Society for Clinical Nutrition and Metabolism
F_iO_2	Inspiratory Oxygen Concentration
FNCJ	Fine-Needle Catheter Jejunostomy
GESKES	Swiss Society for Clinical Nutrition
HN	Hypocaloric Nutrition
IBW	Ideal Body Weight
ISBI	International Society for Burn Injuries
ICU	Intensive Care Unit
LCT	Long-Chain Triglycerides
LOS	Length of Stay
LVAD	Left Ventricular Assist Device
MCT	Medium-Chain Triglycerides
MNA	Mini Nutritional Assessment
MNT	Medical Nutrition Therapy
MRI	Magnetic Resonance Imaging
MUST	Malnutrition Universal Screening Tool
MV	Mechanical Ventilation
N	Nitrogen
NIV	Non-Invasive Ventilation
NRS	Nutritional Risk Score
NUTRIC	Nutrition Risk in the Critically Ill
PN	Parenteral Nutrition
PEG/PEJ	Percutaneous Endoscopic Gastrostomy/Jejunostomy
PICS	Post-Intensive Care Syndrome
PNI	Prognostic Nutritional Index
RCT	Randomized Controlled Study
REE	Resting Energy Expenditure
RQ	Respiratory Quotient
RRT	Renal Replacement Therapy
RVAD	Right Ventricular Assist Device
SLED	Sustained Low-Efficiency Dialysis
SSC	Surviving Sepsis Campaign
SGA	Subjective Global Assessment
SPN	Supplemental Parenteral Nutrition
TPN	Total Parenteral Nutrition
VAD	Ventricular Assist Device
VAP	Ventilator-Associated Pneumonia
VCO_2	Carbon Dioxide Production
VFD	Ventilator-Free Days
VO_2	Oxygen Consumption
WHO	World Health Organization

1. Introduction

1.1. The concept of the "critically ill" patient

The critically ill patient is a heterogeneous individual with regard to the phases of the underlying disease, trigger mechanisms, but also primary or secondary changes of organ function (number and severity of organ dysfunction). It is unlikely that one clinical entity (that of the critically ill patient) can summarize these multiple characteristics adequately, and that this oversimplifying entity is an appropriate subject of general scientific and medical interest, and in particular of medical nutrition therapy (MNT). Pathophysiologic changes or therapeutic measures may vary considerably between individual critically ill patients (Fig. 1). Thus, it is only possible to present a crude approximation concerning the individual metabolic secondary reactions, or the individual benefit or harm of MNT.

To be efficacious, the therapy of a particular disease requires a correct indication; for the latter, one must precisely define the disease, and there must be profound knowledge of the characteristics of the disease to be treated. However, in critically ill patients these conditions are not always fulfilled. Furthermore, MNT in a critically ill patient is an adjuvant therapy just supporting but never replacing the causal therapy of the underlying disease (e.g., sepsis resulting from peritonitis or pneumonia, hemorrhagic shock, severe trauma). The underlying disease, in turn, is cause of the metabolic changes, and, consequently, also a major determinant of MNT.

1.2. Control of medical nutrition therapy by the phase of the disease

Due to specific pathophysiologic changes, it is likely that MNT will have to be adapted to the different phases of critical illness. The systemic metabolic responses observed regularly after a disturbance of homeostasis depend essentially on the time that has elapsed since the onset of the disturbance of homeostasis (Fig. 2). In the following sections, we try to characterize more accurately the various phases of critical illness from a clinical perspective. This characterization should help clinicians to apply MNT according to the phase of the disease. However, characterization of the phases is only empirical, and length of phases may vary depending on the individual case (Table 1).

Immediately after the disturbance of homeostasis, the "acute" phase begins (total duration ≤7 days). This phase can be divided into an "early acute" phase (about 1–3 days post-onset with the possibility of fatality due to the most severe disturbance) and a "late acute" phase (approximately lasting for 2–4 days if the patient survives the early acute phase). The post-acute phase can be described as a "recovery" phase (duration >7 days), which is usually spent in the primary care hospital. After the recovery phase, the "rehabilitation" phase (lasting several months) follows, in which, among others, the metabolic damage suffered initially is repaired slowly. Usually, patients will not go through this phase in the primary care hospital. Alternatively, the "post-acute" phase may merge into a "chronic" phase (of uncertain duration) characterized by persistent organ dysfunction and an uncertain prognosis (possibly death). This particular course may be described as a "persistent inflammatory immunosuppressed catabolism syndrome" [1,2]. If there is a new disturbance of homeostasis, the process will start again with the acute phase.

Table 1 summarizes the empirical clinical definition of these phases of critical illness. Recommendations presented in this guideline will refer to these phases. The definition is the result of a consensus discussion among the authors of the guideline.

2. Methodology

2.1. Scope of this guideline

This guideline applies to all adult patients who present with acute organ dysfunction necessitating medical or mechanical

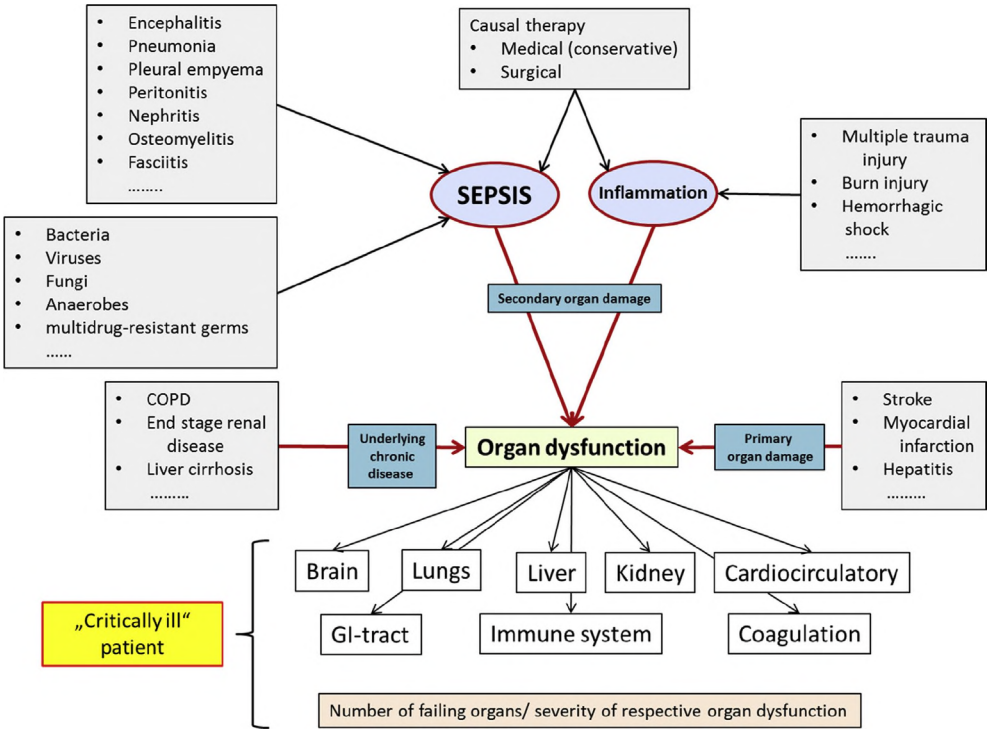

Fig. 1. Etiology and pathogenesis of "critical illness" (according to [1], [2]).

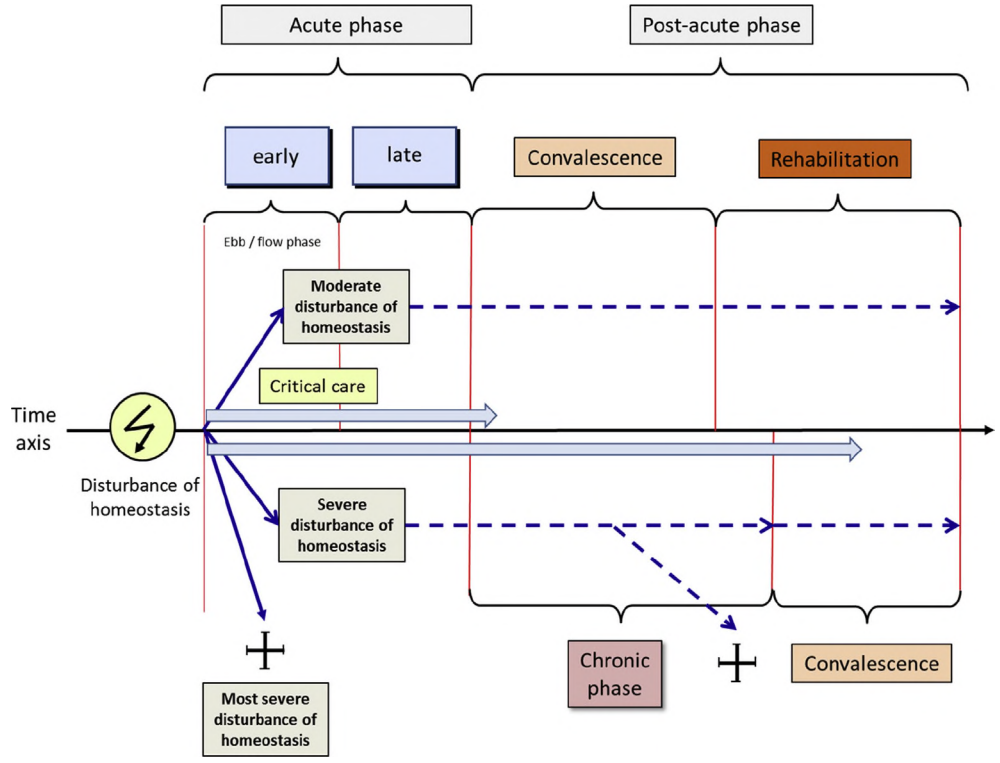

Fig. 2. Phases of „critical illness" according to severity of disturbance of homeostasis. For details see Text.

Table 1
Definition of disease phases in the course of critical illness.

Disease phase	Organ dysfunction	Inflammation	Metabolic state	Approximate duration/period (days)
Acute phase				
Early acute phase	Severe or increasing (multiple) organ dysfunction	Progressive inflammation	Catabolic	1–3
Late acute phase	Stable or improving organ dysfunction	Regressive inflammation	Catabolic-anabolic	2–4
Post-acute phase				
Convalescence/rehabilitation	Largely restored organ function	Resolution of inflammation	Anabolic	>7
Chronic phase	Persistent organ dysfunction	Persistent immune suppression	Catabolic	>7

Through a "second hit" (a new disturbance of homeostasis), a step backwards from the post-acute to the acute phase is possible at any time. The individual course of critical illness must be considered in each patient at all times with regard to the inflammatory and metabolic changes or changes in organ dysfunction, respectively.

support. The individual sections of the guideline will focus on nutrition therapy and specific features of a specific disease (i.e., patients presenting with malnutrition). For pediatric patients, readers may consult the S3 guideline *Parenteral Nutrition in Pediatric and Adolescent Medicine* of the Deutsche Gesellschaft für Ernährungsmedizin e.V. (DGEM; German Society for Nutritional Medicine). For organ-specific nutrition of critically ill patients, please refer to corresponding guidelines issued by the DGEM (www.dgem.de/leitlinien).

This guideline gives general recommendations for MNT of critically ill patients with a special focus on enteral and parenteral nutrition. The guideline will assist clinicians in decision-making in the interdisciplinary, intensive care unit (ICU) setting, and offers support in reviewing active feeding protocols or in creating new protocols.

2.2. Committee members

DGEM is the leading society and responsible for the current S2k guideline *Clinical Nutrition in Critical Care Medicine*. DGEM is a multidisciplinary association comprising all professional groups using MNT. DGEM promotes and addresses practical aspects of MNT and of metabolism research in Germany. DGEM designated Gunnar Elke, MD (associate professor of anesthesia and critical care, University Medical Center Schleswig–Holstein, Kiel, Germany) to be the coordinator of the guideline. The DGEM Guidelines Officer, Stephan C. Bischoff, MD (professor of nutritional medicine, University of Hohenheim, Stuttgart, Germany) assisted in developing the methods and creating the contents pertinent for the guideline.

The responsibility for updating the S2k guideline *Clinical Nutrition in Critical Care Medicine* remains with the DGEM. The following German medical societies and their respective mandate carriers were involved in the creation and development of the guideline:

- German Society of Anesthesiology and Intensive Care Medicine (DGAI): Christian Stoppe, MD (associate professor of anesthesia and intensive care medicine, RWTH Aachen University, Aachen)
- German Society of Surgery (DGCH): Arved Weimann, MD (professor of surgery, Klinikum St. Georg, Leipzig)
- German Society for Thoracic and Cardiovascular Surgery (DGTHG): Bernd Niemann, MD (associate professor of

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- German Cardiac Society (DGK): Stephan Steiner, MD (professor of cardiology, Saint Vincenz Hospital Limburg/Lahn) and Tobias Graf, MD (consultant, University Medical Center Schleswig–Holstein, Campus Lübeck, Lübeck)
- German Sepsis Society (DSG): Gunnar Elke, MD (associate professor of anesthesia and intensive care medicine, University Medical Center Schleswig–Holstein, Campus Kiel, Kiel)

2.3. Conflicts of interest

DGEM was the only sponsor of this guideline. All authors and mandate carriers stated their potential conflicts of interest using the form of the Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V. (AWMF, Association of the Scientific Medical Societies in Germany) available for "*Explanation of Conflicts of Interest in the Framework of Guideline Projects*".

A summary of these statements and judgement of declared conflicts are presented in Appendix A.

2.4. Analysis of evidence

2.4.1. Comparison with current recommendations of valid guidelines

The DGEM recommendations were compared with pertinent recommendations of other national or international societies: American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) [5], European Society for Intensive Care Medicine (ESICM) [6] and Surviving Sepsis Campaign (SSC) [7]. We did not consider older recommendations from the European Society for Parenteral and Enteral Nutrition (ESPEN) [8], as the ESPEN guideline was also revised during preparation of the DGEM guideline.

2.4.2. Consideration of methodologic limitations

When formulating the recommendations, we explicitly considered the limitations of currently available clinical studies. Nutrition studies may be limited by: (i) the absence of individualization of a particular MNT, especially in terms of changes of protein metabolism; (ii) insufficient knowledge regarding physiology and pathophysiology of the human intestinal tract; (iii) the poor design of many clinical (randomized or observational) studies, which can result in significant bias.

2.4.2.1. Personalized approaches to medical nutrition therapy. To generalize MNT recommendations for a target group such as ours, readers must know that metabolic reactions secondary to nutrient supply demonstrate natural, large inter- and intra-individual variations. Even for a very simple metabolic response (e.g., changes in the postprandial blood glucose concentration after a carbohydrate-laden meal), various individual determinants have been identified in healthy adults. These determinants include lifestyle, glycated-hemoglobin levels, cholesterol levels, anthropometric variables, age, activity of specific enzymes, and variables of the intestinal microbiome; consequently, control of metabolic reactions is highly individual [9]. Therefore, a "personalized" MNT would probably be of considerable importance. Unfortunately, however, especially in the (nutrition) care of the critically ill patient, efficacious individual treatment is lacking.

2.4.2.2. Study design. Further limitations result from study design. Controlled trials, which have used well-defined clinical outcomes, may suffer from four main methodological problems:

(i) A monocentric and non-blinded design predispose studies to a high likelihood for false-positive results [10];
(ii) A small sample size (<100 patients) is, in general, associated with uncertainty even if a statistically "significant" result has been obtained;
(iii) Combination of many small studies into meta-analyses does not reduce the uncertainty mentioned in (ii), but may actually increase it because, under such circumstances, a systematic overestimation of the effect ($\leq$20%) may result, which is aggravated further in the case of unreported data, absence of blinding, or poor randomization [11–13];
(iv) Even large controlled trials have resulted in contradictory results because they often do not study comparable patient groups or nutrition interventions. Large randomized trials usually show high internal validity but often the results cannot be applied to other populations than the studied patient cohort ("external validity").

Observational studies allow researchers to evaluate significantly larger patient numbers, thereby facilitating the generalization of results. For observational studies addressing nutrition, however, specific limitations and sources of error exist. They mostly comprise statistical problems within the multivariate analysis of the data. Errors may arise because of two main factors:

(i) Association and causality cannot be separated from each other. A "bad" diet (such as too low a supply of nutrients given *via* the enteral route) can be the cause (resulting in an energy deficit) or the consequence of an increased morbidity (e.g., severe peritonitis may lead to intestinal paralysis, poor tolerance to enteral nutrients, and multiple-organ dysfunction). This phenomenon is called "confounding by indication";
(ii) The intensity of nutrition therapy represents a variable, which is unknown at the beginning of the observation but arises during the observation, thereby becoming a time-dependent variable. Disregarding this fact causes false conclusions to be drawn [14]. Furthermore, conventional statistical tools cannot take into account the daily variations of calorie or protein intake being characteristic of MNT. For example, a patient receiving a severely hypocaloric diet in the early acute phase followed by a severely hypercaloric diet in the late acute phase would, on average, have received a eucaloric diet in the acute phase; the inability to separate these factors distorts the results and assessment of the calorie-associated prognosis [15].

2.4.3. Terminology

A frequent target parameter of clinical trials is mortality or lethality. The "mortality" or "mortality rate" is calculated as the number of deaths in a defined population (group) within a certain

time. For disease-specific mortality (e.g., sepsis), only deaths due to a defined disease are considered. “Lethality” is a measure of the mortality of a particular disease [16]. For simplicity, we use the term “mortality” throughout this guideline.

2.5. Building a consensus

The present guideline is an update of the former DGEM guidelines *Intensive Care Medicine — Guideline on Parenteral Nutrition* [17] and *Intensive Care Medicine — Guideline on Enteral Nutrition* [18]. The updated version is a S2k guideline of the DGEM (AWMF registry number 073-004). The methodology for creating the present guideline is predefined by the rules and regulations set by the AWMF (version 1.0).

Each recommendation was formulated as part of a structured consensus-building process under the auspices of DGEM, and by participation and vote of representatives of the other seven national professional societies. The aim of this consensus-building was to: (i) solve decision-making problems; (ii) evaluate and finalize recommendations; (iii) measure the strength of consensus.

According to the S2k classification, the recommendations contain no statements concerning the level of evidence and grade of recommendation because we did not do a systematic review of the evidence. Instead, we used the level of evidence (i.e., assurance) of the evaluated studies (see below) to define linguistically the strength of a recommendation (Table 2).

As a rationale for the recommendations listed here, we consulted and commented on prospective randomized controlled trials (RCTs) and meta-analyses with high methodological quality, and on observational studies with a large sample size; studies had to be published in English up to and including May 2018; furthermore, we considered recommendations of currently valid guidelines of other aforementioned societies.

In formulating the recommendations, we also considered expected health benefits (prognostic relevance, clinical outcome) and potential side effects and risks of each recommendation. In individual cases, the strength of a recommendation could deviate from the evidence level of an individual study (according to the consensus of the guideline group). In this case, we added a note to the respective comment of the recommendation.

In February 2018, we launched a web-based Delphi process to which we invited all authors of the guideline, all representatives of the involved national medical societies, all members of DGEM, and other experts in the field. In total, 36 individuals participated in the Delphi process. Participants could vote on a recommendation by using a five-step decision scale (“yes”, “rather yes”, “undecided”, “rather no” and “no”). If a recommendation had not received a “yes” vote, or if voters had not accepted the proposed strength of a recommendation, they had to formulate and add an explanatory comment.

The consensus strength was determined according to the scale detailed in Table 3, then set and displayed for each recommendation. The coordinator, the second author of the guideline, the DGEM President, and the DGEM Guidelines Officer reviewed all Delphi comments and amendments to all recommendations. Recommendations that had received a “yes” or “rather yes” vote by $\geq$ 90% of the votes (indicating a strong consensus), and for which no corrections had been proposed, were approved. We revised or complemented 12 recommendations (resulting in 13 new recommendations). For a new vote and final consensus, we sent the new recommendations to the 16 listed guideline authors and elected representatives of the participating medical societies, respectively, using e-mail circulation in June 2018.

We registered four reasons for the amendments/revisions of the 12 recommendations:

(i) a low consensus strength (“majority consensus” indicating that only 50%–75% of the participants had given a “yes” or “rather yes” vote in the Delphi process) (three recommendations);
(ii) comments which presented convincing arguments for a revision of the recommendation, although votes in the Delphi process had revealed a “consensus” or a “strong consensus” (six recommendations);
(iii) re-interpretation of studies which had already been analyzed, although votes in the Delphi process had revealed a “consensus” (one recommendation);
(iv) inclusion of new, recent publications (two new recommendations).

Finally, the coordinator and the second author of the guideline did an editorial revision of the entire guideline before final adoption by all members of the guideline group via an e-mail circulation procedure. Then, the executive committees of the leading and participating medical societies formally adopted the guideline after no further need for an amendment had been identified.

Table 2
Recommendation scale (according to AWMF regulations).

Recommendation Strength	Linguistic expression
Strong recommendation	Shall/Shall not
Weak Recommendation	Should/should not
Uncertain Recommendation	May/may not

Table 3
Consensus finding.

Consensus Strength	% agreement (% of votes indicating “yes” or “rather yes”)
Strong consensus	>90
Consensus	>75–90
Majority consensus	>50–75
No consensus	<50

3. Organization of medical nutrition therapy

Question: Should a feeding protocol be used for MNT?
Recommendation 1:
MNT should include the use of a feeding protocol.
Strong consensus (100%).
Commentary

Several studies have shown that use of a feeding protocol, which is adapted to the specific local ICU setting, results in an earlier start of enteral nutrition, and in a higher calorie or protein intake. Overall, (enteral) MNT will be more adequate (when compared with non-protocolized nutrition strategies) [19–24]. In particular, such protocols make MNT safer and help to prevent errors with regard to metabolic and gastrointestinal tolerance (e.g., aspiration risk with enteral nutrition; “hyperalimentation” with parenteral nutrition).

In the ACCEPT study, introduction of an evidence-based feeding protocol was associated with a significantly shorter length of ICU stay and a trend towards reduced mortality [22]. In contrast, two other cluster-randomized trials found that use of a feeding protocol increased calorie and protein intakes by only 15%, and did

not affect clinical outcomes [25,26]. The A.S.P.E.N. guideline conducted a meta-analysis of two randomized trials examining the usefulness of an enteral feeding protocol for nursing staff. Result of that analysis was that use of a feeding protocol reduced the rate of nosocomial infections [2]. During parenteral nutrition, feeding protocols may help to reduce the rate of general complications (a corresponding literature survey was published in the A.S.P.E.N. guideline [2]).

To step-up enteral calorie intake, various strategies (e.g., volume-based nutrition) are available and have been incorporated into feeding protocols in Anglo-American countries. The A.S.P.E.N. guideline recommends design and implementation of a feeding protocol to increase the intake of target calories (Recommendation D3a, moderate evidence). Furthermore, the authors suggested that use a volume-based feeding protocol be considered (Recommendation D3b) [2].

Volume-based feeding protocols target daily volumes (ml/d) instead of hourly rates of enteral nutrition. Thereby, the hourly feeding rate providing a continuous infusion of substrates is adapted to interruptions in food intake. Two observational studies examined this strategy. In these studies, a volume-based nutrition was associated with an increased intake of calories and protein [23,27]. In a study by McClave et al., a volume-based feeding protocol was associated with a lower rate of gastrointestinal complications [23]. For parenteral nutrition, the A.S.P.E.N. guideline states (based on expert consensus) that use of a feeding protocol, and a nutrition support team can increase the efficacy and minimize the risks of treatment (Recommendation H1). In summary, recommendations made on this subject by DGEM correspond to those of A.S.P.E.N.

4. Assessment of nutrition status

Question: Should nutrition status be assessed at the time of ICU admission?

Recommendation 2:

Nutrition status should be assessed at the time of ICU admission.

Strong consensus (97%).

Commentary

A.S.P.E.N. has defined “malnutrition” etiology-based as a condition of reduced food intake. This condition may arise from a variety of underlying diseases, and leads to a change of cell- and fat-free mass with subsequent reduced physical and mental function resulting in a poorer clinical outcome [28,29]. There are three overlapping categories of malnutrition due to: (i) diet; (ii) chronic illness; (iii) acute illness. Critically ill patients, thus, fall into at least one of these categories. Regardless of the etiology, however, each patient diagnosed as “malnourished” requires a certain form of MNT.

Theoretically, assessment of nutrition status upon ICU admission may be advantageous by improving prediction of outcome, and by optimizing MNT.

4.1. Prognostic relevance of nutrition status

Nutrition status should – irrespective from other prognostic tools – have a close association with mortality and morbidity. Today, this association is firmly established. In a retrospective analysis of 6518 critically ill patients, those with dietary protein-energy malnutrition (defined as disease-related weight loss, underweight, loss of muscle mass, and reduced intake of energy or protein) had twice the mortality risk of those without malnutrition [30]. In two further observational studies, it was shown for mechanically ventilated patients that the muscle mass at the time of ICU admission had a significant association with their outcome [31,32]. ESPEN has already included diminished lean mass as an alternative criterion to define malnutrition [33].

It is, however, still uncertain whether this association is a true causality or an epiphenomenon (expression of a more severe underlying disease). It remains unclear whether nutrition status supersedes the established prognostic factors (e.g., Acute Physiologic Assessment and Chronic Health Evaluation (APACHE), Sequential Organ Failure Assessment (SOFA)) and whether combining nutrition status with established prognostic factors improves prediction.

4.2. Therapeutic relevance of nutrition status

Assessment of nutrition status should also have therapeutic relevance. For example, a pre-existing malnutrition should lead to therapy modification and, thus, improvement in the outcome of critically ill patients. However, no large controlled studies on this topic are yet available. A small RCT on 125 patients showed no significant effects of a higher calorie- and protein intake in patients with a body mass index (BMI) < 25 or ≥ 35 kg/m^2 [34]. General aspects of MNT for malnourished patients are discussed in sections 6.2.6, 6.3.5 and 7.1.3, and for critically ill obese patients in section 11.2.

4.3. Nutrition risk in the critically ill (NUTRIC) score

The NUTRIC score was not developed to assess nutrition status but to assess nutritional risks. The score includes, among other variables, the APACHE II and SOFA scores [35]. For the NUTRIC score, the threshold for distinguishing a patient with a low or high nutrition risk is ≥ 5 (with or without measurement of interleukin (IL)-6 levels).

Therapeutic relevance of the NUTRIC score remains unclear. Thus far, no RCT with adequate sample size tried to validate this concept. Two methodologically limited observational studies found an association between the intensity of MNT and the outcome of patients carrying a high nutrition risk according to the NUTRIC score [36,37]. A *post hoc* analysis of the Redox Deaths due to Oxidative Stress (REDOXS) RCT confirmed this association [38]. However, these findings were in contrast to the results of the *post hoc* analysis of the Permissive Underfeeding versus Target Enteral Feeding in Adult Critically Ill Patients (PermiT) trial. This *post hoc* analysis investigated whether non-protein calorie intake affected outcome depending on the NUTRIC score [39]. In this trial, high nutrition risk was assumed at a NUTRIC score >4. The main result was that the outcome was independent of calorie intake and NUTRIC score.

Although there is no strong evidence, the A.S.P.E.N. guideline, based on expert consensus, recommends assessment of nutrition risk at ICU admission according to the NUTRIC score. In addition, co-morbidities, gastrointestinal function and aspiration risk should be part of nutrition risk assessment (Recommendations A1 and A2) [2]. The rationale behind these recommendations, however, is subject to criticisms as it only relied on observational studies (section 2.4.2).

Conclusion

Assessment of nutrition status mainly allows clinicians to detect indications for a specific care in the context of MNT. Malnourished patients require special attention concerning the indication and individual metabolic tolerance of MNT. Clinicians should do the assessment at the time of ICU admission considering local resources. According to the available evidence, the author group feels that the NUTRIC score is not suitable for assessing nutrition status.

Question: How should nutrition status be assessed upon admission and during stay in the ICU?

Recommendation 3a:

At the time of ICU admission, the criteria for disease-specific malnutrition proposed by DGEM, or the subjective global assessment (SGA) may be used to assess nutrition status.

Consensus (88%)

Recommendation 3b:

Non-invasive serial examinations of skeletal muscle mass by ultrasound, magnetic resonance imaging (MRI) or computed tomography (CT) may help to assess nutrition status at the time of admission and during ICU stay.

Consensus (78%)

Commentary

4.4. Assessment of nutrition status upon ICU admission

Recently, the DGEM has defined the following criteria for the diagnosis of disease-specific malnutrition: (i) BMI <18.5 kg/m^2, or (ii) unintended weight loss >10% in the last 3–6 months, or (iii) BMI <20 kg/m^2 and unintended weight loss >5% in the last 3–6 months, or (iv) fasting >7 days. When there is subclinical, mild or moderate chronic inflammation before the disturbance of homeostasis, additional criteria are available to diagnose malnutrition. They include a reduced energy intake ≤75% of the estimated energy requirement for ≥1 month, or signs of reduced muscle mass (arm muscle area <10th percentile, or creatinine size index <80%) in conjunction with laboratory markers of disease activity (e.g. Crohn's Disease Activity Index) [40]. In contrast, the A.S.P.E.N. guideline speaks out – based on expert consensus – against the use of such traditional criteria (Recommendation A2) [2]. The authors of the DGEM guideline, however, do not see a reason why the DGEM criteria should not be applicable before or immediately after a disturbance of homeostasis (i.e., before a capillary leak has developed).

Alternatively, clinicians may use SGA to assess nutrition status at the time of ICU admission [41]. An additional diagnostic tool is Nutritional Risk Screening (NRS) 2002, which is recommended by ESPEN and A.S.P.E.N.. As criterion for malnutrition, NRS includes a BMI ≤20.5 kg/m^2, weight loss >5% during the last 3 months, reduced food intake, and disease intensity [42]. NRS values >3 indicate at-risk patients, and values ≥5 high-risk patients. The author group feels, however, that the NRS score is not suitable for critically ill patients or the target group defined in this guideline because *per se* a serious illness already has 3 points in the classification system. Therefore, our target group would always be at risk for malnutrition.

DGEM or SGA criteria can be complemented by a (non)-invasive determination of muscle mass using CT, MRI or ultrasound. Among these procedures, determination of muscle mass by CT or ultrasound is certainly at the most advanced stage. However, the CT method is not yet widespread and, for reasons of cost and radiation safety, will be used only if there is an indication for such an examination for other clinical reasons, and if appropriate expertise is available locally.

A major limitation of all of the aforementioned morphological techniques are capillary leaks (enlargements of the third space) caused by infection/inflammation. This limitation also pertains to bioimpedance analysis, which measures body composition indirectly using a phase angle. With large capillary leaks, volumes no longer correlate with protein mass, and results would require specific adjustments to the water content of a single compartment [43–47].

4.5. Assessment of nutrition status during the course of the disease

CT and ultrasound can also be used semi-quantitatively, e.g. to estimate the overall efficiency of anticatabolic therapies (therapy of the underlying disease [sepsis, inflammation] + MNT) over time by serial measurements (starting at the time of ICU admission) [48–51].

5. Indications for medical nutrition therapy

Question: What are the indications for MNT in critically ill patients?

Recommendation 4:

MNT should be initiated within the first 24 h after ICU admission in those patients who are unable to maintain sufficient volitional intake during the early acute phase of critical illness (which means that recommended intake/targets cannot be reached in this way during this phase). MNT should be controlled by the calorie/protein/amino acid intake or corresponsding targets recommended for the acute phase, and by individual metabolic tolerance (**Recommendations 9a–c** and **14a–c**).

Consensus (89%)

Commentary

There are no RCTs comparing early MNT with complete fasting during the acute phase. An observational study by Reignier et al. [52] compared 1171 patients receiving MNT in the early acute phase (<48 h after intubation, systolic arterial blood pressure <90 mmHg) with 1861 patients who had received MNT in the late acute phase (>48 h after intubation). Multivariate analyses showed that early MNT was associated with significantly reduced 28-day mortality (but with an increased risk of developing ventilator-associated pneumonia [VAP]). Similar results (reduced in-hospital mortality) were found in an observational study by Khalid et al. [53], who compared an early onset MNT (provided during the first 48 h after admission) with a late onset MNT (>48 h) in 1174 patients requiring a catecholamine therapy. However, the results of these observational studies all suffer from design-inherent limitations ("confounding by indication") discussed in section 2.4.2.

A meta-analysis of 15 small RCTs by Koretz et al. [54] concluded that "there is no convincing evidence for the use of an early dietary intervention in critically ill patients". A similar result (unchanged mortality/morbidity) came from the SSC guideline aggregating 11 smaller RCTs [4]. However, the A.S.P.E.N. guideline (Recommendation B1) [2] and the ESICM guideline (Question 1B) [3] recommend an early intervention based on their meta-analyses of 21 and 14 small RCTs, respectively. These meta-analyses revealed a better outcome, when patients had received an early (enteral) nutrition. Similar results (lower morbidity/mortality with early [enteral] nutrition in comparison with a late nutrition) found a meta-analysis by Tian et al. [55], who evaluated six RCTs (236 patients). Based on their own meta-analysis and on the axiom "First do not harm", the SSC guideline recommends – despite missing evidence – to start enteral nutrition early in unselected critically ill patients [4].

However, none of the five aforementioned meta-analyses was conclusive. Most of the included studies had a high bias (small number of cases, no blinding) and suffered from a variable implementation of fasting during the acute phase whereby often only a severely hypocaloric diet (≈provisioning of 30% of the calorie target) was compared with a moderately hypocaloric diet (early enteral feeding providing 50–70% of the calorie target). Therefore, the results of the above meta-analyses cannot be related to early fasting or minimal diet (e.g. enteral "trophic feeding"), but only to the comparison between a moderately and a severely hypocaloric diet given to patients during the acute phase. The above meta-analysis by Tian et al. [55] would support this argument by showing that early (enteral) nutrition did not confer an advantage relative to a comparable parenteral nutrition.

The A.S.P.E.N. guideline [2] also recommends (based on expert consensus) that patients who are not malnourished upon ICU admission, who have a low nutrition risk (e.g., NRS-2002 $\leq$ 3 or NUTRIC score $\leq$5), but whose volitional food intake is insufficient, do not need a specific MNT during the first week of ICU stay (Recommendation C1).

This recommendation contradicts Recommendation B1 of the A.S.P.E.N. guideline [2], and is not supported by the results of A.S.P.E.N.'s own meta-analysis, or by the results of the meta-analysis of the ESICM guideline [3]. In fact, these meta-analyses showed (when analyzed from a caloric viewpoint) that a moderately hypocaloric (enteral) diet (provisioning of 50–70% of the calorie target) was superior to a severely hypocaloric diet (provisioning of about 30% of the calorie target). They did not indicate that complete fasting would be acceptable in this phase of the disease.

When analyzing the magnitude of calorie intake (severely *vs*. moderately hypocaloric), three other meta-analyses [56–58] demonstrated that a severely hypocaloric diet was harmful in the acute phase (a severely hypocaloric diet would be equivalent to delayed enteral nutrition or to complete fasting). At least in the meta-analysis of Choi et al., this observation was independent from BMI [56].

Detailed recommendations on the route of MNT (enteral or parenteral) are presented in section 7. The corresponding contraindications for enteral nutrition are discussed in section 7.2.1.

6. Defining nutrition goals

6.1. Determination of energy expenditure and calorie goal

Question: Which method should be used to determine energy expenditure?

Recommendation 5a:

Indirect calorimetry should be used to determine the energy expenditure/calorie target.

Strong consensus (100%)

Recommendation 5b:

When calorimetry is unavailable, energy expenditure or calorie target in non-obese critically ill patients (BMI <30 kg/m^2) should be estimated at 24 kcal/kg actual body weight per day. Complex formulas for calculating energy expenditure should not be used.

Consensus (86%)

Recommendation 5c:

Alternatively, the energy expenditure or calorie target, respectively, may be determined *via* the carbon dioxide (CO_2) production rate (VCO_2 method) when calorimetry is unavailable.

Consensus (87.5%)

Commentary

Energy expenditure of critically ill patients is not constant, but dynamic and may show high intra- and inter-individual fluctuations depending on the phase of the disease [59]. In many patients, variations of energy expenditure over time follow a curved shape with an initial increase and subsequent gradual decline; energy expenditure may also be normal (or even decreased) in patients with sepsis or septic shock [60]. Indirect calorimetry is the only reliable method for determining energy expenditure. However, both patient- and technique-dependent problems exist during implementation [61,62]. For example, when inspiratory oxygen concentration is $\geq$ 60%, indirect calorimetry will not yield reliable values.

The "gold standard" of indirect calorimetry is the Deltatrac® device, which has also been validated in mechanically ventilated patients; this device, however, is no longer available. Studies validating newer devices show a variance of only $\leq$100 kcal per day (energy expenditure) in comparison with the gold standard [63–65]. Recently, technological advances improved measuring technology and facilitated operability allowing for the construction of a new type of indirect calorimeter; a working group supported by ESPEN is currently testing this new device [66].

Calorimetry devices measure resting energy expenditure (REE) which is, in critically ill patients, not multiplied by a "motion factor" (physical activity level). REE is equal to the calorie target, and is commonly used to control nutrition. REE, however, does not necessarily indicate the actual calorie intake; the latter (% of calorie target to be given in the different phases of the disease) is addressed in sections 6.2 and 6.3).

Measurement of energy expenditure is superior to the use of predictive formulas. A recent review [67] analyzed 18 studies with 160 variations of 13 formulas. On average, 38% and 12% of the formulas, respectively, underestimated or overestimated energy expenditure by >10%. At the individual level, however, the formulas overestimated energy turnover in 13–90% of cases; in 0–88% of cases energy expenditure was underestimated. For this reason, complex formulas should not be used to determine energy expenditure.

Thus far, however, no study could demonstrate that guiding MNT by indirect calorimetry also improves patient outcomes. There are only two randomized studies, which exclusively used indirect calorimetry to control energy intake. The study by Singer et al., in 2011 [68] found, oddly enough, that using indirect calorimetry improved mortality, but simultaneously worsened morbidity. In a study by Allingstrup et al., in 2017 [69], the prognosis remained unchanged. Both studies were criticized either because too many calories were given in the intervention group [68], or because differences of calorie balance between control and intervention groups were too small [69]. Furthermore, the results of both studies are limited because - by using indirect calorimetry - the authors tried to administer eucaloric amounts of calories during the acute phase thereby possible worsening outcome (section 6.2.2).

When indirect calorimetry is unavailable, energy expenditure (calorie target) should be estimated in a pragmatic manner. In the acute phase, one may assume 24 kcal/kg body weight per day for non-obese patients; up to 36 kcal/kg per day may be appropriate as calorie target during convalescence or rehabilitation. The estimated rate of 24 kcal/kg per day simplifies administration of calories. When feeding is continuous over 24 h using a standard nutrition formula (1 kcal/mL), the feeding rate (in mL/h) will correspond to the actual body weight.

In a study from Germany in 2004, the mean REE of healthy men and women with a BMI of 25–30 kg/m^2 and age of 50 years was 21.7 and 21.3 kcal/kg actual body weight per day, respectively [70]. In comparison, the recommended rate of 24 kcal/kg per day is slightly higher, but takes into account the increased energy expenditure associated with secondary metabolic reactions in the acute phase. This rate corresponds (at least on average) to the actual turnover rates measured by indirect calorimetry in critically ill patients in the acute phase [68,69,71–74]. During rehabilitation/physical therapy, however, clearly higher turnover rates were observed (up to 36 kcal/kg actual body weight per day) [75].

Measuring VCO_2 represents an alternative method to approximate energy turnover. A corresponding measurement procedure has been incorporated in some ventilators. Since it is not possible to measure oxygen consumption, the VCO_2/RQ ratio must replace missing data. RQ is usually varying, but can be set at a constant value representing the average of the three major types of nutrients ($RQ = 1 + 0.809 + 0.707)/3 = 0.84$). Correspondingly, the Weir formula has to be modified [62]. In some observational studies, this approach was superior to established predictive formulas [76–78]. The validity of this alternative method will increase further, if RQ is calculated more accurately [79]. This calculation relies on the

amount of different macronutrients prescribed per day. When the so-called EE-VCO_2 method is used, however, specific limitations inherent to VCO_2-measurements and to the concept of an average RQ must be kept in mind [80]; a valid determination of energy expenditure (differing by <10% from that obtained by indirect calorimetry) can only be expected in about three quarters of the patients [81].

The measured or estimated energy expenditure (the calorie target), however, is not the sole parameter for determining calorie intake. During the acute phase, most patients are more or less catabolic, characterized by a pronounced gluconeogenesis/glycogenolysis, by an equally pronounced muscle proteolysis, and by an increased lipolysis in adipose tissue. These adaptive responses (increased production of endogenous substrates) were acquired during evolution to maintain an appropriate substrate supply even in the absence of exogenous substrates. Several studies have shown that even an aggressive exogenous substrate supply (which is – in times of modern intensive care – easily possible) cannot reduce endogenous substrate production to an extent that would be clinically relevant [82]. Therefore, it makes sense to control calorie intake not only by the approximated calorie target, but also by the individual metabolic tolerance of the patient (sections 6.2.3 and 6.3.2).

Consistent with our recommendations, the A.S.P.E.N. also recommends considering the use of indirect calorimetry (Recommendation A3a, very low quality of evidence) [2]. Contrary to our recommendations, however, the A.S.P.E.N. guideline suggests use of an estimation formula with 25–30 kcal/kg per day as an alternative for determining energy turnover (Recommendation A3b) [2]. The A.S.P.E.N. guideline does not differentiate between individual disease phases. We recommend using a turnover rate of 24 kcal/kg per day in the acute phase. This recommendation coincides with average rates measured by indirect calorimetry during this phase. Although there is a lack of high-quality studies to give a sufficiently detailed answer to the question, the author group considers a "Should" recommendation to be justified.

We refer to section 11.2 in which we discuss how to determine energy expenditure in overweight critically ill patients.

Question: Which body weight should be used when calculating energy expenditure by the estimation formula?

Recommendation 6:

In non-obese patients (BMI <30 kg/m^2), the actual body weight may be used for calculating energy expenditure by the estimation formula.

Strong consensus (94%)

Commentary

All formulas that were developed to estimate energy expenditure or to assess nutrition status refer to the actual and not to the ideal body weight. The kind of weight clinicians should use for estimating energy expenditure in obese critically ill patients is discussed in section 11.2. Reference value for the actual body weight is the weight obtained prior to the disturbance of homeostasis. In patients who are already hyper-hydrated (capillary leak, congestive heart failure), clinically evident secondary edema/ascites/effusions must be taken into account and subtracted from the measured weight.

6.2. Determination of calorie intake

6.2.1. Macronutrients to calculate calorie intake

Question: Which macronutrients should be considered for calculating calorie intake?

Recommendation 7:

While using enteral and parenteral products, calculation of calorie intake should sum up the total calories of all macronutrients (including protein/amino acids).

Strong consensus (94%)

Commentary

Currently, total calories are listed for enteral formulas while for parental solutions often only non-protein calories are listed. This approach assumes that parenteral amino acids are exclusively processed via anabolic pathways (an argument that, of course, would also apply to protein provided via enteral nutrition). Delivered amino acids or proteins, however, can also serve as energy substrates [83]. Hence, calculation of the total calorie intake - even during parenteral nutrition - should include all administered calories and should not limit itself to non-protein calories. Although there is a lack of high-quality studies to give a sufficiently detailed answer to the question, the author group considers a "Should" recommendation to be justified.

Amino acids or proteins provided during MNT, however, do not replace endogenously catabolized proteins on a one-to-one basis. Even an aggressive enteral nutrition (40 kcal/kg per day, 1.6 g protein/kg per day) reduces the accelerated endogenous protein catabolism of burned patients by no more than 15% [84]. Comparable observations have been made repeatedly during aggressive parenteral nutrition (30–57 kcal/kg per day, 1.5–1.9 g amino acid/kg per day) [85–89]. Consequently, an intake that is high in protein/amino acid is likely to cause a corresponding overload during the acute phase.

Question: Should calories not provided by MNT be considered for calculating calorie intake?

Recommendation 8:

Calculation of total calorie intake should include intake of non-dietary calories (sedation with propofol, use of citrate dialysis).

Strong consensus (91%)

Commentary

Depending on the dose, propofol used for sedating critically ill patients may represent a significant portion of the total calorie intake. For example, 2% propofol contains 0.1 g fat/mL; at a propofol infusion rate of 20 mL/h, fat intake would be 48 g fat per day; thus, assuming a calorie content of ≈9 kcal/1 g fat, ≈432 extra calories would be given per day.

Trisodium citrate (NaCHO) is commonly used for regional anticoagulation during renal replacement therapy (RRT), and, like propofol, contains non-dietary calories. The number of effective calories provided by citrate anticoagulation depends on the citrate concentration/infusion rate needed, the blood flow rate, the filtration fraction of the ultrafiltrate per unit time ("sieving coefficient"), and on the type of filter. Citrate is metabolized rapidly in the citrate cycle, particularly in liver, skeletal muscle and renal cortex [90,91]. For example, a trisodium citrate solution may contain 0.59 kcal/mmol (corresponding to 3 kcal/g, which approximately equals 150–280 kcal per day when using an infusion rate of 11–20 mmol citrate/h).

In a retrospective analysis of 687 critically ill patients, sedation with propofol resulted in an additional calorie intake of 146 ± 117 kcal per day, corresponding to 17% of total calorie intake [92]. A retrospective study of 146 critically ill patients showed that the median propofol and citrate contribution to total calorie intake was 6–18% during the first seven days after ICU admission. In individual cases, however, this portion may increase up to one third of total calorie intake [93].

Although there is a lack of high quality studies to answer this question, the author group considers a "Should" recommendation to be justified.

6.2.2. Calorie intake in the acute phase

Question: How many calories should a patient receive in the acute phase?

Recommendation 9a:

Calorie intake should begin with 75% of the measured or estimated energy expenditure (the calorie target) and should be

increased subsequently according to individual metabolic tolerance to provide patients with 100% of the calorie target by the end of the acute phase (4–7 days after the onset of critical illness).

Strong consensus (94%)

Recommendation 9b:

When there are distinct signs of individual metabolic intolerance (blood glucose concentration >180 mg/dL despite an insulin infusion rate >4 IU/h, plasma phosphate concentration <0.65 mmol/L), the calorie/macronutrient intake should be reduced to an extent that tolerance is established again, or that a phosphate supplementation is no longer necessary, respectively (section 6.2.3).

Strong consensus (97%)

Recommendation 9c:

A persistent substrate intolerance (**Recommendation 9b**) may require a complete interruption of calorie intake (possibly combined with a further increase of the insulin infusion rate) to control blood glucose concentration.

Strong consensus (94%)

Commentary

Recommendations on calorie intake in obese patients can be found in section 11.2. One goal of MNT in the acute phase is to minimize endogenous substrate production (especially the loss of muscle protein). Simultaneously, however, the combination of exogenous substrate intake and ongoing endogenous substrate production should not lead to an excessive total nutrient supply. Hence, in the acute phase and depending on individual metabolic tolerance, calorie intake will often be below the calorie target (the measured or estimated energy expenditure) [94]. Thus far, however, there are no bedside techniques enabling clinicians to determine exactly the individual rate of endogenous substrate production. For fat or carbohydrate tolerance, only a rough estimate is clinically available by using blood glucose and triglyceride concentrations, or insulin infusion rates.

In determining exogenous calorie intake, it is important to understand that exogenous calories will not necessarily replace endogenous substrates on a one-to-one basis. It is still controversial, which percentage of the true (actually measured) energy expenditure (30–50%, 50–70% or 70–100%) should be administered as exogenous calories in a certain phase of the disease, and to what extent calorie intake is dependent on covariates (e.g. type of underlying disease, nutrition status before the disturbance of homeostasis, extent of organ dysfunction).

The effect of calorie intake on the prognosis of critically ill patients was examined in numerous observational studies (Table 4), in several prospective RCTs (of which four tested a eucaloric diet (calorie intake approaching 100% of target, Table 5) as well as in several meta-analyses (Table 6). The observational studies summarized in Table 4 showed four different patterns of association between calorie intake and mortality:

(i) mortality was lower when daily calorie intake (by enteral nutrition) was higher in patients suffering from sepsis [95] or presenting with a high NUTRIC score [36,38], with a BMI <25 or ≥35 kg/m^2 [96], or with acute renal failure [97].
(ii) a non-linear (U-shaped) association between mortality and daily calorie intake; mortality was at its minimum during a calorie intake in the range of 50–70% of target [73,98].
(iii) mortality was higher when daily calorie intake was higher; comparisons included >110% of target per day *vs.* ≤110% of target per day in non-septic patients [72]; 90% of target per day *vs.* 60% of target per day [99]; 81% of target per day *vs.* 63% of target per day [100]; >66.6% of target per day *vs.* ≤33.3% of target per day [101].
(iv) no association between daily calorie intake and mortality; comparisons included ≥20 kcal/kg day *vs.* <20 kcal/kg day [52]; target per day reached *vs.* target per day not reached [71]; in septic patients: >110% of target per day *vs.* ≤110% of target per day [72]; ≥80% of target per day *vs.* <80% of target per day [37].

Results with respect to morbidity were similarly inconsistent; three different patterns of association between calorie intake and morbidity were observed:

(i) morbidity was lower with a higher calorie intake, as demonstrated by fewer days with mechanical ventilation [95,96].
(ii) morbidity was higher with a higher calorie intake, as demonstrated by a longer hospital LOS [98], by an increased rate of nosocomial infections [99], and by a prolonged MV and time to hospital discharge (surviving patients) [37,101].
(iii) no association between the daily calorie intake and morbidity; outcome variables were the rate of ventilator-associated pneumonia [52], hospital LOS [36] and the number of days without RRT, or ICU LOS [97].

Several RCTs have examined the effect of calorie intake during the acute phase on the prognosis of critically ill patients, either as a primary target or as incidental finding to another scientific objective. 11 meta-analyses evaluated these RCTs (Table 6). For mortality, seven meta-analyses showed no difference between a mildly hypocaloric and a severely hypocaloric (enteral) nutrition [3,4,102–106], or between a largely eucaloric and a moderately hypocaloric diet (one meta-analysis) [107]. Three meta-analyses found a U-shaped relationship between calorie intake and mortality (minimum when 33.3–66.6% of target, or when a moderately hypocaloric diet was provided) [56–58].

For morbidity, a meta-analysis (published in the ESICM guideline on enteral nutrition [3]) showed that – when compared to a severely hypocaloric nutrition - a mildly hypocaloric diet reduced the rate of new nosocomial infections significantly. However, there was a high bias in this analysis because evaluated studies were monocentric, unblinded and had a very small sample size. Four other meta-analyses found no relationship between the calorie intake and the rate of new nosocomial infections or ICU- or hospital LOS [4,56,58,107]; in three meta-analyses, a slightly hypocaloric diet increased the rate of positive blood cultures [102], the duration of MV [103,105] or hospital LOS [103] when compared to a moderately hypocaloric nutrition. Three meta-analyses could not find a negative effect of a slightly hypocaloric nutrition on the duration of MV [56,58,104].

Only four randomized studies (Table 5) specifically evaluated the effect of a predominantly eucaloric diet (defined as ≈25 kcal/kg per day, or controlled by indirect calorimetry). Studies were conducted during the acute phase and in critically ill patients who had pronounced organ dysfunction. In comparison to a moderately hypocaloric nutrition, a eucaloric diet increased morbidity (rate of nosocomial infections) in two of the four studies [68,108]; mortality increased [108], decreased [68], or remained unchanged [69,109].

The exact metabolic course during the acute phase is unpredictable. Hence, it would make sense to “tailor” calorie intake individually according to metabolic tolerance. Calorie intake should begin with 75% of the measured or estimated energy expenditure (the calorie target) and should be advanced according to individual metabolic tolerance. Intake should increase in a way that - by the end of the acute phase (4–7 days after the start of critical illness) - 100% of the calorie target is achieved. With distinct signs of individual metabolic intolerance (caused by a persistent production of

Table 4
Observational studies (n > 300) on the association of calorie intake with clinical outcomes of critically ill patients.

Study	Number of patients	Design	Inclusion criteria	Variable of interest	Primary dependent variable (I)	Secondary dependent variable (II)	Result
Alberda et al., 2009 [96]	2772	Retrospective multicenter	MV, ICU LOS> 3 days	Calorie intake (EN/PN) between day 1 and day 12 (mean) (per Δ1000 kcal per day)	60-day hospital mortality	VFD	Sign. negative (I) or positive (II) linear association if BMI <25 or ≥ 35
Arabi et al., 2010 [101]	523	Retrospective multicenter, post-hoc RCT	ICU stay, blood glucose > 110 mg/dL	Calorie intake (EN/PN) between days 1 and 7: % of target per day in tertiles (3rd vs. 1st)	Hospital mortality	Nosocomial infection, Duration of MV, ICU-/hospital LOS	Sign. positive association with (I) and (II)
Heyland et al., 2011 [116]	7872	Retrospective multicenter	MV, ICU LOS> 3 days	Calorie intake (EN/PN) between days 1 and 12 (mean of % target per day)	60-day hospital mortality		Sign. negative association with (I)
Kutsogiannis et al., 2011 [100]	2920	Retrospective multicenter	MV, early EN, ICU LOS >3 days	EN + PN before or after day 2 (81% of calorie target) *vs.* EN (63% of target)	60-day hospital mortality		Sign. positive association with (I)
Weijs et al., 2012 [71]	886	Prospective multicenter	Predicted duration of MV > 4 days	Calorie intake (EN/PN) during MV: Target per day reached (yes/no)	28-day mortality		No association with (I)
Elke et al., 2013 [99]	353	Retrospective multicenter, post-hoc RCT	Sepsis; ICU LOS >7 days	Calorie intake (EN/PN) between days 1 and 21 (90% *vs.* 60% of target per day)	90-day mortality	Nosocomial infections	Sign. positive association with (I) and (II)
Bellomo et al., 2014 [97]	1456	Retrospective multicenter, post-hoc RCT	Acute kidney failure	Non-protein calories during ICU stay (maximum 28 days): per Δ 100 kcal per day)	90-day mortality	Days without RRT during ICu stay	Marginal (p = 0.06) negative association with (I), no association with (II)
Elke et al., 2014 [95]	2270	Retrospective multicenter	MV, ICU LOS >3 days	Calorie intake (EN) between days 1 and 12 (mean) (per Δ 1000 kcal per day)	60-day hospital mortality	VFD	Sign. negative (I) or positive (II) linear association
Weijs et al., 2014 [72]	843	Retrospective monocenter	Predicted duration of MV > 4 days	Calorie intake (EN/PN) on day 4:> 110% (IBW) *vs.* ≤110% of target	Hospital mortality		Sign. positive association with (I) if no sepsis; no association with (I) in sepsis
Crosara et al., 2015 [98]	1004	Retrospective multicenter, post-hoc RCT	ICU stay	Calorie intake (EN/PN) during ICU stay: kcal/kg per day in quartiles	Hospital mortality	Hospital LOS	Sign. non-linear association with (I) (minimum at 25–50% of target), sign. positive association with (II)
Reignier et al., 2015 [52]	1398	Retrospective multicenter	MV > 3 days, arterial blood pressure <90 mmHg, no patients after abdominal operations	Calorie intake (EN/PN) on days 2 and 3: ≥20 *vs.* <20 kcal/kg per day	28-day mortality	Frequency of VAP	No association with (I) and (II)
Nicolo et al., 2016 [37]	2828	Retrospective multicenter	MV, ICU LOS >3 days	Calorie intake (EN/PN, not volitional) between days 1 and 12 (mean of % target per day) ≥80% of target *vs.* <80%; Duration of EN/PN ≥ 4 days	60-day hospital mortality	Time to hospital discharge (surviving patients)	No association with (I), sign. positive association with (II)
Rahman et al., 2016 [38]	1199	Retrospective multicenter, post-hoc RCT	MV, ICU LOS >5 days	Calorie intake (EN/PN, not volitional) during MV (max. 28 days) (mean of % of target per day): per Δ25% of target per day	28-day mortality		Sign. negative linear association with (I) only at a high NUTRIC score (6–9)
Zusman et al., 2016 [73]	1171	Retrospective monocenter	ICU LOS >4 days	Calorie intake (EN/PN) during ICU stay: mean of % of target per day (IBW)	60-day mortality		Sign. non-linear association with (I) (minimum at 70% of target)
Compher et al., 2017 [36]	2853	Prospective multicenter	MV > 3 days, low *vs.* high NUTRIC score	Calorie intake (EN/PN) between days 1 and 12 (mean) (per Δ10% of target)	60-day hospital mortality	Time to hospital discharge (surviving patients)	Sign. negative linear association with (i) only at a high NUTRIC score, no association with (II)

EN: enteral nutrition; IC: indirect calorimetry; IBW: ideal body weight; ICU: intensive care unit; LOS: length of stay; MV: mechanical ventilation; PN: parenteral nutrition; RCT: randomized controlled trial; RRT: renal replacement therapy; sign.: significant; VAP: ventilator-associated pneumonia; VFD: ventilator-free days.

Table 5
RCTs specifically investigating the effect of a eucaloric diet on clinical outcomes of critically ill patients.

Author	Number of patients	Calorie target	Calorie intake	Endpoint of mortality	Effect on mortality	Effect on morbidity	Notes
Bauer et al., 2000 [109]	120	25 kcal/kg per day	25 *vs.* 14 kcal/kg per day	90-day mortality	Ø	Infections: Ø Duration of MV: Ø ICU-LOS: Ø	Blinded
Singer et al., 2011 [68]	130	Resting energy expenditure	26 *vs.* 19 kcal/kg per day	90-day mortality	Lower	Infections: ↑ Duration of MV: ↑ Hospital-/ICU LOS: ↑	Use of Indirect calorimetry
Braunschweig et al., 2015 [108]	78	30 kcal/kg per day	25 *vs.* 17 kcal/kg per day	Hospital mortality	Higher	Infections: ↑ VFD: Ø ICU-LOS: Ø	BMI 30 kg/m^2
Allingstrup et al., 2017 [69]	199	Resting energy expenditure	24 *vs.* 13 kcal/kg per day	6-month mortality	Ø	Infections: Ø Organ failure: Ø Physical performance: Ø	Use of Indirect calorimetry Results independent from: age, SOFA score and extent of kidney failure

Ø: no effect; BMI: body mass index; ICU: intensive care unit; LOS: length of stay; MV: mechanical ventilation; VFD: ventilator-free days; ↑: increased.

Table 6
Meta-analyses on the effect of calorie intake on clinical outcomes of critically ill patients.

Author	Number of studies	Number of patients	Calorie intake	Endpoint of mortality	Effect on mortality	Effect on morbidity	Covariates without effect on clinical outcomes
Reintam Blaser et al., 2017 [3]	12	662	Moderate (e.g., ≈70% of target) *vs.* severe (e.g., ≤30% of target) hypocaloric EN	Not specified	Ø	Infections: ↓ (high bias due to small sample size of individual studies)	
Al-Dorzi et al., 2016 [102]	21	4717	Δ ≈ 445 kcal per day EN ± PN intended + unintended hypocaloric nutrition	Hospital mortality	Ø	Infections: Ø RRT: Ø positive BC: ↑	• Age:< 65 *vs.* ≥65 years • APACHE II: <20 *vs.* ≥ 20
Marik et al., 2016 [104]	6	2517	74% *vs.* 37% of target EN ± PN intended hypocaloric nutrition	Hospital mortality	Ø	Infections: Ø VFD: Ø ICU LOS: Ø	
Choi et al., 2015 [56]	4	1540	81% *vs.* 44% of target EN intended hypocaloric nutrition	Not specified	Total: Ø (U shaped: Minimum 33.3 −66.6% of target)	Infections: Ø ICU-/hospital LOS: Ø Duration of MV: Ø	• BMI
Parikh et al., 2016 [105]	16	3473	≈1400 *vs.* ≈950 kcal per day EN ± PN intended + unintended hypocaloric nutrition	Hospital mortality	Ø	Duration of MV: ↑ ICU-/hospital LOS: Ø Pneumonia: Ø	• Admission category (e.g. surgical) • EN *vs.* EN + PN • BMI • protein intake
Tian et al., 2015 [58]	8	1895	80% *vs.* 48% of target EN ± PN intended + unintended hypocaloric nutrition	Not specified	Total: Ø (U-shaped: Minimum 33.3 −66.6% of target)	Infections: Ø (>0.85 g protein/kg IBW per day *vs.* ≤0.68 g protein/kg IBW per day: ↓) ICU-/hospital LOS: Ø Duration of MV: Ø	• On mortality or ICU-/hospital LOS: • protein intake
Chelkeba et al., 2017 [103]	17	3593	≈470−2100 *vs.* ≈130 −1500 kcal per day EN ± PN intended + unintended hypocaloric nutrition	Not specified	Ø	Hospital LOS: ↑ MV Duration of MV: ↑ Infections: Ø	On mortality: • EN *vs.* EN + PN • BMI • APACHE II • % of calorie target reached
Ridley et al., 2017 [107]	10	3155	89% *vs.* 70% of target EN ± PN intended + unintended hypocaloric nutrition	Not specified	Ø	ICU-/hospital LOS: Ø Infections: Ø	On mortality: • Extent of bias • Endpoint for mortality • EN *vs.* EN + PN
Rhodes et al., 2017 [4]	7	2665	"Full" *vs.* "trophic" EN	Not specified	Ø	ICU LOS: Ø Infections: Ø	
Phan et al., 2017 [106]	7	2684	≈1200 *vs.* ≈600 kcal per day "Full" *vs.* "trophic/hypocaloric" EN	28-day mortality	Ø		
Stuani Franzosi et al., 2017 [57]	5	2432	16−25% *vs.* 46−72% *vs.* ≈100% of target EN intended hypocaloric nutrition	Not specified	Total: Ø (U-shaped: Minimum 46 −72% of target)	Infections: Ø ICU-/hospital LOS: Ø MV duration: Ø	

APACHE: Acute Physiology and Chronic Health Evaluation, BC: Blood culture, BMI: Body Mass Index; EN: enteral nutrition; ICU: intensive care unit; LOS: length of stay; PN: parenteral nutrition; RRT: renal replacement therapy; VFD: ventilator-free days; ↑: increased; ↓: decreased; Ø: no effect.

endogenous substrates), the exogenous calorie/macronutrient intake should be reduced until tolerance is reached or phosphate supplementation is no longer necessary (see section 6.2.3). Thus far, only one study examined individual metabolic tolerance as a concept of early MNT [111]. Nevertheless, the author group considers a "Should" recommendation to be justified.

The guidelines of SSC or A.S.P.E.N. (Recommendation C2) [2,4] recommend that patients with sepsis, septic shock, acute respiratory distress syndrome/acute lung injury (ARDS/ALI) or an expected duration of MV ≥72 h should receive either a hypocaloric or a eucaloric enteral diet in the acute phase. Results of the 11 meta-analyses presented in Table 6 do not consistently support the equivalence of these different diets. Thus, during a slightly hypocaloric or eucaloric diet, mortality remained unchanged in eight meta-analyses, but increased in three; morbidity was unchanged in six, increased in three, and decreased only in one meta-analysis [3] (the latter having a high bias due to the very low sample size of individual studies). Taken together, one can conclude that a moderately hypocaloric nutrition in the acute phase is the most likely diet to be associated with the most favorable outcome.

Recommendations 9a–c equally apply to critically ill patients with or without preexisting diabetes mellitus.

6.2.3. Individual control of calorie intake in the acute phase

When there is an excessive need for insulin in the acute phase (>4 IU/h to maintain blood glucose concentration <180 mg/dL), MNT should be consistent with the recommendations made in the DGEM S3 guideline "*Monitoring of Artificial Nutrition: Specific Aspects*", which endorses a reduction of calorie intake [110]. The precise threshold of intolerance, however, is unknown; the recommendations made above are based on observations in clinical practice (especially on the average insulin requirement). An uncontrollable intolerance (**Recommendation 9b**) may make it imperative to completely interrupt calorie intake and, possibly, to further increase insulin infusion rate to control blood glucose concentration.

Fig. 3 shows a practice-oriented concept for the individual control of substrate supply according to the maximum daily insulin requirement. The goal is to maintain a blood glucose concentration <180 mg/dL "Day-0" refers to the day of disturbance of homeostasis.

The results of a single RCT suggests reduction of the pre-existing calorie intake to a minimum (5–6 kcal/kg actual body weight per day), when hypophosphatemia (<0.65 mmol/L, a surrogate marker of refeeding syndrome) occurs. Only when phosphate concentrations are in the reference range, or when there is no longer a need for phosphate substitution, the daily calorie intake should be increased gradually again [111]. Fig. 4 presents a practice-oriented concept for individual control of substrate intake based on serum phosphate levels. This concept, however, does not apply to patients receiving RRT. When insulin requirement rises and phosphate concentrations are simultaneously falling, that parameter should dominate the control of substrate supply which requires the strongest absolute change of calorie intake. Thus, at normal phosphate concentrations, insulin requirement should control calorie intake.

Of note, the algorithms presented in Figs. 3 and 4 are not validated, and are only based on expert consensus considering pathophysiological evidence. "Day 0" refers to the day of the disturbance of homeostasis.

6.2.4. Calorie intake in the post-acute (convalescence/rehabilitation) phase

Question: How many calories should a patient receive in the anabolic recovery phase (convalescence/rehabilitation)?

Recommendation 10:

In the anabolic recovery phase (convalescence/rehabilitation), calorie intake should be at ≥ 100% of the measured/estimated energy expenditure (i.e., the calorie target) and should respect individual metabolic tolerance.

Strong consensus (100%)

Commentary

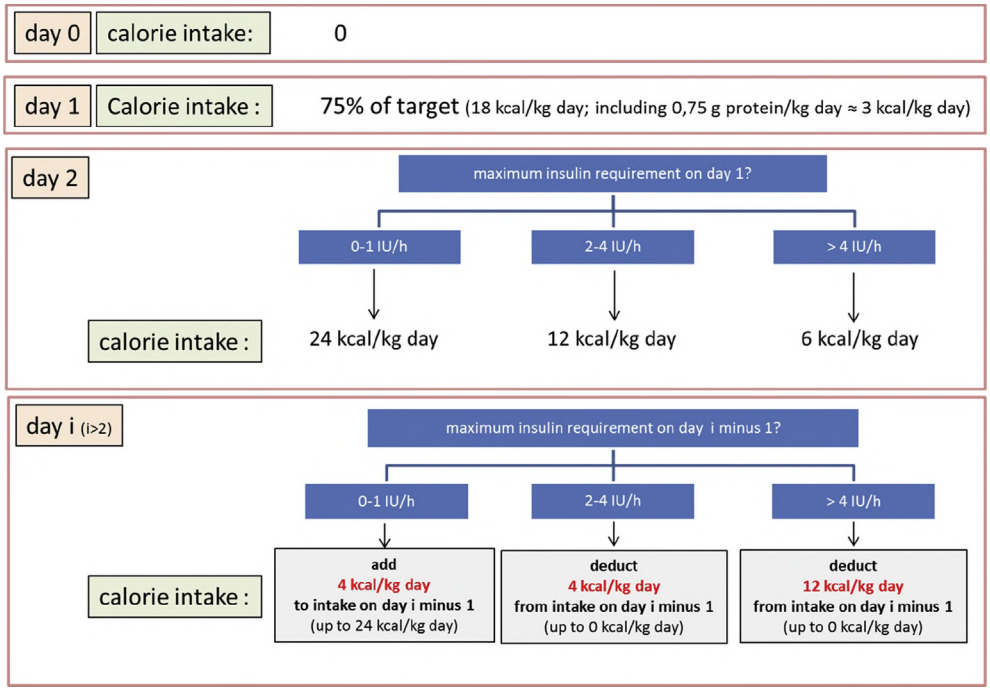

Fig. 3. Individual control of calorie intake by insulin requirement; blood glucose concentration should not be > 180 mg/dl; day 0 indicates the day of disturbance of homeostasis.

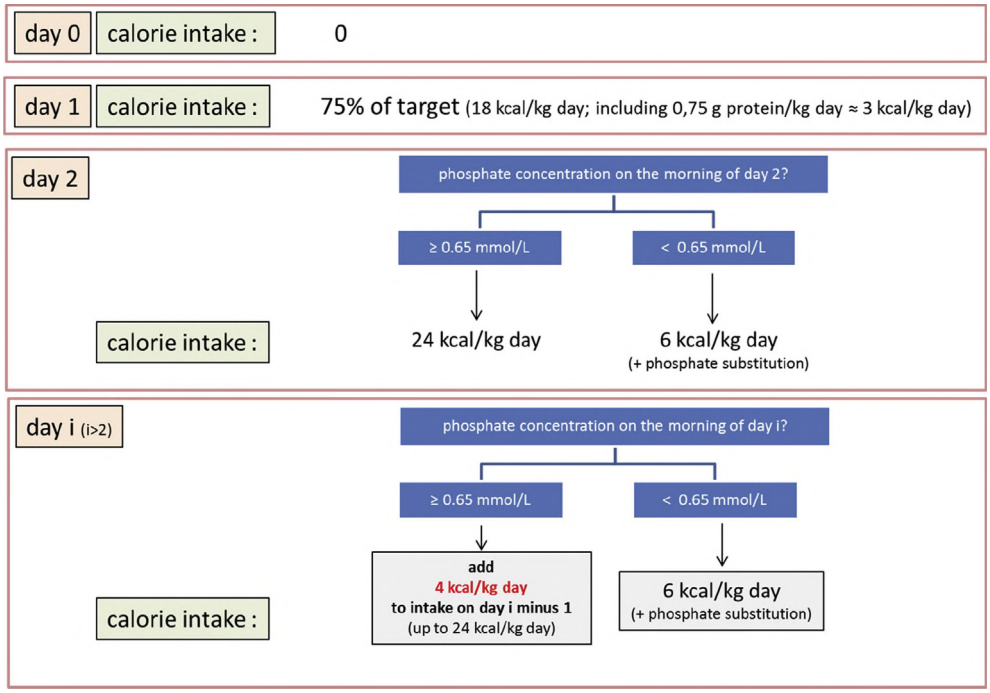

Fig. 4. Individual control of calorie intake by phosphate concentration; day 0 indicates the day of disturbance of homeostasis; flow diagram cannot be used in patients receiving renal replacement therapy (RRT).

After disappearance of catabolic signals and resolution of organ failure, patients should receive a eucaloric diet or a diet delivering >100% of the energy expenditure, respectively. Rationale for this recommendation were recommendations for sarcopenia prevention in the elderly [112,113]. In their guideline, A.S.P.E.N. recommends a calorie intake of >60% of target for the post-acute phase. If this intake cannot be achieved by enteral nutrition, parenteral supplementation is recommended (Recommendation G3, moderate quality of evidence) [2].

As energy expenditure is expected to increase in the convalescence phase combined with an attenuation of metabolic resistance, we would recommend a higher calorie intake in the convalescence phase (>100% of target, ≤ 36 kcal/kg per day [75]) (respecting the individual metabolic tolerance). Although there is a lack of high-quality studies to give a sufficiently detailed answer to the question for the target group, the author group considers a "Should" recommendation to be justified.

6.2.5. Calorie intake in the chronic phase

Question: How many calories should a patient receive in the chronic phase?

Recommendation 11:

In the chronic phase, patients should receive a eucaloric diet (100% of the measured/estimated energy expenditure) respecting the individual metabolic tolerance.

Strong consensus (97%)

Commentary

For the chronic phase (persistent organ dysfunction without acute inflammatory/infectious exacerbation), large RCTs in critically ill patients have not been conducted so far [114,115]. An optimal preservation of muscle-mass, and the ongoing need to support reparative/immunologic processes in these patients, requires the continuation of MNT. The measured/estimated energy expenditure (eucaloric diet, 100% of target) should control calorie intake. Again, clinicians should individualize MNT by adjusting calorie intake to the extent of insulin resistance/hyperglycemia/hypophosphatemia, and should avoid a prolonged hypocaloric nutrition throughout the whole course of the disease.

Although there is a lack of high quality studies to answer the question, the author group considers a "Should" recommendation to be justified.

6.2.6. Calorie intake with pre-existing malnutrition

Question: How many calories should a patient receive who presents with a preexisting malnutrition?

Recommendation 12:

For patients with a pre-existing malnutrition, calorie intake and calorie targets may be the same as in patients without a preexisting malnutrition. Intake should be adjusted to the individual metabolic tolerance and phase of disease.

Consensus (85%)

Commentary

The current definition of malnutrition and the assessment of nutrition status/risk is presented in section 4.

Several meta-analyses could not find an association between the efficacy of a particular MNT and BMI (as a surrogate parameter for nutritio status) of critically ill patients [56,103,105]. However, patients who had been severely malnourished before the disturbance of homeostasis (BMI <18 kg/m^2) were excluded from these studies.

A *post hoc* analysis of the PermiT trial investigated whether the pre-albumin concentration before the disturbance of homeostasis was important for the efficacy of calorie intake (carbohydrates/fats) [39]. The authors diagnosed a malnutrition, if pre-albumin concentration was ≤0.1 g/L. An increase in carbohydrate/fat intake from 45% to 70% of calorie target was associated with an increase in 90-day mortality, and in the need for RRT. Due to the analytical design, however, conclusions can only be hypothesis-generating.

In severely malnourished individuals (weight loss >25%) who were not critically ill, an older study found that a rapid step-up of volitional intake to eucaloric amounts also increased the infection rate from 5% (before the onset of nutrition) to 30% (after two weeks of feeding) [117].

Thus, it seems reasonable to avoid an aggressive MNT in severely malnourished patients. Particularly in this patient group, however, MNT should start early within the first 24 h after the onset of the acute phase. Calorie intake may be the same as that recommended for non-malnourished patients (see section 6.2.2) and should respect individual intolerance or side effects ("refeeding syndrome"), respectively [118]. Control of MNT according to serum phosphate concentrations (avoidance of a refeeding syndrome) is discussed in section 6.2.3.

The DGEM recommendation differs significantly from the corresponding recommendations of the 2016 A.S.P.E.N. guideline [2]. The latter recommends for malnourished patients or patients with a high nutrition risk, respectively, to step-up calorie intake (enteral and parenteral) faster (reaching the calorie and protein target within the first 48 h after the onset of illness) (Recommendation C3, expert consensus, and Recommendation H2, low quality of evidence). Only two of the studies that were the rationale of Recommendation C3, however, were RCTs. The study by Jie et al. [119] investigated the benefit of a preoperative MNT in malnourished/non-malnourished general surgical patients, and the study by Taylor et al. [120] examined patients with traumatic brain injury but did not stratify them according to nutrition status before trauma. Both studies cannot contribute to the formulation of a recommendation regarding the matter in question (control of calorie intake according to the initial nutrition status of critically ill patients). Further rationale for the A.S.P.E.N. recommendations were the results of one observational study that has, however, design-inherent limitations (section 2.4.2). This study examined associations of an aggressive MNT with outcome in critically ill patients with a low or high NUTRIC score [35].

A.S.P.E.N. further recommends (with low quality of evidence) that severely malnourished patients requiring parenteral nutrition should receive a hypocaloric diet (≤20 kcal/kg per day, or 80% of estimated energy needs) with a high amino acid content (1.4 g amino acid/kg per day) in the acute phase. Rationale for the Recommendation H2 of the A.S.P.E.N. was a separate meta-analysis of four RCTs in which all patients were on exclusive parenteral nutrition. This meta-analysis showed no harmful effects of a hypocaloric nutrition. No data were provided on the efficacy of a diet with a high amino acid content. However, the results of this meta-analysis were highly biased because each study enrolled <60 patients. In addition, two of the four studies examined exclusively or predominantly non-critically ill patients, and another study only obese patients (BMI = 34 kg/m^2); one of the four studies compared 14 *vs*. 18 kcal/kg per day, and another study 26 *vs*. 37 kcal/kg per day. Finally, one study only compared a complete parenteral diet (containing linoleic acid thereby providing 4 kcal fat/kg per day) with a partial parenteral nutrition (without fat) [2].

6.3. Determination of the protein target and of protein intake

6.3.1. Reference weight for the protein target

Question: What is the reference weight for the protein target?

Recommendation 13:

In non-obese patients (BMI <30 kg/m^2), reference for the protein target should usually be the actual body weight.

Strong consensus (100%)

Commentary

Two variables are important when defining the target for protein-/amino acids intake: the size of the protein pool in the body and the severity of the disease. These variables determine the extent to which proteins are degraded or synthesized. Total body protein is difficult to quantify; therefore, lean body mass, which comes closest to total body protein mass, should control intake of proteins or amino acids [121]. Lean body mass can be quantified by CT, MRI, bioimpedance or muscle ultrasound imaging. However, numerous limitations (see section 4) largely restrict the clinical application of these methods during ICU routine.

Only one meta-analysis (by Tian et al. [58]) related protein/amino-acid intake to ideal body weight (which, however, the authors had calculated retrospectively at the time of the meta-analysis). Ideal body weight (referred to a normal BMI of 22 kg/m^2) can be calculated as:

$$\text{ideal weight (kg)} = 48.4 + 77.0 \times (\text{body height} - 1.50\ \text{m})$$ [122].

Drawback of this approach is that no further studies used ideal body weight as a reference for protein intake, so no further evidence regarding the clinical benefit of this reference weight exists.

The author group felt that it would be the best for clinical routine to use the actual body weight, which was present before the onset of critical illness, as reference for the protein target in non-obese patients. In patients already hyperhydrated (capillary leak), clinically evident secondary edema/ascites/effusions must be taken into account and subtracted from the current weight. Epidemiologically, the average actual (normal) weight of the German population is about 20–25% above the ideal weight [123].

Although there is a lack of high-quality studies to give a sufficiently detailed answer to the question, the author group considers a "Should" recommendation to be justified. For the recommendation on the protein target in obese patients, see section 11.2.

6.3.2. Protein target and protein intake in the acute phase

Question: How is the protein target defined?

Recommendation 14a:

Usually, the target of protein or amino acid intake in the acute phase should be at 1.0 g or 1.2 g/kg of actual body weight per day, respectively.

Consensus (87.5%)

Question: How much protein should a patient receive in the acute phase?

Recommendation 14b:

Protein-/amino acid intake should begin with 75% of the protein target and should be increased subsequently according to individual metabolic tolerance to provide patients with 100% of the protein target by the end of the acute phase (4–7 days after the onset of critical illness).

Consensus (82%)

Recommendation 14c:

When there are distinct signs of individual metabolic intolerance (blood glucose concentration >180 mg/dL despite an insulin infusion rate >4 IU/h, plasma phosphate concentration <0.65 mmol/L), the protein-/amino acid intake may be reduced in proportion to the corresponding reduction of total calorie intake.

Consensus (80%)

Commentary

Calculation of infusion rates of amino acids requires a correction factor to convert protein intake into amino acid intake. This correction is necessary because - per weight unit - solutions with free amino acids contain ≈17% less protein equivalents than formed protein [124].

The author group cannot define a mandatory protein target because conclusive evidence is missing. For critically ill patients, protein needs depend on the nature of the underlying disease and on the phase of critical illness. Targets are still not clear and subject to an intense discussion, as are exact dose-response relationships and the effect of a high protein intake on outcome [125]. Nevertheless, the author group has decided to define a protein target and protein intake thereby giving directives for clinicians; furthermore, recommendations should help to avoid an unintentional significant deviation from protein targets or intakes.

Table 7
Observational studies (n > 300) on the association of protein/amino acid intake with clinical outcomes of critically ill patients.

Study	Number of patients	Design	Inclusion criteria	Variable of interest	Primary dependent variable (I)	Secondary dependent variable (II)	Results
Alberda et al., 2009 [96]	2772	Retrospective multicenter	MV, ICU LOS > 3 days	Protein intake (EN/PN) between days 1 and 12 (mean) (per Δ30 g per day)	60-day hospital mortality	VFD	Sign. negative (I) association only if BMI <25 or ≥35; no association with (II)
Kutsogiannis et al., 2011 [100]	2920	Retrospective multicenter	MV, early EN, ICU LOS >3 days	EN + PN before or after day 2 (80% of protein target) *vs.* EN (59% of target)	60-day hospital mortality		Sign. positive association with (I)
Weijs et al., 2012 [71]	886	Retrospective multicenter	Predicted duration of MV > 4 days	Protein and calorie intake (EN/PN) during MV: protein/calorie target per day reached (yes/no)	28-day mortality		Sign. negative association with (I)
Bellomo et al., 2014 [126]	1457	Retrospective multicenter post-hoc RCT	Acute kidney injury	(a) Protein and calorie intake during ICU stay (max. 28 days) (mean) (b) > 1 g protein/kg per day vs. ≤ 1 g protein/kg per day	(a) 90-day mortality (b) 28-day mortality	Days without RRT/stay in ICU	No association with (I) and (II) for (a) and (b)
Elke et al., 2014 [95]	2270	Retrospective multicenter	MV, ICU-LOS >3 days	Protein intake (EN) between days 1 and 12 (mean) (per Δ30 g per day)	60-day hospital mortality	VFD	Sign. negative (I) or positive (II) linear association
Weijs et al., 2014 [72]	843	Retrospective multicenter	Predicted duration of MV > 4 days	Protein intake (EN/PN) on day 4: 0.8 *vs.* 1.0 *vs.* 1.2 g/kg per day	Hospital mortality		Sign. negative association with (I) (>1.2 g/kg per day) if no sepsis; no association with (I) in sepsis
Nicolo et al., 2016 [37]	2828	Retrospective multicenter	MV, ICU LOS >3 days	Protein intake (EN/PN, not volitional) between days 1 and 12 (mean of % of target per day): ≥80% of target *vs.* <80%; Duration of EN/PN ≥ 4 days	60-day hospital mortality	Time until hospital discharge (survivors)	Sign. negative association with (I), no association with (II)
Zusman et al., 2016 [73]	1171	Retrospective multicenter	ICU LOS >4 days	Protein intake (EN/PN) during ICU stay: mean of % of target per day	60-day mortality		Sign. negative association with (I)
Compher et al., 2017 [36]	2853	Prospective multicenter	Duration of MV > 3 days, low *vs.* high NUTRIC score	Protein intake (EN/PN) between days 1 and 12 (mean) (per Δ10% of target)	60-day hospital mortality	Time until hospital discharge (survivors)	Sign. negative linear association with (I) only at high NUTRIC score; no association with (II)
Koekkoek et al., 2018 [127]	455	Retrospective multicenter	Duration of MV > 6 days	Protein intake (EN/PN) between days 1 and 3, days 4 and 7, and days 1 and 7 (mean): >0.8 g/kg per day *vs.* <0.8 g/kg per day	6-month mortality	Duration of MV and of RRT, ICU LOS	Sign. positive association with (I) for day 1–3; sign. negative association with (I) for day 1–7; no association with (II)

EN: enteral nutrition; ICU: intensive care unit; LOS: length of stay; MV: mechanical ventilation; PN: parenteral nutrition; RRT: renal replacement therapy; RCT: randomized controlled trial; sign.: significant; VFD: ventilator-free days.

Exogenous protein intake tries to minimize endogenous amino acid production thereby attenuating the metabolic consequences of stress-induced catabolism. Simultaneously, however, the sum of exogenous and endogenous amino acids should not result in amino acid overload. During the acute phase, even an aggressive enteral/parenteral nutrition can never completely suppress endogenous amino acid release and protein catabolism, respectively. Thus, an amino acid excess is possible in clinical practice in the presence of a high amino acid intake and ongoing catabolism [86,87,89].

Table 7 gives an overview on the observational studies which had a comparably large sample size (n > 300), and examined the association between different protein intakes and the outcomes of critically ill patients. Five different patterns of association between protein intake and morbidity were observed:

(i) a quasi-linear, inverse relationship between higher protein intake and lower mortality in unselected critically ill patients: per Δ 30 g per day during enteral nutrition [95]; per % of target reached per day during parenteral/enteral nutrition [73];
(ii) mortality was only lower, when a certain intake had been exceeded; thresholds were: simultaneously reaching the protein and calorie target during parenteral/enteral nutrition [71]; providing >1.2 g protein/kg per day during parenteral/enteral nutrition [72]; providing ≥80% of the protein target during parenteral/enteral nutrition [37];
iii) associations between protein-/amino acid intake and mortality existed only in certain patient subgroups: patients with a high NUTRIC score during parenteral/enteral nutrition [36]; patients with a BMI <25 or ≥35 kg/m^2 [96]; non-septic patients [72];
(iv) no association between protein-/amino acid intake and mortality: patients with acute renal failure [126];
(v) a higher protein-/amino acid intake was associated with increased mortality. Comparisons included: 80% *vs.* 59% of the protein target during parenteral/enteral nutrition [100]; >0.8 g protein/kg per day *vs.* <0.8 g protein/kg per day in the acute phase [127].

It has become evident that results on morbidity a similarly conflicting when analyzed by large observational studies (e.g., "ventilator-free days" [VFD] or time to hospital discharge among survivors). In all but one study protein intake was not associated with morbidity [36,37,96,126]. One study found a lower number of VFDs when patients had received more protein/amino acids [95]. Small observational studies even found that a higher protein intake was associated with an accelerated loss of muscle protein [49] and increased in-hospital mortality [128].

Due to their heterogeneity and the limitations described in section 2.4.2, observational studies cannot contribute much to the formulation of recommendations. Furthermore, in observational studies, protein-/amino acid intake never varied exclusively, but was always associated with corresponding changes of calorie intake. Therefore, it is difficult to separate protein-related associations with outcome from those related to calories. This phenomenon further weakens the importance of observational studies.

Unfortunately, there are also no appropriate RCTs allowing for definite recommendations on protein-/amino acid intakes in the acute phase. Four studies (Table 8) investigated, in critically ill patients, the extent to which an increased protein-/amino acid intake (with a constant or reduced carbohydrate/fat intake) influenced morbidity and mortality; a clinically relevant effect could not be demonstrated. The RCTs may be criticized because.

Table 8
RCTs on the effect of protein-/amino acid intake on clinical outcomes of critically ill patients.

Author	Number of patients	Design	Protein intake	Calorie intake comparable	Effect on ICU-/hospital length of stay	Effect on morbidity	Effect on mortality
Mesejo et al., 2003 [129]	50	EN for 14 days	1.14 *vs.* 1.25 g protein/kg per day	Yes	Ø	Ø	Ø
Rugeles et al., 2013 [131]	115	EN for 7 days	0.8 *vs.* 1.4 g protein/kg per day	Yes	Ø	↓[a] (Δ SOFA 48 h)	Not reported
Doig et al., 2015 [132]	474	Parenteral supplement until ICU discharge	0.75 *vs.* 1.75 g amino acids/kg per day	No	Ø[b]	Ø[b]	Ø[b]
Ferrie et al., 2016 [130]	119	PN for 10 days	0.9 *vs.* 1.1 g amino acids/kg per day	Yes	Ø[c]	Ø[c]	Ø

Ø: no effect; ICU: intensive care unit; SOFA: Sequential Organ Failure Assessment; EN: enteral nutrition; PN: parenteral nutrition; ↓: decreased.
[a] No intention-to-treat analysis.
[b] Tertiary target variable.
[c] According to a secondary intention-to-treat analysis.

(i) sample size was small (n ≤ 50) [129])
(ii) differences of protein intake between the study arms were small [129,130], and the outcome variable was not subject of an intention-to-treat analysis [130].
(iii) the outcome variable was questionable (Δ SOFA score in the first 48 h after ICU admission) and was not subject of an intention-to-treat analysis [131].
(iv) calorie intake was not comparable, and morbidity/mortality were only tertiary outcome variables [132].

Despite methodologic limitations, several meta-analyses analyzed protein intake of randomized studies originally focusing on calorie intake [58,105,133] (Table 9). The corollary result was that an increased protein-/amino acid intake did not improve mortality. However, the meta-analyses could only compare relatively small differences of protein intake (e.g. 0.7 *vs.* 1.0 g protein/kg per day). A meta-analysis by Tian et al. [58] showed that an intake >0.85 g protein/kg ideal body weight per day in the acute phase reduced the rate of infection (compared with an intake <0.65 g protein/kg ideal body weight per day), regardless of calorie intake. Thus, according to this study, protein intake in the acute phase should not be < 0.85 g protein/kg ideal body weight per day. This recommendation coincides largely with the protein target (1 g protein/kg body weight per day) stated in **Recommendation 14a**, which refers to the actual body weight; on average, actual body weight of the German population is about 20–25% higher than the ideal body weight [123].

The hypothesis-generating results of the *post hoc analyses* of the PepaNIC trial and (to a lesser extent) of the EPaNIC trial suggested that amino acid intake in the acute phase was associated with increased morbidity/mortality [134,135]. However, the PepaNIC trial was not conducted in the target group of this guideline, but in critically ill children [134,135].

Despite a very low quality of evidence (Recommendation C4), the A.S.P.E.N. guideline recommends that protein intake should be high in the acute phase assuming that protein needs are high in this phase (1.2–2.0 g/kg per day) and possibly even higher in burns and trauma patients. These recommendations did not take into account (i) studies published since the end of the literature search of the A.S.P.E.N. guideline (December 2013), in particular the study by Doig et al. listed in Table 7 [132], (ii) the so-called EAT-ICU trial [69], and (iii) the current meta-analysis on the topic [133] (Table 8). Rationale of the A.S.P.E.N. expert consensus were the results of observational studies by Weijs et al. [71] and Allingstrup et al. [136]; due to their design, however, these studies only found an association, but no causality, and are subject to indication bias.

Furthermore, the A.S.P.E.N. authors ignored that (i) even under extreme circumstances postabsorptive release of amino acids from the musculature is ≤ 1.5 g/kg per day, and (ii) MNT never completely suppresses endogenous release of amino acids or protein catabolism (the residual release of muscular amino acids in sepsis, even under an aggressive diet, is ≥ 0.5 g/kg per day). Thus, with a high exogenous intake of amino acids and robust catabolism, an excess is always possible [86,87,89].

Although there is a lack of high-quality studies to give a sufficiently detailed answer to the question, the author group considers a "Should" recommendation to be justified. To achieve 100% of the protein target (1.0 g/kg of actual body weight per day) when using commercial products (and simultaneously to avoid an increased intake of non-protein calories), it may be necessary to supplement protein concentrates together with standard enteral nutrition (the same applies to the provisioning of amino acids).

As the voting results indicate, a few members of the author group did not share the majority opinion expressed in

Table 9
Meta-analysis on the effect of different protein intakes on clinical outcomes of critically ill patients.

Author	Number of studies	Number of patients	Protein intake	Endpoint for mortality	Effect on mortality	Effect on morbidity	Remarks
Davies et al., 2017 [133]	14	3238	0.67 *vs.* 1.02 g protein/kg per day (average protein intake across all studies)	various	Ø	Ø	Results were independent from: • Number of days with MNT • APACHE II score • Gender • Route of protein intake • calorie intake

Meta-analyses by Tian et al. [58] and Parikh et al. [105] addressing this topic are listed in Table 6. APACHE: Acute Physiology And Chronic Health Evaluation; Ø: no effect.

Recommendations 14a–c. A therapeutic alternative pushed forward by these members was to provide patients with a larger amount of protein early during the acute phase. According to their opinion, protein intake should be below 0.8 g/kg actual body weight per day on day 1; subsequently, protein intake should be increased up to 1.2 g/kg actual body weight per day until the end of the acute phase (day 4–7). This intake should be accompanied by a simultaneous restriction of calorie intake to 80–90% of the estimated or measured energy expenditure [36,72,127]. In patients with sepsis, however, intake should be lower [72]. The majority of the members of the author group did not accepted this therapeutic alternative, which was only based on selected observational studies. Therefore, we did not include this alternative as a recommendation. Since there is an ongoing international discussion on the subject, however, we felt it would be appropriate to present this therapeutic alternative.

Individual control of protein intake in the acute phase. There is no bedside method to monitor the individual changes of endogenous amino acid production when supplying exogenous proteins or amino acids. However, there is a close correlation between the endogenous activation of carbohydrate and amino acid/protein metabolism [82]. Therefore, it may be reasonable to use the parameters of the readily measured insulin resistance or phosphate concentration as indicators for anabolic resistance (= inability to use exogenous amino acids adequately). From this the recommendation may be formulated to reduce not only exogenous intake of carbohydrates in the case of pronounced glucose intolerance (insulin requirement >4 IU/h ± hypophosphatemia) (see section 6.2.3), but also to reduce protein-/amino acid intake to the same extent (Figs. 3 and 4). However, this concept only reflects an expert consensus of the author group, which believes that it would make sense to homogenize the intake of carbohydrates, fat and protein.

6.3.3. Protein intake in the post-acute phase (convalescence/rehabilitation phase)

Question: How much protein should a patient receive in the post-acute phase (convalescence/rehabilitation phase)?

Recommendation 15:

In the anabolic recovery phase (convalescence), the protein-/amino acid intake should be at ≥ 100% of the target proposed for the acute phase (1.0 g protein or 1.2 g amino acids per kg actual body weight per day).

Consensus (88%)

Commentary

After catabolic signals have vanished and organ dysfunction has resolved, protein/amino-acid intake should be at least at 100% of target (1 g protein or 1.2 g amino acids per kg actual body weight per day, representing the target during the acute phase). This recommendation is based on the recommendations on the prevention of sarcopenia in the elderly [82,112,113,137]. In addition, studies in healthy individuals during exercise showed that – in combination with intensive resistance training – increase of muscle protein mass was at its maximum with a simultaneous intake of 1.6 g protein/kg per day [138].

Although there is a lack of high-quality studies to answer the question in the target group, the author group considers a "Should" recommendation to be justified.

6.3.4. Protein intake in the chronic phase

Question: How much protein should a patient receive in the chronic phase?

Recommendation 16:

In the chronic phase, the protein-/amino acid intake should be at 100% of the target proposed for the acute phase (1.0 g protein or 1.2 g amino acids/kg per day).

Strong consensus (91%)

Commentary

There are no prospective studies, which had an adequate sample size to study MNT in the chronic phase (persistent organ dysfunction without acute inflammatory/infectious exacerbation). To conserve protein as much as possible and to support reparative/immunologic processes, these patients require a continuous protein intake [114,115]. Wolfe and colleagues [139] conducted a prospective mechanistic study on six patients about one month after a burns injury. The patients were fed a hypercaloric mixed enteral–parenteral diet (41 kcal/kg and day), of which either 1.4 g or 2.2 g protein/kg and day were given via the enteral route over 3 days (eucaloric groups, corresponding to 1.7 g or 2.7 g amino acids/kg and day). Control studies were conducted after overnight fasting. Protein intake minimized net protein loss compared to that observed with fasting (as shown by isotope studies). In a direct comparison, however, a different protein intake was not associated with a different rate of net protein loss. Hence, at least from the perspective of this surrogate parameter, protein intake in the chronic phase should not surmount 1.4 g protein/kg and day. The A.S.P.E.N. guideline [2] recommends, based on expert consensus, that chronically critically ill patients (defined as persistent organ dysfunction with the need for intensive care treatment >21 days) should receive an aggressive high-protein enteral diet combined with other specific treatments (physiotherapy, endocrine therapy) (Recommendation P1).

When a patient enters the chronic phase of critical illness, at least the protein target (100%) should be reached. Protein intake should be individualized as suggested for the acute phase (adjusting protein intake to the extent of insulin resistance/hyperglycemia).

Although there is a lack of high-quality studies to give a sufficiently detailed answer to the question, the author group considers a "Should" recommendation to be justified.

6.3.5. Protein intake in patients with pre-existing malnutrition

Question: How much protein should a patient receive who presents with a pre-existing malnutrition?

Recommendation 17:

For critically ill patients with pre-existing malnutrition, protein-/amino acid intake or protein/amino-acid target may be the same as in patients without pre-existing malnutrition.

Consensus (85%)

Commentary

There are no controlled studies on this issue. In several meta-analyses of studies in critically ill patients, it was not possible to identify an interaction between the efficacy of a specific calorie or protein intake and BMI (as a surrogate parameter for nutrition status) [56,103,105]. However, patients who had already been severely malnourished (BMI <18 kg/m^2) before the disturbance of homoeostasis were excluded from the studies, and no study examined the effect of an increased protein intake independent from that of calories.

In severely malnourished non-critically ill patients (kwashiorkor, BMI ≈ 13 kg/m^2) receiving a largely eucaloric diet, increasing the protein intake doubled the 1-month mortality rate (51.9% *vs.* 25.9%) and prevented weight gain. Patients had received diets with a relative protein content of 16.4% (corresponding to about 0.8–1.0 g/kg per day) or 8.5% [140]. It is unknown to what extent these negative effects would also occur in malnourished critically ill patients. For safety reasons, we opted – in accordance with the recommendations for non-malnourished critically ill patients – for a restrained protein/amino-acid intake.

Protein intake should (similar to calorie intake) be adjusted to the individual tolerance (giving special consideration to a refeeding

syndrome and to changes of phosphate concentration) (section 6.2.3).

The recommendations for the protein target are, in principle, independent from the route of nutrient delivery (enteral or parenteral). Details are presented in section 7.1.

6.3.6. Protein intake during renal replacement therapy

Question: How much protein should a patient receive who is on continuous/intermittent RRT?

Recommendation 18:

For critically ill patients receiving continuous/intermittent RRT, protein-/amino acid intake, or protein/amino-acid targets may be the same as in patients not having such treatment. With regard to additional compensation of losses during RRT, see **Recommendation 19**.

Strong consensus (93.75%)

Commentary

Recommendations on the overall protein intake in critically ill patients having a continuous RRT are controversial. The A.S.P.E.N. guideline recommends to increase daily protein intake up to 2.5 g/kg and day due to increased catabolism (Recommendation J2, very low quality of evidence) [2]. This recommendation is based on a controlled study (n = 60) that investigated different rates of protein intake in this specific patient group [141]. The study showed that only at an intake of 2.5 g protein/kg body weight and day nitrogen balance was no longer negative. In a study by Bellomo et al. [142] nitrogen balance was slightly negative during RRT when amino acids had been infused at a rate of 2.5 g/kg and day. However, a positive nitrogen balance (especially at a high protein intake) is not directly associated with an actual increase in body protein mass (but can also result from substrate shifts or expansions of the urea pool) [143], so the nitrogen balance is a poor surrogate for beneficial clinical effects.

For this reason, the DGEM had recommended in its S1 guideline *Enteral and parenteral nutrition of patients with renal insufficiency* from 2015 that acutely ill patients suffering from acute renal failure, acute-on-chronic renal failure or from chronic renal failure should receive - depending on the individual metabolic tolerance - only 1.2–1.6 (maximum 1.8) g protein-/amino acids/kg and day. This intake represented a baseline support during RRT. Protein-/amino acid intake was controlled by nitrogen balances determined during RRT [144]. A study by Doig et al. [132] failed to show a clinical benefit in critically ill patients at a high risk for developing kidney failure when increasing amino acid intake from 0.75 to 1.75 g/kg and day.

In view of these findings and in contrast to the older DGEM S1 guideline, we now recommend a relatively lower protein target for the acute phase. Since scientific evidence has changed since the publication of the S1 guideline, protein-/amino acid intake and targets for patients on RRT can be the same as for patients in the acute phase who do not need RRT. (**Recommendation 14**); however, additional losses due to RRT should be compensated (**Recommendation 19**). For the convalescence phase, we recommend - again similar to patients not requiring RRT – a higher protein intake and target (up to 1.6 g protein [1.9 g amino acids]/kg and day) (**Recommendation 15**).

Question: Is it necessary to compensate for losses of amino acids during continuous/intermittent RRT?

Recommendation 19:

In patients receiving continuous/intermittent RRT, a corresponding continuous infusion of amino acids should compensate for the loss of amino acids, and should be added to the *baseline* calorie-/protein-/amino acid intake (controlled by the phase of the disease and by individual metabolic tolerance).

Consensus (85%)

Commentary

Intermittent or continuous RRT commonly used in critically ill patients has a fundamental effect on metabolism and nutrient balances. In terms of protein metabolism, cytokine-mediated proteolysis results from blood exposure to a biocompatible membrane. Furthermore, amino acids are lost *via* the dialyzate [145]. Overall, use of RRT may aggravate the negative protein balance (catabolism > synthesis) already present as a sequelae of critical illness ("dialysis-associated catabolism"). The RRT-associated loss of amino acids may amount up to ≈2 g/h during hemodialysis depending on the dialysis dose, up to 0.2 g/L of filtrate or dialyzate during continuous veno-venous hemofiltration [CVVH]), and up to 0.6 g/h during continuous veno-venous hemodialysis [CVVHD]) [144,146,147]. Thus, an infusion of corresponding amounts of amino acids should compensate for the extra loss of amino acids during RRT and should be added to by the *baseline* calorie-/protein-/amino acid intake. Again, the *baseline* intake should be controlled by the phase of the disease and by individual metabolic tolerance.

According to one study, loss of amino acids during a "sustained low-efficiency dialysis (SLED)" corresponds to that observed during CVVH [148]. Depending on the type of filter membrane, however, loss of specific amino acids may vary [149].

In line with our recommendations, an opinion paper [150] and the A.S.P.E.N. guideline (Recommendation J2, very low quality of evidence) [2] also recommend replacing the loss of amino acids during RRT.

Although there is a lack of high-quality studies to give a sufficiently detailed answer to the question, the author group considers a "Should" recommendation to be justified.

7. Technical aspects of medical nutrition therapy

7.1. Routes for nutrient delivery

7.1.1. Routes for nutrient delivery in the acute phase

Question: Which route (enteral or parenteral) should be used for nutrient delivery in the acute phase of critically ill patients?

Recommendation 20:

In all phases of the disease, the enteral route should be favored for nutrient delivery in the critically ill patient who is unable to maintain sufficient volitional intake (which means that recommended intake/targets cannot be reached in this way).

Strong consensus (97%)

Commentary

Using the evidence from experiments in small rodents, and from randomized human-biological studies with a small number of cases, it has been postulated that early enteral nutrition ("villus" or "trophic" feeding) would be superior to parenteral nutrition, even if intake is low. Several studies reported favorable effects on mortality and the frequency of secondary inflammatory/infectious complications. As a result, numerous guidelines incorporated corresponding recommendations.

Enthusiasm for enteral nutrition, however, ignored the fact that also a parenteral supply of substrates can be beneficial to intestinal health [151]: parenteral nutrition supports the renewal rate of intestinal cells, increases the rate of intestinal protein synthesis, and reduces the apoptosis rate. Beneficial intestinal effects of parenteral nutrition relate to the fact that this route of nutrition directly provides the basis of the crypts with substrates. Furthermore, even after several weeks of exclusively parenteral nutrition, no significant changes in intestinal protein content, enterocyte proliferation or microvillus morphology were observed in humans. On the contrary, an aggressive enteral nutrition (in the absence of parenteral intake) in critically ill patients neither prevents a significant

increase in liver fat content nor a persistent protein catabolism [84,152].

Two recent large RCTs compared an exclusively enteral nutrition with a comparable parenteral nutrition in critically ill patients whose intestinal tract was functioning, and who all received the same amount of calories. Nutrition included a moderately hypocaloric (18–20 kcal/kg per day), low-protein (0.7 g protein/kg per day) diet which was delivered during the acute phase (first 5 days after ICU admission, intervention period). Principle finding was that the route of nutrient delivery was either unimportant for the outcome [153], or that an exclusively enteral nutrition even increased the frequency of severe intestinal complications (ischemia/obstruction) in patients suffering from severe circulatory dysfunction [154].

A recent meta-analysis (18 studies, n = 3347 critically ill patients) comparing both routes of nutrient delivery showed no difference in mortality, but a significant reduction in infectious complications when exclusive enteral nutrition had been used [155]. However, this benefit was most likely due to the reduced intake of macronutrients during enteral nutrition, and a publication bias. Parenteral nutrition was only harmful when it was associated with an increased calorie intake. Three other meta-analyses found that the association between mortality and calorie intake did not depend on the route of nutrient delivery (enteral vs. enteral + parenteral) [103, 105, 107].

The ESICM guideline on enteral nutrition [3] performed a separate meta-analysis (eight RCTs) on this subject. Since this meta-analysis showed that morbidity was lower during enteral nutrition, ESICM incorporated a corresponding recommendation into the guideline (recommendation 1A). The author group of the DGEM feels, however, that the results of the ESICM meta-analysis are limited because:

(i) at least three of the included studies delivered more calories in the parenteral arm (different calorie intake);
(ii) none of the studies were blinded, and seven of the eight studies included < 100 patients thereby causing a significant risk of effect overestimation.

The same limitations apply, in principle, to the comparable recommendations of the A.S.P.E.N. guideline [2] and SSC guideline [4], which both carried out their own meta-analyses on this subject. The meta-analysis of the A.S.P.E.N. [2] evaluated nine RCTs and found that enteral nutrition reduced the frequency of infections and reduced ICU LOS. Five of the nine RCTs, however, did not administer comparable amounts of calories (more calories were given during parenteral nutrition), one study did not state calorie intake, and the CALORIES trial [153] was not included into the meta-analysis.

The meta-analysis by the SSC analyzed 10 RCTs showing that ICU LOS was somewhat lower during enteral nutrition. There was, however, a wide 95% confidence interval (CI) (0.38–1.42). Two of the 10 RCTs did not administer comparable amounts of calories, and two other studies did not state calorie intake. The meta-analyses of the A.S.P.E.N., ESICM and SSC did not include the NUTRIREA-2 study [154].

If function of the intestinal tract is normal and if energy intake is comparable, however, an enteral low-protein diet which is moderately hypocaloric will be superior to a comparable parenteral nutrition due to economic reasons (costs per QUALY) [156]. Thus, under these specific conditions, the enteral route for nutrient delivery is preferable.

However, it is unknown which route of nutrient delivery would be superior if intake of protein/amino acids or calories would have been different. Superiority of the enteral route is also uncertain in particular patient subgroups (e.g., patients after a severe trauma injury) because the published RCTs all suffer from significant methodological weaknesses, and because a large multicenter RCT is lacking.

In summary, the author group feels that the enteral route of nutrient delivery should still be preferred in the acute phase largely because of economic but not clinical superiority. Enteral calorie intake should be controlled by individual metabolic and gastrointestinal tolerance (sections 6.2.3, 6.3.2 and 10).

When it is not possible to reach the recommended calorie-protein target/intake via the enteral route, patients should receive supplemental or even all nutrients via the parenteral route (section 7.4.1).

7.1.2. Routes for nutrient delivery in the post-acute phase (convalescence/rehabilitation phase) or chronic phase

Question: Which route (enteral or parenteral) should be used for nutrient delivery in the post-acute phase (convalescence/rehabilitation phase) or chronic phase?

Recommendation 21:

In the post-acute phase or chronic phase, volitional intake should be preferred. If a critically ill patient is unable to maintain sufficient volitional intake (which means that recommended intake/targets cannot be reached in this way), supplemental or even all nutrients should be delivered via the enteral route.

Strong consensus (94%)

Commentary

There are no RCTs examining MNT in patients in the chronic phase of critical illness. Therefore, the clinical advantages and disadvantages of different routes of nutrient delivery are unknown [114,115]. During convalescence, physiology tells us to prefer a volitional nutrient intake. If a critically ill patient is unable to maintain a sufficient volitional intake (which means that recommended intake/targets cannot be reached in this way), when there are anatomical problems in the pharynx, or when a patient is on MV, supplemental or even all nutrients should be delivered via the enteral route. This route is economically superior to the parenteral route (section 7.4.1).

Although there is a lack of high-quality studies to give a sufficiently detailed answer to the question, the author group considers a “Should” recommendation to be justified.

7.1.3. Routes for nutrient delivery in patients with pre-existing malnutrition

Question: Which route (enteral or parenteral) should be used for nutrient delivery in patients with pre-existing malnutrition?

Recommendation 22:

In the case of pre-existing malnutrition, supplemental calories may be delivered via the parenteral route early in the acute phase to reach the recommended calorie/protein intake/targets according to individual metabolic tolerance.

Strong consensus (91%)

Commentary

In healthy subjects, there is physiologic protein retention in the intestines. Proteins important for digestion must be synthesized in the mucosa. The post-absorptive acceleration of intestinal protein synthesis may consume ≤50% of the luminal protein intake (≤100% for glutamate/aspartate) [117,140]. Furthermore, trauma, shock or sepsis often leads to enterocyte dysfunction [157], thereby reducing intestinal amino-acid absorption [158,159]. Similar mechanisms may impair absorption of carbohydrates and triglycerides (reduction by ≤ 50%) [160,161]. A concomitant malnutrition may further aggravate these changes because malnutrition alone is associated with mucosal dysfunction and a modified microbiome [162].

Accordingly, data from older studies and from a *post hoc* analysis of the recent PermiT study suggested that aggressive enteral nutrition in patients with pre-existing malnutrition is associated with increased morbidity and mortality [39,117,140] (sections 4 and 6.2.6).

When malnutrition is combined with a severe disturbance of homeostasis, it may be advisable – at least during the acute phase - to deliver nutrients via the enteral route very carefully. A fast step-up of enteral nutrient intake may cause harm, and nutrient supply should be closely controlled by individual metabolic tolerance including insulin requirement and changes of serum phosphate concentration. If gastrointestinal tolerance/absorption of substrates is impaired, the parenteral route should be used early to reach the appropriate calorie/protein intake/targets (section 7.4.1 and **Recommendation 38c**). For recommendations on how to avoid a refeeding syndrome, see sections 6.2.3 and 6.3.2.

7.2. Technical aspects of enteral nutrition

7.2.1. Contraindications

Question: When should the enteral route not be used for nutrient delivery?

Recommendation 23:

When there is severe intestinal dysfunction, nutrients should not be delivered via the enteral route. Instead, the patient should receive parenteral nutrients to reach calorie and protein targets (adjusted to individual metabolic tolerance).

Strong consensus (91%)

Commentary

According to the ESICM guideline 2017 [3] contraindications for enteral nutrition included uncontrolled shock, metabolic derailment with uncontrolled hypoxemia and acidosis, uncontrolled upper-gastrointestinal hemorrhage, residual gastric volume >500 mL/6 h, mesenteric ischemia, intestinal obstruction, abdominal compartment syndrome, and a high-output fistula without distal access to the GI-tract. A recent review stated similar, severe contraindications mandating an interruption of enteral nutrition: severe restrictions of intestinal motility (paralytic/mechanical small-bowel ileus, pseudo-obstruction of the colon), severe anatomic lesions (e.g., small-bowel leakage), severe inflammatory changes of the large intestine (necrotizing clostridium difficile-induced colitis), intestinal ischemia and severe absorption disorders (stool weight >350 g per day) [161]. In contrast, isolated gastric-emptying disorders/upper-abdominal atony did not constitute a contraindication *per se* because it is possible to overcome those barriers with comparably little effort.

In principle, an increased stool weight could result not only from an absorption disorder, but also from an increased proportion of macronutrients in feces (increased loss of bacterially fermentable macromolecules from food and cell ablation). Unfortunately, in the case of diarrhea, clarification of this differential diagnosis is not easy. To avoid a severely hypocaloric diet in the event of an absorption disorder, we would always refrain from using the enteral route and argue for the parenteral route especially in those patients where a severe diarrhea persists. Thereby, one may also avoid an excess calorie intake when there is only a loss of macromolecules.

During enteral nutrition, especially with early high intakes, case reports have stated repeatedly the risk of intestinal strangulation or ischemic bowel necrosis, with ischemic non-occlusive bowel necrosis presenting a life-threatening complication associated with a mortality of ≤70% [163–166]. The pathophysiology of ischemic bowel necrosis is not clear. When there is gastrointestinal dysfunction, delivery of large amounts of nutrients directly into the jejunum will be most likely disadvantageous. Additional pathophysiological mechanisms may involve metabolic stress and an abnormal bacterial colonization [167]. Although there is a lack of high-quality studies to give a sufficiently detailed answer to the question, the author group considers a “Should” recommendation to be justified.

Question: Is hemodynamic instability/therapy with vasoactive drugs a contraindication for the enteral route of nutrient delivery?

Recommendation 24:

In patients with hemodynamic instability (high or increased doses of vasoactive drugs, persistent or progressive signs of organ hypoperfusion), the enteral route should not be used and the parenteral route be preferred. Parenteral substrate intake should be controlled by individual metabolic tolerance and phase of the disease.

Consensus (86%)

Commentary

The intensity of MNT should be independent from the route of nutrient delivery, but should be controlled by, inter alia, the extent and number of organs failing. In patients with severe multiple-organ failure, the body utilizes exogenous substrates poorly, and a high exogenous intake (relative to the endogenous production of substrates) increases the risk of an excessive nutrient supply, with adverse effects on outcome [82,168]. In patients with hemodynamic instability (high or increasing doses of vasoactive drugs [e.g., noradrenaline ≥0.5 μg/kg per min], persistent or progressive signs of organ hypoperfusion [e.g., increased lactate or myoglobin concentrations]), the enteral route of nutrient delivery should not be used. Only after hemodynamics have stabilized (e.g., with doses of vasoactive drugs declining or remaining constant, or with ameliorated signs of organ hypoperfusion (falling lactate concentrations)) the enteral route may be used delivering small amounts of calories (<25 kcal/h). In case of doubt, the parenteral route is preferable.

Several observational studies included patients with circulatory failure requiring a catecholamine therapy. Despite this type of organ failure, early minimal enteral nutrition was associated with a better outcome (compared with late nutrition) in four studies [52,53,169,170], One study could not identify an association between an early hypocaloric enteral nutrition and morbidity/mortality [171]. Due to the observational design, however, it is not possible to deduce causality from these results, and there is a high risk of indication bias.

The NUTRIREA-2 study [154] focused on 2410 mechanically ventilated medical patients requiring pharmacologic hemodynamic support (average norepinephrine dose 0.5 μg/kg per min). The authors compared two equivalent enteral or parenteral diets providing 18–20 kcal/kg and day and 0.7 g protein/kg and day). The enteral route of nutrient delivery was associated with a mildly (but significantly) increased rate of intestinal ischemia (2% *vs*. 0.4%) or pseudo-obstruction of the colon (1% *vs*. 0.3%). It is unknown, however, whether such unwanted side effects would also occur with less intensive catecholamine support or lower calorie intake, or if the study would have focused on surgical patients.

There is consensus that, in principle, the enteral route of nutrient delivery is feasible and safe even during catecholamine therapy [167,172]. Safety will be enhanced further, if a proven and well-established feeding protocol is available [19,23,163,173]. The precise maxima of calorie intake and of the intensity of circulatory support limiting the usefulness of the enteral route of nutrient delivery, however, are still unclear.

Our recommendation is in accordance with the recommendation of the A.S.P.E.N. guideline (Recommendation B5, expert consensus) [2] stating that one should not use the enteral route if patients are hemodynamically unstable (defined as mean arterial pressure <50 mmHg and/or as a new need for or intensification of catecholamine therapy). If catecholamine requirement is declining or absent, clinicians may resume enteral nutrition, but should simultaneously

adjust calorie intake to the individual metabolic tolerance (section 6.2.3, **Recommendations 9b** and **9c**, and section 6.3.2).

Similarly, the author group of the ESICM [3] recommends that clinicians should delay enteral nutrition if shock is uncontrolled, and if it is not possible to reach hemodynamic and tissue perfusion goals. Minimal enteral nutrition should be started, if shock is controlled by giving fluids and vasopressors/inotropes (Recommendation 2, expert consensus, grade 2D). The latter recommendation was based on an observational study by Khalid et al. [53], enrolling >1000 patients. Early enteral nutrition (<48 h) in patients with stable hemodynamics after fluid resuscitation, whilst receiving at least one vasopressor, was associated with reduced mortality compared to late enteral nutrition (>48 h). However, due to the observational design, on cannot separate causality from mere association, and there is a high risk of indication bias in this study.

Although there is a lack of high-quality studies to give a sufficiently detailed answer to the question, the author group considers a "Should" recommendation to be justified.

7.2.2. Access routes for enteral nutrition

Question: Which access route should be used for enteral nutrition?

Recommendation 25:

The gastric access route should be preferred to the jejunal access route. When aspiration risk/gastric residual volume is high, and when there is little technical effort to insert a feeding tube, a jejunal access route may be used.

Strong consensus (97%)

Commentary

The question was addressed by a recent Cochrane meta-analysis (14 studies, 1109 patients) [174] and by meta-analyses by Li et al. (eight studies, 835 patients) [175], Deane et al. (15 studies, 1178 patients) [176], Wang et al. (five studies, 325 patients) [177] and Alhazzani et al. (19 studies, 1394 patients) [178]. Uniformly, these analyses showed that, compared with gastric feeding, jejunal feeding was associated with a lower rate of ventilator-associated pneumonia (<30%);

There was, however, no effect on mortality, LOS, or duration of MV. The authors recommended a jejunal feeding particularly in those patients in whom it would be possible to insert a jejunal tube could without great effort. However, all meta-analyses are subject to a significant bias because no study was blinded, all studies had a small sample size increasing the likelihood of an effect overestimation, and because there were significant uncertainties concerning the diagnosis of the outcome variable (VAP). Therefore, the quality of evidence can only be "low".

A gastric access route is probably more advantageous because (i) drug absorption in the jejunum often is uncertain, (ii) it is easier to insert a feeding tube into the stomach than into the jejunum, and (iii) the risk of tube clogging is much lower (due to the usually larger diameter of the gastric tube). Furthermore, it is easier to give drugs via a gastric than via a jejunal feeding tube [179].

According to the recommendations of the A.S.P.E.N. guideline (Recommendations B4a and b, moderate-to-high quality of evidence, and expert consensus, respectively) [2], it is acceptable for most critically ill patients to start enteral nutrition *via* a gastric access. In patients with high aspiration risk or gastric intolerance, nutrients may be delivered via a jejunal tube (see section 7.2.2). The recommendation of the A.S.P.E.N. guideline was based on a separate meta-analysis (12 RCTs, 976 patients), which showed that jejunal feeding (compared with gastric feeding) significantly reduced the risk of pneumonia [2]; again, this meta-analysis is subject to a significant bias (see above).

Our recommendation is in line with the recommendation of the SSC guideline for septic patients; by a separate meta-analysis (21 RCTs), the SSC noted lower rates of pneumonia during a jejunal feeding (mortality and other morbidities were not affected) [4].

Although there is a lack of high-quality studies to give a sufficiently detailed answer to the question, the author group considers a "Should" recommendation to be justified.

7.2.3. Bolus (intermittent) vs. continuous feeding

Question: Should gastric nutrients be delivered either as a continuous infusion or as an intermittent feeding?

Recommendation 26:

Gastric nutrients may be delivered either as a continuous infusion or as an intermittent feeding.

Strong consensus (91%)

Commentary

The different approaches of gastric feeding (continuous infusion or bolus feeding) are still controversial. After having analyzed six RCTs (including small numbers of patients) the A.S.P.E.N. guideline recommends that bolus feeding is possible. If intolerance occurs (e.g., increase of residual gastric volume), however, patients should be switched early to a continuous delivery (Recommendation D4b) [2]. One study identified a trend towards a lower mortality during continuous gastric feeding, whereas five smaller RCTs found that a continuous enteral substrate infusion just allowed for the delivery of higher volumes without, however, changing outcomes [2].

So far, no study could show that the type of enteral nutrient delivery (continuous infusion or bolus feeding) affects outcomes. However, there is a high degree of uncertainty because relevant studies uniformly had a small sample size. Advantages of bolus feeding may be that the calorie target is reached faster [180–182] and that constipation rates are lower [183].

Furthermore, several hormonal, endocrine and mechanic qualities of gastric physiology would be in favor of bolus feeding (which may have a pro-peristaltic action by stretching of the stomach) [184]. Besides gastric tolerance, the type of enteral feeding may also affect metabolic stability (e.g., blood glucose concentration). A pilot RCT included a small number of critically ill patients, who all had a percutaneous endoscopic gastrostomy (PEG), and examined the effect of the type of enteral nutrient delivery on the variability of blood glucose concentration and on insulin requirement [185]. Key finding was that, during the whole course of the disease, outcome variables did not differ between continuous infusion and intermittent feeding. The study, however, did not include patients with severe diabetes mellitus/insulin resistance who might particularly benefit from a continuous enteral nutrient infusion.

Thus, both approaches may be used in critically ill patients. Beyond the acute phase, gastric bolus feeding will be a safe approach to provide patients with nutrients via the enteral route [186].

Question: Should jejunal nutrients be delivered either as a continuous infusion or as an intermittent feeding?

Recommendation 27:

Jejunal nutrients shall be delivered as a continuous infusion.

Strong consensus (94%)

Commentary

There are no studies, which have addressed this question; physiology suggests a benefit when jejunal nutrients are delivered as a continuous infusion. During the first phase of digestion, nutrients mix with gastric juice in the stomach, and are broken down to a particle size of 1–2 mm. Then, nutrients pass the pylorus gradually in a way that flow velocity is increasing linearly. When nutrient supply to the duodenum is high, however, gastric

emptying will slow down ("duodenal brake") to ensure a constant concentration of nutrients in the small intestine [187,188]. Therefore, if the jejunal route is used for nutrition, we recommend a continuous nutrient infusion, which is ideally controlled by a pump.

Although there is a lack of high-quality studies to give a sufficiently detailed answer to the question, the author group considers a "Shall" recommendation to be justified.

7.2.4. Interruption of nutrient supply according to the time of the day

Question: Should nutrient supply be interrupted according to the day/night cycle?

Recommendation 28:

Enteral nutrients may be delivered regardless of the day/night cycle (as a 24-hour continuous infusion or as an intermittent feeding).

Strong consensus (97%)

Commentary

In critically ill patients, two RCTs [189,190] and one before-and-after observational study [191] compared a 24-hour continuous gastric nutrient infusion with a feeding protocol, which included an interruption of gastric feeding at night. There was no difference regarding gastric pH, colonization rate, and frequency of VAP. For an optimal absorption, however, some drugs (e.g., thyroxine) require a gastric acidic milieu. To deliver those drugs enteral nutrition is paused for several hours before application.

To manage enteral/gastric nutrient intake, readers may consult the S3 guideline "*Monitoring of Artificial Nutrition: Specific Aspects*" of the DGEM, GESKES and AKE [110].

7.2.5. Prone position and open abdomen

Question: Should enteral nutrient supply be interrupted in patients treated with an open abdomen or a prone position?

Recommendation 29:

When the gastrointestinal tract is functioning, nutrients may be provided via the stomach/jejunum also to patients treated with a prone position or having an open abdomen.

Strong consensus (100%)

Commentary

The prone position or 135°-position, respectively is an essential part of ARDS treatment [192,193]. It was hypothesized that a prone position increases the intra-abdominal pressure thereby worsening gastrointestinal motility and visceral perfusion. Secondary changes of nutrient transport and absorption might affect MNT. Consequently, it was questioned whether it would be advisable to start or continue an enteral nutrition in these patients. The available evidence to support/contradict this hypothesis is low, but indicates that it is probably safe to provide patients treated in a prone position with enteral nutrients [194–198].

For clinical practice, we suggest to manage patients treated with a prone position as follows: if a patient requires an enteral nutrition, and if hemodynamics are sufficiently stable, the entire bed is brought to a Trendelenburg position. During an intensified oral hygiene, nurses should actively search for clinical signs of regurgitation (identification of food particles in the oral cavity). When a patient presents with a history of delayed gastric emptying, clinicians should initiate early the insertion of a jejunal feeding tube.

The available evidence does not indicate that patients treated with a prone position develop relevant absorption disorders. Nevertheless, in the early phase after a change of a patient's posture it is advisable to monitor blood glucose concentration closely, particularly during insulin infusion.

Success of a surgical therapy is often measured by the time to wound closure. In a retrospective multicenter study, 234 of 597 trauma patients treated with an open abdomen (39%) could be fed via the enteral route. 307 patients did not have an intestinal injury. A logistic regression analysis of data from this subgroup showed that enteral feeding was associated with a significantly shorter time to wound closure, lower rate of pneumonia, and lower mortality [199]. Another retrospective analysis obtained similar results indicating a significant association between an early onset enteral nutrition (<4 days after admission) and a shorter time to wound closure and a lower rate of new intestinal fistulas. There were no associations with mortality [200]. Due to the observational design, however, both studies are at a high risk of an indication bias.

The current A.S.P.E.N. guideline [2] recommends - based on expert consensus - early enteral nutrition (24–48 h post-injury) in patients treated with an open abdomen in the absence of a bowel injury (Recommendation M3a). The current ESICM guideline [3] recommends that a prone position or open abdomen should not delay initiation of an early enteral nutrition (24–48 h). This recommendation, however, only applies to patients who do not have additional bowel injury.

One rationale for the recommendation was the observation that gastric residual volume is independent from the patient's posture [198]. However, quality of evidence was low. Only seven observational studies could be analyzed showing that an early enteral nutrition (*vs*. no enteral nutrition) was associated with a lower morbidity [3]. These studies are, again, at a high risk of an indication bias (see section 2.4.2).

Question: Is it necessary to compensate for protein losses *via* drains/dressings in patients treated with an open abdomen?

Recommendation 30:

Protein losses *via* drains/dressings should be compensated in patients treated with an open abdomen.

Strong consensus (91%)

Commentary

In patients treated with an open abdomen, loss of protein through vacuum dressings/drains may amount to 15–30 g/L exudate (overview in [2]). In accordance with the A.S.P.E.N. guideline [2] (Recommendation M3b), we recommend that corresponding losses should be compensated.

The optimal way in which clinicians may compensate these losses, however, is controversial. The A.S.P.E.N. guideline [2] recommends – based on expert consensus - an additional enteral protein intake at the level indicated above. As an alternative, however, losses may be compensated through an intravenous albumin supplementation. This concept is in line with recommendations made for patients suffering from liver cirrhosis and undergoing paracentesis (ascites drainage). To reduce mortality risk, the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases recommends that 6–8 g of albumin should be administered intravenously per liter of drained ascites [201]. For further details, readers may consult the organ-specific guideline of the DGEM *"Clinical Nutrition in Gastroenterology (Part 1) – Liver"* [202].

Although there is a lack of high-quality studies to give a sufficiently detailed answer to the question, the author group considers a "should" recommendation to be justified.

7.2.6. Mechanical non-invasive ventilation (NIV)

Question: Which route of nutrient supply should be used for MNT in patients requiring NIV?

Recommendation 31:

Patients requiring NIV, who have an indication for MNT, may receive MNT via the enteral route, if they have effective reflexes protecting the airways, and if the gastrointestinal tract is functioning.

Strong consensus (100%)

Commentary

NIV is of great importance as an alternative to intubation in the treatment of acute respiratory failure [203]. However, only a few studies have examined whether the route of nutrient supply during NIV affects morbidity. A retrospective analysis showed that NIV in combination with an enteral MNT was associated with a significantly higher rate of pulmonary complications and with prolonged NIV [204,205]. There is recent evidence that use of a helmet rather than a full-face mask can reduce the overall complication rate significantly, especially when nutrients are delivered via the enteral route [206]. A multicenter observational study of 1075 critically ill patients with an indication for NIV $\geq$2 days showed that enteral nutrition (*vs*. no nutrition) was associated with increased 28-day mortality and a lower rate of VFDs [207].

In patients on chronic, intermittent NIV who do not have a disturbed consciousness and/or a swallowing disorder, enteral nutrition may be initiated or continued. If NIV has to be started acutely, it may be required to discontinue enteral MNT temporarily, particularly in those patients whose ability to swallow/cough and vigilance is impaired (due to mild sedation for NIV tolerance). It appears to be preferable to use a helmet for NIV, thereby reducing the aspiration risk associated with an enteral nutrient supply. As a matter of principle, the S2e guideline *"Positioning therapy and early mobilization for prophylaxis or therapy of pulmonary function disorders"* of the German Society of Anaesthesiology and Intensive Care Medicine recommends elevating the upper-body by 20–45° (preferably $\geq$30°) to position a patient (evidence level 3, Recommendation grade B) [192]. Current A.S.P.E.N. and ESICM guidelines do not make specific recommendations on this topic [2,3].

7.2.7. Percutaneous enteral access

Question: What are the indications for a percutaneous-enteral access?

Recommendation 32:

Critically ill patients most likely requiring an enteral MNT for >4 weeks, may have a PEG (percutaneous endoscopic gastrostomy)/PEJ (percutaneous endoscopic jejunostomy).

Strong consensus (94%)

Commentary

A percutaneous enteral access (PEG, PEJ) is at a significantly lower risk of dislocating, and may be used in patients who presumably need enteral MNT for several weeks (usually >4 weeks). Potential candidates are in particular neurological/neurosurgical critically ill patients. We refer to the current S3 guidelines of the DGEM "*Clinical Nutrition in Surgery*" [208] and "*Clinical Nutrition in Neurology*" [209]. The indication for inserting a PEG/PEJ depends on the nature of the underlying disease, on its prognosis and on the presumed course of treatment (thereby differentiating between an early and a late insertion). In critically ill patients having an indication for a laparotomy (e.g., necrotizing pancreatitis), it may be advantageous to perform a fine-needle catheter jejunostomy during the operation without simultaneously increasing the morbidity of the patient [210].

7.2.8. Motility disorders

Question: When do critically ill patients need a prokinetic therapy during MNT?

Recommendation 33:

Critically ill patients may benefit from a prokinetic therapy while being on MNT, when they present with a gastrointestinal dysmotility caused by gastric atony and/or intestinal paralysis.

Strong consensus (97%)

Question: Which prokinetics should be used?

Recommendation 34a:

In critically ill patients suffering from a paralytic gastric motility disorder, clinicians may use prokinetic agents such as metoclopramide and/or erythromycin separately or in combination, if time limits are strictly observed.

Strong consensus (100%)

Recommendation 34b:

In critically ill patients suffering from a paralytic intestinal motility disorder, clinicians may use prokinetic agents (e.g., neostigmine, distigmine, sincalide), plasticizers (e.g., paraffin oil) or osmotic substances (e.g., macrogol, amidotrizoic acid), if the respective contraindications are strictly observed.

Strong consensus (97%)

Commentary

A paralytic gastrointestinal motility disorder is the most common source for an impaired delivery of enteral nutrients. The underlying mechanisms for such disorders are only partially known; in critically ill patients, sepsis (peritonitis) or multiple organ failure may reduce splanchnic perfusion thereby affecting motility [161,211]. Furthermore, numerous supportive medications (catecholamines, opiates, beta-2-mimetics, sedatives) do have an antiperistaltic effect.

The pharmacological options to treat a paralytic gastrointestinal dysmotility are limited. Due to neurological side effects (dyskinesia, convulsions) the European Medicines Agency recommended in 2013 that metoclopramide should remain available only for a short-term treatment ($\leq$30 mg per day or 0.5 mg/kg for a maximum of 5 days) regardless of the administration route. Erythromycin is an "off-label" intravenous alternative at $\leq 3 \times 250$ mg for a maximum of 3 days. Both drugs can be administered via the enteral or parenteral route. Possible side effects of erythromycin are tachyphylaxis and bacterial resistance. Both drugs may cause QT prolongation and cardiac arrhythmias [161,211,212].

The ESICM clinical practice guideline "*Early Enteral Nutrition in Critically Ill Patients*" and the consensus paper of the ESICM working group on abdominal problems recommend use of a protocol when administering prokinetic agents, or to switch patients to jejunal feeding, when they present with a gastric motility disorder, and do not show signs of a distal intestinal paralysis [3,213]. The SSC guideline recommends (based on expert consensus) to use prokinetics in patients suffering from sepsis or septic shock (weak recommendation, low quality of evidence), provided that potential side effects of these drugs are adequately monitored [4].

The A.S.P.E.N. guideline recommends use of prokinetic agents (metoclopramide, erythromycin) in patients being at a high risk for aspiration (Recommendation D4c, expert consensus) [2]. To make this recommendation, eight RCTs (of which seven exclusively tested metoclopramide, and one a combination of metoclopramide and erythromycin) were aggregated in a meta-analysis. Prokinetic therapy had no effect on mortality and infection rate but led to lower gastric residual volumes. These studies administered 3–7 mg erythromycin/kg per day, and 10 mg metoclopramide four times per day. A small RCT found that erythromycin was more effective than metoclopramide in promoting gastric motility [214]. Another RCT in 75 mechanically ventilated patients demonstrated that a combination therapy (metoclopramide + erythromycin) was superior to a monotherapy in terms of reducing gastric residual volume; there were no differences in morbidity or mortality [215]. A recent pilot study enrolled 50 patients on MV who had a gastric residual volume >250 mL despite prokinetic therapy (metoclopramide); after patients had been switched to jejunal feeding, enteral nutrient intake was greater than during continuous gastric feeding combined with a prokinetic combination therapy (metoclopramide and erythromycin). The study, however, did not examine morbidity and mortality [216].

A recent meta-analysis (13 RCTs 1341 patients) showed that prokinetics (erythromycin, metoclopramide, domperidone) significantly improve tolerance to enteral nutrition, reduce gastric residual volume, and increase the likelihood to successfully insert a post-pyloric tube. However, morbidity, ICU LOS and mortality remained unchanged [217]. In addition, responsiveness to these prokinetics seems to differ between individuals. If prokinetics are not effective in a short period of time, treatment failure may be diagnosed, and treatment should be stopped.

No recommendations can be made on the usefulness of newer substances (such as the opioid antagonist alvimopan and the motilin agonist mitemcinal); there is too little information on the clinical effects of these drugs in patients belonging to the target group of this guideline.

If a patient develops a proximal or distal intestinal paralysis, clinicians should first assess risks and benefits associated with a reduction or discontinuation of drugs having anti-peristaltic side effects (see above). In addition, it is possible to stimulate small/large bowel motility by administering paraffin oil (castor oil), osmotic substances such as polyethylene glycol (Macrogol®, molecular weight 3350–4000 D) or the water-soluble contrast agent amidotrizoate (Gastrografin®), or drugs such as the cholecystokinin analog sincalide (Kinevac®) or the acetylcholinesterase inhibitors pyridostigmine (Kalymin®) and neostigmine (Prostigmin®); most of these compounds can only be used in off-label ways respecting their specific contraindications. Amidotrizoic acid has a strong laxative effect and is only approved for radiologic diagnostics.

A small randomized trial studied 50 critically ill patients requiring MV whose gastric residual volume was >120 mL; intravenous administration of neostigmine (2.5 mg twice daily) improved gastric emptying compared to metoclopramide (10 mg). Again, clinical outcome was not investigated in this study [218].

Question: When should enteral MNT be discontinued for diarrhea?

Recommendation 35:

Enteral nutrition should be discontinued in refractory severe diarrhea.

Consensus (88%)

Commentary

"Diarrhea" is commonly defined as an increased stool frequency of ≥3 unformed stools per day [219], but this definition is vague and arbitrary. Various other definitions of diarrhea are based essentially on consistency (unformed, liquid), stool weight (>200 g, >300 g), duration of diarrhea (>24 h, >48 h) and a combination of these variables. Another monitoring tool used to describe stool qualities in critically ill patients is the Bristol Stool Scale (BSS), which was originally developed for healthy subjects [220].

Diarrhea is common in critically ill patients (prevalence 15–38%) and is associated with a prolonged ICU LOS and higher costs. Diarrhea is rarely caused by a clostridium difficile infection [221,222]. In an observational study of 278 critically ill patients receiving continuous enteral MNT, Thibault et al. showed that 14% of patients had at least one day of diarrhea during the first 14 days, and that 89% of diarrheal episodes lasted ≤4 days [223]. Enteral nutrition *per se* was not identified as an independent risk factor for diarrhea while an intake of >60% of the energy requirement and a simultaneous administration of antibiotics or fungicides were significantly associated with diarrhea.

The A.S.P.E.N. guideline advocates that clinicians should not automatically interrupt enteral nutrient supply in the case of diarrhea; they should rather try to identify the etiology of diarrhea and initiate a causative treatment (Recommendation D6, expert consensus) [2]. Furthermore, the A.S.P.E.N. guideline suggests considering use of small peptide formulations for enteral nutrition in patients with persistent diarrhea, with suspected malabsorption, ischemia or a lack of response to fiber (Recommendation E4b). The ESICM guideline [3] recommends using early enteral nutrition even in patients with diarrhea. This recommendation is based on the results of observational studies showing that diarrhea could be controlled despite a continuation of enteral MNT, if protocol-based measures had been implemented (exclusion of a Clostridium difficile infection, selective bowel decontamination etc.) [224,225].

Clinical evaluation of diarrhea includes abdominal examination, quantification of stools, microbiological analyses of a stool specimen for Clostridium difficile (including determination of Clostridium difficile toxin A and B), measurement of electrolyte concentrations, and exclusion of drug-induced side effects (antimicrobial therapy). In addition, a distinction should be made between infectious (i.e., secretory) and osmotic diarrhea which usually stops during fasting.

We agree with the recommendations made by A.S.P.E.N. and ESICM. To treat a refractory severe diarrhea, clinicians should reduce or even interrupt enteral nutrient intake. On clinical grounds, it seems advisable to resume enteral MNT after diarrhea has stopped. Initially, nutrient intake should be low, and should be increased according to gastrointestinal tolerance. A retrospective study showed that enteral formulations, which do not contain fermentable oligosaccharides, disaccharides, monosaccharides and polyols ("FODMAPS"), may protect patients against diarrhea during enteral MNT [226]. The SPIRIT study found that, compared to standard polymeric formulations, an enteral formulation containing hydrolyzed protein did not reduce the number of days without diarrhea [227]. Potential benefits of fiber enriched enteral formulations are discussed in section 7.3.1.

Although there is a lack of high-quality studies to give a sufficiently detailed answer to the question, the author group considers a "Should" recommendation to be justified.

7.3. Supplements of enteral nutrition

7.3.1. Fiber

Question: Should fiber-enriched enteral formulas be used routinely?

Recommendation 36a:

Fiber-containing or fiber-enriched enteral formulas ("standard diet") should not be used in the acute phase, particularly when there is a high risk of intestinal ischemia.

Strong consensus (93.75%)

Recommendation 36b:

Fiber-containing or fiber-enriched enteral formulas ("standard diet") may be used beyond the acute phase in patients with a low risk for intestinal ischemia, particularly when there is evidence of diarrhea.

Strong consensus (100%)

Recommendation 36c:

Fermentable soluble fibers (fuctooligosaccharides, pectin, inulin) may be used in patients placed on a standard fiber-containing enteral formulation.

Strong consensus (93.75%)

Commentary

In general, the A.S.P.E.N. guideline suggests using a "standard polymeric formula" with a calorie density of 1–1.5 kcal/mL for enteral MNT [2]. This enteral formula may contain small amounts of fiber. In addition, there are nutrient-defined enteral formulas enriched with fiber and recommended as a standard MNT for non-critically ill patients [208,228]. Advantages of such formulas to critically ill patients, however, are uncertain.

7.3.1.1. Nutrition for prevention of diarrhea. A meta-analysis of seven trials including 400 critically and non-critically ill patients showed no clear benefits regarding fiber-enriched enteral formulas

[229]. A recent meta-analysis evaluated eight RCTs in 376 critically ill patients; again, the frequency of diarrhea did not depend on the type of diet (fiber-enriched or fiber-free) [230]. In high-risk patients (intestinal ischemia, paralysis), fiber-containing enteral formulas (especially those enriched with non-fermentable fiber) increased the rate of intestinal obstruction. Hence, in accordance with the A.S.P.E.N. guideline (Recommendation E4a) [2], we do not suggest using such enteral formulas routinely in the acute phase. We also do not recommend that patients presenting with an ileostomy, a short-bowel syndrome or a newly constructed colon anastomosis should receive fiber-containing enteral formulas.

However, in certain patients (e.g., those suffering from sepsis and receiving a broad-spectrum antibiotic therapy), enteral formulas enriched with fermentable or non-fermentable fiber, respectively may reduce the intensity of diarrhea [231,232]; fibers may explain this finding because they improve the tolerance to enteral formulas. A few studies examined the specific effect of fermentable fibers on the frequency of diarrhea in critically ill patients (except those with pancreatitis). Three of four RCTs found a significantly lower rate of diarrhea but no changes of secondary clinical outcomes such as duration of MV or ICU LOS [232–235]. Overall, however, these studies only examined 167 patients.

7.3.1.2. Nutrition for therapy of diarrhea. When there is evidence of persistent diarrhea, the A.S.P.E.N. guideline suggests considering use of a commercial mixed fiber-containing (fermentable dietary fiber) formulation (Recommendation E4b, expert consensus) [2]). This recommendation was based on the results of five small RCTs showing that fiber-enriched enteral diets significantly decreased intensity and frequency of diarrhea. We would follow the recommendation of the A.S.P.E.N.

7.3.1.3. Dosing of supplemental fermentable fibers. The A.S.P.E.N. guideline suggests using a supplement of 10–20 g of fermentable fibers (fructooligosaccharides, pectin, inulin) as prebiotic additives, when critically ill patients are hemodynamically stable and need an enteral MNT. Supplements should be given in divided doses over 24 h as adjunctive therapy (Recommendation F1, expert consensus). This recommendation is based on the results of an observational study of 63 critically ill patients [236]. In this study, such use of prebiotics was associated with an increased density of commensal gut bacteria, a decreased the rate of bacteremia, and a lower mortality.

7.3.2. Probiotics

Question: Should probiotics be used for enteral MNT?

Recommendation 37:

Lactobacillus plantarum and *Lactobacillus rhamnosus* GG may be used in patients after a severe trauma injury or liver transplantation requiring critical care.

Strong consensus (90%)

Commentary

The World Health Organization (WHO) defines “probiotics” as living microorganisms that confer health benefits to the host organism when administered in sufficient quantities [237]. Commercially available products contain (i) mainly lyophilized bacteria that can enter the intestine, and revitalize and multiply there, or (ii) killed microorganisms and/or their constituents and metabolites (e.g., enterococci, lactobacilli, *Bifidobacterium* species, *Propionibacterium* species, *Escherichia coli*, *Saccharomyces boulardii*, *Saccharomyces cerevisiae*). Use of these probiotics may be advantageous since they may (i) modify the microbiome by inducing cellular antimicrobial peptides, (ii) suppress the proliferation of pro-inflammatory immune-cells, (iii) inhibit the activation of the nuclear factor-kappa B pathway in epithelial cells, (iv) stimulate mucus and Ig-A production, and antioxidative processes [238].

In critically ill patients, several RCTs and meta-analyses examined the effect of probiotics on various clinical outcomes, such as prevention of VAP, reduction of gastrointestinal intolerance (diarrhea) and mortality. A meta-analysis of five RCTs involving 281 patients showed significant benefits for probiotics given to patients after a severe trauma injury; these additives reduced the rate of nosocomial infections and of VAP (three studies), and ICU LOS (two studies) [239]. There was no effect on mortality. The authors, however, stated that these results should be interpreted cautiously due to the heterogeneous study design. A RCT in patients after a skull and brain trauma showed that a formula containing glutamine and probiotics reduced infection rate and ICU LOS [240].

In another meta-analysis comprising 30 controlled studies in 2972 critically ill patients, early use of probiotics lowered the rate of infection and pneumonia. By means of subgroup analyses, it was shown that these favorable effects were particularly pronounced when *L. plantarum* was used instead of *L. rhamnosus* GG or concomitant fibers. However, methodologic quality of this analysis was low and risk for a publication bias high [241].

According to the most recent meta-analysis (13 RCT, 1969 mechanically ventilated patients), a combined application of different probiotics significantly lowered overall rate of VAP [242]. This effect was also confirmed by a “trial-sequential” analysis. There were, however, no significant differences with regard to other clinical outcomes (mortality, ICU LOS, frequency of diarrhea, duration of MV).

The A.S.P.E.N. guideline could not make a general recommendation for the routine use of probiotics across the general population of ICU patients. Based on expert consensus (Recommendation F2), certain probiotic species should be only used in selected medical and surgical patient groups (liver transplantation, trauma, pancreatectomy) [2]. For this recommendation, the A.S.P.E.N. guideline cited a Cochrane analysis showing that mainly *L. rhamnosus* GG reduced the frequency of infectious complications and VAP [243]. However, the methodologic quality of the studies (eight RCT, 1083 patients) included in this Cochrane analysis was low.

Conclusion

It is still unclear which of the available probiotic species is advantageous to unselected critically ill patients. Results are heterogeneous, and studies differ in terms of the type of species tested and dose used.

For certain diseases (patients with pancreatitis), severe adverse effects have been observed [244,245], which may, however, be attributed to the particular modes of administration, and to particular strains which have not been adequately studied by clinical trials.

According to current evidence, however, on cannot exclude that distinct bacterial strains (*L. plantarum, L. rhamnosus* GG) may be advantageous in certain clinical conditions. Therefore, the author group considers an open “may” recommendation to be justified.

7.4. Technical aspects of parenteral nutrition

7.4.1. Indications

Question: What is the indication for parenteral nutrition?

Recommendation 38a:

Parenteral nutrition should be initiated, if there are contraindications for an enteral nutrient supply (section 7.2.1**, Recommendations 23** and **24**); thereby, MNT should guarantee a calorie and protein intake according to the disease phase and individual metabolic tolerance.

Strong consensus (97%)

Recommendation 38b:

Parenteral nutrition may be initiated in malnourished patients (section 7.1.3, **Recommendation 22**), thereby providing calories and proteins according to the disease phase and individual metabolic tolerance.

Strong consensus (97%)

Recommendation 38c:

Parenteral nutrients should be added to enteral nutrients (sections 6.2 and 6.3), when exclusive enteral nutrition cannot deliver calories/proteins to the patient at a rate specified by disease phase and individual metabolic tolerance.

Strong consensus (97%)

Commentary

Our recommendations clearly differ from those made by the SSC and A.S.P.E.N. guideline. The SSC guideline recommends that septic patients whose enteral nutrient intake is inadequate during the first week should not receive parenteral nutrients (strong recommendation, moderate quality of evidence) [4]. The A.S.P.E.N. guideline suggests initiating exclusive PN as soon as possible following ICU admission in patients determined to be at a high nutrition risk (for example, NRS-2002 $\geq$ 5 or NUTRIC score $\geq$ 6) or severely malnourished, when EN is not feasible (Recommendation G2, expert consensus) [2]. A.S.P.E.N. further suggests that, in the patient at low nutrition risk (for example, NRS-2002 $\leq$ 3 or NUTRIC score $\leq$ 5), exclusive PN be withheld over the first seven days following ICU admission if the patient cannot maintain volitional intake and if early EN is not feasible (Recommendation G1, very low quality of evidence). Regardless of the degree of nutrition risk, A.S.P.E.N. recommends that early exclusive or supplemental PN should not be used in the acute phase of severe sepsis or septic shock, and that use of supplemental PN be considered only after 7–10 days if unable to meet >60% of energy and protein needs by the enteral route alone (Recommendations G3 and N2, moderate and very low quality of evidence, respectively). Consequently, for certain patients, A.S.P.E.N. suggests accepting a severely hypocaloric nutrition in the acute phase.

To support these recommendations, A.S.P.E.N. uses several arguments, which in our view, however, are open to criticism and cannot justify the recommendations (Table 10). In context with this recommendation, A.S.P.E.N. discusses the SPN trial [246]. Results of the SPN trial would rather support early use of supplemental SPN, if early EN is insufficient. A.S.P.E.N., however, did not accept these results as the SPN trial used an outcome variable (number of infections developing beyond day five after the initiation of supplemental PN) which excluded early infections during supplemental PN. On the contrary, A.S.P.E.N. did not consider three subsequently published meta-analyses [56–58], which showed that providing <33% of target calories in the acute phase (compared to >33%) increased mortality (see Table 5); according to the results of the meta-analysis conducted by Choi et al. [56], this effect was also independent of the BMI.

Conclusion

Studies cited by A.S.P.E.N. or SSC to support their restrictive attitude toward the use of a supplemental PN all have significant methodological weaknesses; results of current meta-analyses strongly suggest avoiding a very low calorie intake during the acute phase of critical illness. Therefore, we would recommend supplemental PN for all patients in whom exclusive EN cannot guarantee a calorie and protein intake according to the phase of the disease and individual metabolic tolerance.

To guarantee an equivalent amino acid intake, it is necessary to multiply protein intake by the factor 1.2. Based on the weight unit, solutions with free amino acids contain ~17% less protein equivalent than formed protein [124].

7.4.2. Access routes

Question: Which access route should be used for parenteral nutrition?

Recommendation 39a:

A central venous line shall be used in patients receiving parenteral solutions with high osmolarity (>900 mosmol/L).

Strong consensus (100%)

Recommendation 39b:

(Supplemental) parenteral nutrition ($\leq$900 mosmol/L) may be administered via a peripheral vein.

Strong consensus (97%)

Commentary

Usually, patients of the target group (as defined for the purpose of this guideline) all have a central line in place allowing for a safe administration of parenteral solutions with high osmolarity. Central, large-diameter veins usually tolerate hyperosmolar solutions (>900 mosmol/L) well. Alternatively, one may also use peripheral veins for infusing parenteral solutions. However, peripheral veins are poorly tolerant to hyperosmolar solutions and require lower infusion rates. Glucose and amino acid solutions are the major determinants of osmolarity; it may rise further by the simultaneous administration of drugs such as heparin or steroids thereby increasing the risk of thrombophlebitis.

Table 10
Arguments presented by A.S.P.E.N. and SSC against the use of supplementary parenteral nutrition in the acute phase.

Rationale of recommendations made by A.S.P.E.N. [2] and SSC [4]	Criticism of the rationale by the author group of the DGEM guideline
Negative results of meta-analyses by Heyland et al., 1998 [247] and Braunschweig et al., 2001 [248]	• Meta-analyses compared total (eu-/hypercaloric) parenteral nutrition with hypocaloric standard nutrition • Number of RCTs which had been conducted in critically ill patients and which were included in the meta-analyses: ◦ Heyland et al.: 2 of 28 studies ◦ Braunschweig et al.: 0 of 8 studies
Negative results of the observational studies by Kutsogiannis et al. [100] and Elke et al. [99,249]	High indication bias in observational studies: • Confounding by indication: parenteral nutrition ↑ → Outcome ↓ *vs.* disease severity ↑ (→ Outcome ↓) → tolerance of enteral nutrition ↓ → parenteral nutrition ↑
Negative results of the EPaNiC trial [250]	EPaNiC trial: • No severely hypocaloric control group (mean calorie intake in the acute phase: 22 *vs.* 13 kcal/kg per day) • carbohydrate-based parenteral nutrition in the intervention arm • Patients only had a moderate organ dysfunction (mortality ≈ 10%)
Marginal results of the Early PN trial [251]	• No severely hypocaloric control group (mean calorie intake in the acute phase: 15 *vs.* 11 kcal/kg per day)

↑: increasing or increased use; ↓: decreased use or worsened.

Alternatively, for (supplemental) parenteral nutrition clinicians may use solutions of lower osmolarity (≤900 mosmol/L) suited for peripheral infusion, as are 10–20% fat emulsions (270–345 mosmol/L for 10% fat emulsions, 270–410 mosmol/L for 20% fat emulsions). The current A.S.P.E.N. guideline "*Parenteral Nutrition Ordering, Order Review, Compounding, Labeling and Dispensing*" states that parenteral solutions with a maximum osmolarity ≤900 mosmol/L can be administered safely when infused through a peripheral vein (weak recommendation) [252]. Rationale for this recommendation was a systematic review of eight studies on peripheral vein tolerance to various parenteral solutions of different osmolarity. These studies, however, were limited by their observational design and small sample size.

Before administering parenteral solutions via a peripheral vein, clinicians must pay attention to the osmolarity of the solution specified in the respective product information. Furthermore, hygiene of the peripheral access route is a serious matter; since infusion pumps should not be used, a peripheral catheter cannot guarantee a specific infusion rate and, correspondingly, a specific calorie and protein intake adapted to the disease phase and individual metabolic tolerance (this is a particular limitation during exclusive peripheral administration of parenteral solutions).

Although there is a lack of high-quality studies to give a sufficiently detailed answer to the question, the author group considers a "Shall" recommendation to be justified.

7.4.3. Three-chamber bags vs. single components

Question: Should three-chamber bags or single components be used for parenteral nutrition?

Recommendation 40:

For parenteral nutrition, three-chamber bags may be used preferably.

Strong consensus (94%)

Commentary

Only a few studies compared use of a three-chamber bag with that of single components in critically ill patients requiring TPN; evidence is predominantly based on retrospective, observational studies. In addition, data concerning the safety of three-chamber bags vs. single components are still scarce [252,253]. Only one multicenter RCT including 406 critically ill patients (EPICOS) investigated the differences of infectious complications associated with two different PN systems (multi-chamber bag or compounded PN). That study found that compounded PN increased the incidence of BSIs and of central line-associated bloodstream infections. There was, however, no effect on 28-day mortality, organ failure, or duration of ICU stay [254].

Two large retrospective studies analyzing a US database of 68,984 hospitalized patients, or the Premier Perspective™ database of 15,328 patients with a ICU-LOS ≥ 3 days, respectively, both found that use of a three-chamber bag was associated with significantly fewer sepsis episodes/number of bloodstream infections [255,256]. In contrast, a recent multicenter RCT of 240 postoperative non-critically ill patients (minimum duration of parenteral nutrition ≥ 6 days), could not identify relevant effects of three-chamber bags on clinical outcomes, but found that use of such bags reduced the "workload" of the nursing personal [257]. Based on the marginal results of EPICOS [254], the A.S.P.E.N. guideline stated that use of standardized commercially available PN versus compounded PN admixtures in the ICU patient offers no advantage in terms of clinical outcomes (Recommendation H4, expert consensus) [2].

Since there is no convincing evidence calling for the use three-chamber bags in this guideline's target group, the author group felt that clinicians may or may not use three-chamber bags for parenteral nutrition. Three-chamber bags always provide patients with a predefined calorie and amino acid intake, which, however, must not dictate the individual calorie and protein intake of a patient according to the phase of the disease and metabolic tolerance (sections 6.2 and 6.3).

Use of three-chamber bags must strictly respect the maximum application time of 12–24 h (depending on the product and body weight) as specified by the manufacturer. Further specifications may arise from product-specific technical information, and from recommendations made by the German Commission for Hospital Hygiene and Infection Prevention (KRINKO) to prevent healthcare-associated infections [258].

8. Macronutrient intake

8.1. Immunonutrition

Question: Should critically ill patients receive immune-modulating enteral formulations?

Recommendation 41:

Critically ill patients should not receive immune-modulating enteral formulations.

Consensus (83%)

Commentary

Immune-modulating enteral formulations are primarily pharmacologic "cocktails" largely containing the amino acids arginine and glutamine, omega-3 fatty acids, ribonucleotides, gamma-linolenic acid, butyrate and the antioxidants vitamin E, carotenoids, selenium and zinc. Benefits of an exclusive enteral supplementation of omega-3 fatty acids are discussed in section 8.3.2.

The major problem to be faced when evaluating the potential benefits of "cocktail" studies is their heterogeneity in terms of composition, route of delivery (enteral, parenteral or both) and dose. Despite these limitations, several meta-analyses have been conducted on the subject [259]. A further, potentially important drawback may be the interaction between compounds given simultaneously. Animal experiments revealed antagonistic effects between arginine and omega-3 fatty acids in terms of the production of pro-inflammatory mediators IL-6 and TNF-alpha and of nitric oxide (NO) synthetase [260].

8.1.1. Arginine-enriched immune-modulating enteral formulations

Several RCTs examined potential benefits of formulations containing arginine, omega-3 fatty acids and ribonucleotides; these studies, however, largely included patients who were not critically ill (not reflecting the target group of this guideline), but were studied before/after large elective abdominal operations possibly requiring intensive care during the postoperative course. We refer to current guidelines of the DGEM and ESPEN addressing the clinical relevance of perioperative enteral immune-modulating formulations in patients undergoing elective operations [208,228].

One of the first large multicenter RCTs enrolling critically ill septic patients revealed that arginine-enriched immune-modulating formulations significantly improved survival in those patients who had had an admission APACHE score of 10–15; in patients who had had higher scores, however, mortality increased [261].

To corroborate clinical benefits of an enteral, arginine-enriched formulation in critically ill patients further, Heyland et al. performed a meta-analysis including 13 RCTs of which some also had enrolled patients after a severe trauma injury [262]. This analysis revealed a trend towards an increased mortality among those patients who had received such a formulation. A subsequent meta-analysis by Montejo et al. included 26 RCTs and showed that arginine-enriched immune-modulating formulations significantly improved morbidity; this meta-analysis, however, combined

studies on both critically and non-critically ill patients [263]. A subsequent meta-analysis of 24 RCTs exclusively enrolling 3013 critically ill patients was no longer able to demonstrate clinical benefits of arginine-enriched immune-modulating formulations irrespective of whether or not they had contained additional glutamine or fish oil [264].

Based on their own separate meta-analysis (20 RCTs), the current A.S.P.E.N. guideline [2] suggests avoiding immune-modulating enteral formulations (arginine with other agents, including eicosapentaenoic acid, docosahexaenoic acid, glutamine, and nucleic acid) in medical ICU patients. Consideration for these formulations should be reserved for patients with traumatic brain injury and perioperative patients in the surgical ICU (Recommendation E2, very low quality of evidence).

8.1.2. Immune-modulating formulations not enriched with arginine

In a RCT of septic patients, Beale et al. found that an enteral formulation containing glutamine, vitamins C and E, and butyrate [265] significantly reduced SOFA scores in the intervention group, but had no effect on mortality or hospital LOS.

The MetaPlus RCT compared a high-protein immune-modulating formulation containing glutamine, omega-3 fatty acids, and antioxidants with a standard diet [266]. 301 critically ill patients with an estimated duration of MV > 72 h were randomized; all patients had an indication for enteral nutrition. Enteral nutrition was started after 48 h, and was continued during ICU stay for $\leq$28 days. The formulation neither had an effect on the primary outcome (new infections) nor on secondary outcomes (mortality, SOFA score, duration of MV, ICU-/hospital LOS).

Several RCTs tested immune-modulating formulations containing omega-3 fatty acids, gamma-linolenic acid and antioxidants in patients with acute lung injury and ARDS. Gadek et al. observed a significantly shorter length of MV and ICU stay [267]. Singer et al. confirmed these results showing that such a formulation significantly improved pulmonary function (F_iO_2/P_aO_2 ratios on day 5 and 7 of the study), without, however, affecting survival rates [268]. In contrast, Pontes-Arruda et al. found, that use of this particular type of immune-modulating formulation in septic patients was not only associated with better pulmonary function and shorter ICU LOS, but also with a significantly higher survival rate [269]. A subsequent meta-analysis of three RCTs (411 patients) confirmed these benefits (lower mortality and shorter duration of MV) [270]. Results, however, were biased by the small sample size of the individual studies.

A subsequent larger RCT (44 hospitals of the US National Heart, Lung, and Blood Institute ARDS Clinical Trials Network Participations, OMEGA trial) enrolled 272 patients <24 h after diagnosis of an acute lung injury [271]. Both study arms received comparable amounts of calories including a supplement (omega-3 fatty acids, gamma-linolenic acid and antioxidants) in the experimental group. Both supplements (placebo and immune-modulating formulation) were given twice a day, irrespective of the intensity of enteral nutrition. The primary outcome was ventilator-free days to study day 28. In the experimental group, plasma eicosapentaenoic acid levels increased significantly. The study was terminated early, because the immune-modulating formulation had significantly reduced the number of ventilator-free days, and days without intensive care. The formulation did not affect 60-day mortality, but increased the number of days with diarrhea significantly. The study was criticized because (i) total calorie intake had been low in both study arms, (ii) the immune-modulating formulation had been administered as a bolus, and (iii) protein intake had been higher in the control group.

Based on a meta-analysis of six RCTs, the A.S.P.E.N. author group found that it could neither recommend nor speak out against the use of this specific formulation (omega-3 fatty acids, gamma-linolenic acid, antioxidants) in patients with ARDS (Recommendation E3, low-to-very-low quality of evidence) [2]. The A.S.P.E.N. guideline, however, did not consider two meta-analyses on the subject. The meta-analysis by Li et al. [272] evaluated six RCTs testing this formulation in patients with ARDS. The authors could not find an overall benefit, but stated that it was not possible to rule out benefits in high-risk patients. The meta-analysis by Santacruz et al. [273] evaluated seven RCTs involving 802 patients, and did not identify beneficial effects on mortality or morbidity. A subgroup analysis, however, revealed that omega-3 fatty acids, gamma-linolenic acid and antioxidants improved survival if fat accounted for 55% of total calories in both study arms (thereby also providing comparably large amounts of omega-6 fatty acids in the control group). If fat accounted for only 30% of total calories in both study arms, use of the formulation was associated with a trend towards a higher mortality in the intervention group.

Conclusion

Considering the available evidence, arginine-enriched immune-modulating enteral formulations do not appear to have a therapeutic benefit in critically ill patients. Consequently, we would not recommend using such formulas. For immune-modulating formulations not enriched with arginine, results are controversial, and in certain patient subgroups, such formulations may be beneficial or cause harm. Respecting the axiom “first do no harm” we speak out against the use of such enteral formulations.

8.2. Carbohydrates

8.2.1. Type of carbohydrates

Question: Which type of carbohydrates should critically ill patients receive during parenteral nutrition?

Recommendation 42a:

Critically ill patients shall only receive glucose as a carbohydrate source.

Strong consensus (97%)

Recommendation 42b:

Sugar substitutes should not be part of MNT.

Strong consensus (94%)

Commentary

No RCTs exist on the effect of different parenteral carbohydrate sources on the clinical outcomes of critically ill patients. Older mechanistic studies have investigated mainly the metabolic effects of different carbohydrate sources. There is no reference to this topic in the current A.S.P.E.N. guideline [2]. However, in general, use of carbohydrates as a primary energy source – enteral and parenteral – is not under discussion due to their physiologic relevance [274].

Carbohydrates are essential macronutrients. Glucose is the standard carbohydrate for humans because it is not only a precursor for the synthesis of glycoproteins, glycolipids and mucopolysaccharides, but is also an energy source essential to maintain cellular metabolism; furthermore, plasma glucose concentration is easy to measure. Many tissues may use fatty acids as an alternative source of energy to glucose. Cells of the central nervous system (except for utilization of ketone bodies), immunocompetent cells, erythrocytes, cells involved in wound healing of rapidly proliferating tissues, and tubular epithelial cells do all require glucose for energy metabolism, which makes this substrate essential for MNT [275].

In the past, several studies examined sugar substitutes (e.g., fructose, sorbitol, xylitol) as an alternative energy source. Xylitol may be harmful because it cannot be reabsorbed in the kidney at higher intakes thereby causing osmotic diuresis and, thus, considerable fluid losses. Furthermore, oxalate crystals may originate in individual organs; the monitoring is complicated and compliance

with intake limits is essential. Since there are specific side effects, and since authorities have suspended marketing authorization for some sugar substitutes, they have long been absent from recommendations for MNT [276–278].

Although there is a lack of high-quality studies to give a sufficiently detailed answer to the question, the author group considers a "Shall" recommendation (**Recommendation 42a**) or a "Should" recommendation (**Recommendation 42b**) to be justified.

8.2.2. Dosage of parenteral carbohydrates

Question How many carbohydrates should a patient receive during parenteral nutrition?

Recommendation 43:

During parenteral nutrition glucose should be administered according to the phase of the disease and individual metabolic tolerance (section 6.2.3); MNT should respect (i) a maximum intake of 4 g glucose/kg per day, (ii) the caloric carbohydrate:fat ratio, and (iii) the caloric carbohydrate:amino acid ratio (sections 8.3.4 and 8.4.6).

Strong consensus (97%)

Commentary

Glucose is *per se* not an essential nutrient, but can be synthesized by an energy-consuming pathway in the liver and, to a lesser extent, in the kidney. Substrates of gluconeogenesis are lactate and pyruvate, which arise from anaerobic glycolysis or from the breakdown of gluconeogenic amino acids released from skeletal muscle [279,280]. The primary aim of an exogenous supply of glucose is to preserve the body's skeletal muscle by minimizing use of endogenously released gluconeogenic amino acids via hepatic gluconeogenesis ("protein-sparing effect") [281].

There are no clinical data indicating an absolute maximum for carbohydrate intake. Small mechanistic studies in humans have shown that – in comparison to healthy subjects - hepatic glucose production may double in septic patients (~4 g glucose/kg and day). High rates of insulin infusion (4–5 IU/h) may reduce production rates down to normal values in many patients [282]. It is, however, not possible to increase the total-body glucose oxidation rate to more than 4 g/kg per day, even if insulin infusion rates are extraordinarily high (13–14 IU/h) [283]. Thus, a maximum of 4 g glucose/kg per day seems appropriate, if insulin requirement is < 2 IU/h (Fig. 3) [275,284], and if there is no hyperglycemia (>180 mg/dL, see the current DGEM S3 guideline "*Monitoring of Artificial Nutrition: Specific Aspects*" [110]). This maximum is slightly above the value recommended in the former (2007) DGEM guideline on parenteral nutrition (3.0–3.5 g glucose/kg and day) [285]. This earlier recommendation was based on expert consensus, and not on scientific evidence. The same limitations apply for the recommendation of the older A.S.P.E.N. guideline (2004) suggesting a maximum of 7 g/kg and day during parenteral nutrition [286]. The current A.S.P.E.N. guideline (2016) [2] does not make a recommendation on upper limits of glucose intake.

As a minimum glucose intake, the old (2007) DGEM guideline on parenteral nutrition [285] and the old (2009) ESPEN guideline on parenteral nutrition [5] recommended 1–2 g glucose/kg and day estimated from the daily energy need of organs for which glucose is the major obligate energetic fuel (brain, adrenal glands and erythrocytes). These recommendations were based on expert consensus considering the carbohydrate requirement of healthy subjects [287], while ignoring individual pathophysiologic changes of substrate metabolism in critically ill patients.

There are no clinical data indicating an absolute minimum of glucose intake. If individual tolerance is respected (section 6.2.3, **Recommendations 9b** and **9c**, and section 6.3.2), it may be necessary to interrupt glucose intake completely in those patients in whom insulin requirement is very high (>4 IU/h) indicating a pronounced insulin resistance and non-suppressible endogenous glucose production. Under such circumstances, substrate requirements are met exclusively by endogenous sources. Our recommendation is only based on expert consensus, but corresponds to the older (expert) recommendation of the DGEM guideline (2007) on parenteral nutrition [285].

Although there is a lack of high-quality studies to give a sufficiently detailed answer to the question, the author group considers a "Should" recommendation to be justified.

8.3. Lipids

8.3.1. Type of lipids

Question: Which type of fat should critically ill patients receive during enteral or parenteral nutrition?

Recommendation 44a:

Fat shall be an integral part of enteral and parenteral nutrition.

Strong consensus (97%)

Recommendation 44b:

In critically ill patients, parenteral nutrition shall include fat emulsions containing reduced amounts of omega-6 fatty acids (fat emulsions containing olive oil or supplemented with coconut and fish oils, or with coconut, olive and fish oils).

Strong consensus (94%)

Commentary

In contrast to carbohydrates, lipids are characterized by their increased calorie content representing an attractive source of energy. Routine use of fat is an integral part of enteral and parenteral nutrition, and serves to prevent hyperglycemia, steatosis hepatis and deficiencies of essential fatty acids (linoleic acid and α-linolenic acid). In addition, fat emulsions provide cell membranes with lipid components.

In critically ill patients, the metabolic stress response includes an altered pattern of substrate utilization; for hepatocytes, myocardial cells and skeletal muscle cells, in particular, lipids are the preferred energy source [288]. Besides serving as energy substrates and components of cell structure, certain fatty acids may also modulate the inflammatory response [289].

Sepsis is associated with an activation of the inflammatory cascade, and with the release of large amounts of arachidonic acid (omega-6) from cell membranes of immunocompetent cells. Specific enzymes may convert arachidonic acid into pro-inflammatory eicosanoids (prostaglandin (PG)-2 and leukotriene (LTD)-4) [290]. Fish oil contains omega-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid) that alter the pattern of eicosanoid mediator synthesis thereby increasing the production of prostanoids with reduced pro-inflammatory or even anti-inflammatory activity (PG-3, LTD-5 and thromboxane) [291–293].

In addition, omega-3 fatty acids may be metabolized into compounds (resolvins, protectins and maresins) exerting specific anti-inflammatory effects in a variety of cell types [294,295]. A small RCT (42 healthy subjects exposed to inhaled lipopolysaccharides) showed that fish oil-induced synthesis of anti-inflammatory lipid mediators could be advantageous during the treatment of ARDS and peritonitis [296].

Although fat plays an important role in (patho-)physiology and MNT of critically ill patients, there are only a few large RCTs examining the effect of different types of fat on clinical outcomes. Interpretation of studies on enteral fat intake is particularly difficult since these studies did not only test different types of fat, but also the combination with other immune-modulating components (such as arginine or antioxidants).

8.3.2. Fat intake

8.3.2.1. Parenteral fat emulsions containing reduced amounts of omega-6 fatty acids. A Canadian meta-analysis reviewed ten RCTs comparing different types of intravenous fat emulsions containing reduced amounts of omega-6 fatty acids [297]. Four studies compared emulsions containing a mixture of long-chain triglycerides (LCT) and medium-chain triglycerides (MCT), with emulsions only containing pure LCT [298–301]. Three studies compared LCT or LCT/MCT containing fat emulsions supplemented with fish oil, with emulsions only containing LCT or a combination of LCT/MCT [302–304]. Two studies compared an olive oil-based emulsion with a LCT/MCT emulsion [305,306]. One study compared two different LCT emulsions [307]. In summary, the meta-analysis found that fat emulsions containing reduced amounts of omega-6 fatty acids did not improve mortality or morbidity. There was only a trend towards a shorter duration of MV or reduced ICU LOS. A retrospective observational study (n = 451) in mechanically ventilated ICU survivors found a significant association between the use of balanced fat emulsions and a shorter duration of MV and reduced ICU LOS [308].

The A.S.P.E.N. guideline recommends that parenteral nutrition may include modern balanced fat emulsions containing reduced amounts of omega-6 fatty acids, and increased amounts of coconut oil, olive oil and/or fish oils (Recommendation H3b, expert consensus) [2].

A Canadian meta-analysis compared an olive oil-based fat emulsion (80%) with a coconut oil-based emulsion [297]; the olive oil-based fat emulsion shortened the duration of MV, but did not affect other outcome variables.

A meta-analysis published in 2013 (eight RCTs, 391 patients) compared a "conventional" parenteral nutrition with a regimen administering fat emulsions supplemented with fish oil. Outcomes did not differ significantly between both regimens [309].

A subsequent larger RCT by Grau-Carmona et al. (159 critically ill patients) compared two different TPN regimens containing either a soybean oil- based intravenous fat emulsion, or a fat emulsion supplemented with fish oil [311]. The use of a fat emulsions supplemented with fish oil significantly reduced the number of nosocomial infections (primary outcome). This study, however, is subject to significant criticism since the recruitment period was comparably long, the study did not reach the pre-calculated sample size, and the authors did not publish data on 28-day mortality. Furthermore, there was a trend towards a higher 6-month mortality in the intervention group causing a bias. A shorter survival time in the intervention group also shortened the length of time in which nosocomial infections could have developed.

A meta-analysis by Manzanares et al. evaluated 10 RCTs (733 critically ill patients) including the study by Grau-Carmona et al. [311]. These RCTs had compared intravenous fat emulsions supplemented with fish oil with EN, with PN using soybean oil-based fat emulsions or other fat emulsions not supplemented with fish oil, or with saline solutions [310]. The authors found that fat emulsions supplemented with fish oil may reduce the number of infections, and possibly also the duration of MV and hospital LOS. However, the study by Grau-Carmona et al. [311] contributed to 52% of the effect size in this meta-analysis.

The most recent review (34 RCTs) by Abbasoglu et al. concluded that there are very few high-quality studies showing that fat emulsions supplemented with fish oil improve outcomes [312]. A meta-analysis by Lu et al. [313] evaluating 17 RCTs on enteral and/or parenteral use of fish oil in septic patients, came to a similar conclusion.

8.3.2.2. Enteral fat. An older meta-analysis evaluated three studies on enteral administration of fish oil in 411 critically ill patients; the authors found that fish oil significantly reduced mortality and the number of organ dysfunctions, and shortened duration of MV and LOS [270]. Two newer studies suggested that fish oil together with antioxidants will reduce LOS and the frequency of a newly developed septic shock if these compounds are administered preemptively before the onset of organ dysfunction [311,314]. Both studies administered fat continuously. Two other studies, which had used a bolus application, however, could not confirm these results [271,315]. In the OMEGA trial, a mixture of omega-3 fatty acids, gamma-linolenic acid and antioxidants even prolonged the duration of MV, and ICU-LOS [271]; the study, however, was criticized for its poor comparability between study groups, different protein intakes, and mode of (bolus) application [316].

Overall, there are no conclusive data on potential benefits of fish oil administered during enteral nutrition; most of the studies administered fish oil as part of an enteral immunonutrition (together with glutamine, arginine, gamma-linolenic acid and antioxidants) and, thus, do not allow for conclusions concerning the effect of a single substrate (section 8.1). The application mode (bolus vs. continuous feeding) of single compounds is controversial, and bolus application may have even caused harm.

Conclusion

The SSC guideline [4] speaks out strongly (with, however, a low quality of evidence) against enteral and/or parenteral use of omega-3 fatty acids as an immunomodulating supplement in patients with sepsis/septic shock. This recommendation is based on the results of two meta-analyses on enteral [317] or parenteral [318] supplementation, and on the unfavorable results of the OMEGA trial conducted in patients with ARDS [271]. The SSC guideline also performed a systematic review of 16 RCTs (1216 patients) administering enteral or parenteral omega-3 fatty acids in the intervention arm; the authors concluded that fish oil did not affect mortality but reduced ICU LOS; quality of evidence, however, was very low.

Overall, results on the optimal type of fat are inconsistent or insufficient. Our author group recommends, in accordance with current recommendations from the ESPEN expert group "*Lipids in the Intensive Care Unit*" [319], that fat shall be an integral part of parenteral nutrition of critically ill patients. For parenteral nutrition, fat emulsion containing reduced amounts of omega-6 fatty acids (fat emulsion based on olive oil, or supplemented with coconut oil and fish oil, or with coconut, olive and fish oils) should be used because harmful effects have not been described yet, and clinical and experimental studies suggest a benefit.

Although there are no high-quality studies to give a sufficiently detailed answer to the question, the author group considers a "Shall" recommendation to be justified.

8.3.3. Dosage of parenteral fat

Question: How much fat should a critically ill patient receive during parenteral nutrition?

Recommendation 45a:

Patients should receive parenteral fat according to the phase of the disease and individual metabolic tolerance (section 6.2.3); MNT should respect a maximum of 1.5 g fat/kg per day.

Strong consensus (97%)

Recommendation 45b:

During parenteral nutrition, patients should receive a continuous infusion of fat emulsions for 12–24 h (no bolus application).

Strong consensus (100%)

Recommendation 45c:

Patients on parenteral nutrition should receive fat from the end of the acute phase at the latest.

Consensus (88%)

Recommendation 45d:

To avoid a deficiency of essential fatty acids, the minimum daily fat intake should take into account linoleic acid and α-linolenic acid content of the fat emulsion.

Strong consensus (97%)

Commentary

The recommendations for fat intake are based on nutrition physiology and individual "safety studies" that were not necessarily conducted in critically ill patients [319]. Infusion of soybean oil-based fat emulsions at ≤1.5 g/kg per day was safe according to a multicenter study in 256 patients after major abdominal surgery not requiring intensive care [320]. A multicenter RCT included 661 critically ill patients who all had an indication for parenteral nutrition. The association between parenteral fish oil intake and a shorter ICU-LOS or lower infection rate was the strongest, if patients had had an i.v. fish-oil intake of 0.15–0.2 g/kg per day (using a commercial 10% fat emulsion) [321].

However, when using three-chamber bags (in which the caloric ratios of substrates are fixed), a fat intake of 1.5 g/kg per day will be only possible if total calorie intake is very high (40 kcal/kg per day).

A systematic review (87 studies in pediatric and adult subjects, 27 experimental studies in animals) by Hayes et al. [322] analyzed the frequency of toxic or unwanted side effects of fat emulsions, which patients had received for parenteral nutrition (<14 days) or as an antidote for intoxications by local anesthetics. Studies mostly were case reports or had an observational design. Adverse events were acute renal failure, venous thromboembolism or fat embolism, allergic reactions, fat overload syndrome, pancreatitis, acute respiratory failure or ventilation–perfusion mismatch, and obstructions during extracorporeal membrane oxygenation (section 11.3.1). The frequency of immediate adverse events (<48 h) was proportional to the dose and infusion rate of lipids. Adverse events related to fat emulsions (cholestasis, immunological, pulmonary or hepatic complications, hypertriglyceridemia) will be lower, when fat is administered continuously (no bolus application) and when the relative fat content of the emulsion is low [281,286,323,324]. Three small mechanistic studies in critically ill patients with ARDS and sepsis examined the association between the daily infusion rate of lipids, and changes of organ function. Fat emulsions contained varying amounts of omega-6 fatty acids or MCT [325–327]. The studies found that pulmonary and circulatory function may deteriorate, when total fat infusion rate is < 12 h.

The A.S.P.E.N. guideline (2016) [2] did not specifically address dose ranges or infusion rates of fat emulsions during parenteral nutrition. The ESPEN expert group "*Lipids in the Intensive Care Unit*" [319], however, stated that parenteral fat emulsions can be administered safely at a rate of 0.7–1.5 g/kg per day, if patients do not receive a fat bolus, but a continuous infusion >12 h [319]. This recommendation, however, is only based on expert consensus, and corresponds to that made in the 2009 ESPEN guideline "*Parenteral Nutrition: Intensive Care*" [5].

For parenteral fat intake, the older A.S.P.E.N. guideline (2004) [286] recommended a maximum fat intake of 2.5 g/kg per day, which was significantly higher than that recommended by ESPEN. The A.S.P.E.N. recommendation, however, was only based on expert consensus, and was not supported by studies on pathophysiology, or by RCTs. In adults, the currently recommended, daily parenteral intake of fat emulsions is 0.7–1.3 g/kg per day.

A major rationale for providing fat is to avoid a deficiency of essential fatty acids, i.e., linoleic acid and α-linolenic acid. To meet minimum fat requirements, the A.S.P.E.N. guideline (2004) [286] recommended that at least 2–4% of total calorie intake should be linoleic acid, and 0.25–0.5% α-linolenic acid [328]. Quantitatively, these recommendations correspond to a daily linoleic acid intake of 15–45 kcal (1.8–5.4 g), and to a daily α-linolenic acid intake of 3–7.5 kcal (0.3–0.75 g). Using soybean-based fat emulsions, this minimum requirement would be met by administering 2.9–8.7 g fat per day, or 29–87 mL of a 10% fat emulsion per day. However, only soybean oil-based fat emulsions contain high amounts of linoleic acid and α-linolenic acid (55–60% and 3–4%, respectively). Modern fat emulsion (based on olive oil, or supplemented with coconut oil, fish oil or palm kernel oil) contain significantly less linoleic acid (e.g., only ~20% in emulsions based on olive oil). Therefore, when MNT uses modern fat emulsions, their infusion rates should be adjusted to the reduced content of essential fatty acids to avoid a corresponding deficiency [329].

The A.S.P.E.N. guideline (2016) (Recommendation H3a, very low quality of evidence) [2] speaks out against the use of soybean oil-based fat emulsions during the acute phase. To avoid a deficiency of essential fatty acids, soybean oil-based fat emulsions should be given up to a maximum intake of 100 g/week (divided into two doses per week). Whether this recommendation is also appropriate for modern fat emulsion containing significantly less omega-6 fatty acids is unknown.

The time required to become deficient in essential fatty acids is highly variable and depends on nutrition status, age and type of the underlying disease. Non-critically ill patients, in general, develop a deficiency of essential fatty acids after ~4 weeks of a fat-free diet. Times may be shorter in obese patients (three weeks) [286]. In critically ill patients, deficiency states may occur already after one week of a fat-free diet [328,330]. Thus, the author group recommends that MNT should contain fat from the end of the acute phase at the latest.

Fat intake should be controlled by triglyceride concentration, which should not surmount 400 mg/dL (see recommendations of the DGEM S3 guideline "*Monitoring of Artificial Nutrition: Specific Aspects*") [110]. Contraindications for fat are rare and include congenital disorders of fat metabolism, and clinical signs of severe hypoxia (arterial oxygen saturation <85%, lactic acidosis and disseminated intravascular coagulation) [319].

Although there is a lack of high-quality studies to give a sufficiently detailed answer to the question, the author group considers a "should" recommendation (**Recommendations 45b–d**) to be justified.

8.3.4. Caloric carbohydrate: fat ratio during parenteral nutrition

Question: Which caloric carbohydrate: fat ratio should be used in parenteral nutrition?

Recommendation 46:

The caloric carbohydrate: fat ratio (energy percent, E–%) may range from 70 E–%: 30 E–% to 50 E–%: 50 E–%.

Strong consensus (100%)

Commentary

The caloric carbohydrate: fat ratio describes the ratio (relative proportion) of carbohydrate and fat calories provided during MNT. No large RCT investigated the effect of different carbohydrate: fat ratios on the outcome of critically ill patients. Two older studies, which provided a small number of patients (n = 32 and n = 40) with an enteral diet, compared a carbohydrate: fat ratio of 34 E–%: 76% E–% with a ratio of 44.2 E–%: 55.8 E–% [331,332]. As expected, the reduced ratio also reduced RQ; effects on other clinical outcomes, however, were absent.

A study by Garrel et al. compared a low-fat (15 %) with a high-fat (35 %) enteral diet in 43 patients with severe burns; the low-fat diet was associated with significantly fewer infectious complications [333]. RCTs were summarized in a meta-analysis in 2015, which, however, was unable to make specific recommendations on the carbohydrate: fat ratio due to insufficient data [334,335].

Another RCT included 47 critically ill patients having an indication for parenteral nutrition, who received diets providing either 80% or 50% of calories as carbohydrates. A proportionally higher

carbohydrate intake showed a slightly better protein-sparing effect (as measured by daily nitrogen balance and the urinary 3-methylhistidine: creatinine ratio) [336]; clinically relevant outcomes, however, were not improved.

A recent RCT in 42 critically ill patients tested three different enteral diets. The control group received a carbohydrate-based diet (protein 20 %, fat 30 %, and carbohydrate 50 %). Study groups received two types of a high-fat diet (A: protein 20 %, fat 45 % including olive oil and sunflower oil, and carbohydrate 35 %; B: protein 20 %, fat 45 % including sunflower oil, and carbohydrate 35 %) in the first 48 h after admission [337]. The type of diet was unimportant for the primary outcomes (blood glucose and lipid concentrations), but patients who received the high-fat diet based on olive oil and sunflower oil had higher concentrations of high-density lipoprotein-cholesterol and a shorter ICU LOS.

Since the evidence is insufficient, the author group does not favor a specific caloric carbohydrate: fat ratio, but rather suggests to control fat and carbohydrate intake according to the individual metabolic tolerance (section 6.2.3) simultaneously respecting specific dose limits (section 8.2.2, **Recommendation 43** and section 8.3.3, **Recommendation 45a**) and the caloric carbohydrate: amino acid ratio (section 8.4.6). The caloric carbohydrate: fat ratio may vary between 70 E−%: 30 E−% and 50 E−%: 50 E−% depending on the specific products available for enteral and parenteral nutrition. Thus, in three-chamber bags the caloric carbohydrate: fat ratio is fixed.

Due to the lack of evidence, the author group considers an increase of the dietary fat content >50 % in patients with ARDS, chronic obstructive pulmonary disease, sepsis not to be justified.

8.4. Amino acids

8.4.1. Amino acid intake

Question: Should critically ill patients receive amino acids during parenteral nutrition?

Recommendation 47:

Amino acids should be an integral part of parenteral nutrition.

Strong consensus (100%)

Commentary

A sufficient supply of amino acids is a central prerequisite for effective wound healing (synthesis of structural proteins) and function of the immune system (synthesis of antioxidants, acute-phase proteins, immunoglobulins etc.). Furthermore, certain amino acids may be cytoprotective, and are important sources of energy for immunocompetent cells [82,279]. Amino acids are manufactured synthetically in crystalline form; the composition of commercially available amino acid solutions largely depends on the requirement of healthy subjects [338] and has been modified in the past to optimize nitrogen balance [339].

This concept, however, is under discussion for more than three decades, because the proportional need for individual amino acids (especially in the acute phase after a severe disturbance of homoeostasis) is presumably not identical with that of healthy individuals. Correspondingly, a zero nitrogen balance does not necessarily indicate that the amino acid infusion matches the specific amino acid requirement of reparative or immunologic pathways [340]. A disproportionate amino acid intake in the acute phase may cause a relative excess of those amino acids not required in this phase of the disease possibly harming the organism [341]; exogenous amino acid excess – as demonstrated for high glutamine intake – may be clinically relevant [342]. Whether similar problems would arise with other amino acids is unknown. Nevertheless, supply of amino acids will be indispensable during parenteral nutrition, if MNT shall minimize use of endogenous amino acids, and loss of muscle mass.

Although there are no high-quality studies to give a sufficiently detailed answer to this question, the author group considers a "Should" recommendation to be justified.

8.4.2. Glutamine pharmacotherapy

Question: Should glutamine be part of a pharmacotherapy in MNT?

Recommendation 48a:

Enteral glutamine pharmacotherapy should not be used.

Strong consensus (94%)

Recommendation 48b:

Parenteral glutamine pharmacotherapy may be used in patients needing TPN who do not have severe hepatic, renal or multiple-organ failure.

Consensus (87%)

Commentary

Glutamine is a natural constituent of animal and vegetable protein. Almost all commercially available enteral formulas contain glutamine (5–6 g/L); glutamine is also available as an enteral concentrate. For PN, however, galenics prevent an administration of glutamine in pure form; intravenous administration is only possible via specific parenteral solutions supplemented with glutamine-containing dipeptides (alanyl-glutamine, glycyl-glutamine), or via dipeptide concentrates.

Glutamine is important for various biosynthetic pathways and for the immune response. Cells with a high proliferative activity, such as intestinal epithelial cells and immunocompetent cells, rely on glutamine as an energy substrate. In addition, glutamine is a precursor for glutathione, which is, quantitatively, the most important endogenous scavenger of free radicals. Catabolism and oxidative stress can cause or exacerbate glutamine deficiency rendering glutamine (which usually is a non-essential amino acid) a conditionally essential amino acid [343,344]. In critically ill patients, plasma glutamine concentrations correlate inversely with disease severity and outcome [345]. It remains, however, controversial whether low glutamine concentrations are the cause or the (mal)adaptive consequence of critical illness [346].

8.4.2.1. Enteral glutamine. The largest RCT on enteral glutamine pharmacotherapy examined the effect of glutamine and antioxidants in 1223 critically ill patients with ≥2 organ dysfunctions using a 2 × 2 factorial, blinded and placebo-controlled design (REDOXS trial) [347]. Glutamine and antioxidants were administered in the acute phase of the disease via the enteral (30 g glutamine per day) and parenteral (0.35 g glutamine/kg and day) route. Simultaneously, patients received 500 μg of parenteral sodium selenite, and 300 μg of enteral selenium, 20 mg of zinc, 10 mg of β-carotene, 1500 mg of vitamin C, and 500 mg of vitamin E. Glutamine pharmacotherapy did not depend on calorie intake. In the intervention arm, about 50–60% of the total daily nitrogen intake consisted of glutamine. On average, mortality was 29.8%, and none of the interventions had a significant effect on 28-day mortality (primary outcome). However, glutamine significantly increased hospital and 6-month mortality (secondary outcomes). The study was the first to show a harmful effect of glutamine pharmacotherapy, and one of the reasons to explain this was the extraordinarily high glutamine intake (≤0.78 g/kg and day).

A meta-analysis published in 2015 (11 RCTs, 1079 critically ill patients, including those after a severe trauma injury) analyzed the use of an enteral glutamine pharmacotherapy, and could not show a clear clinical benefit [348]. Average intake of enteral glutamine in the intervention group was 0.16–0.50 g/kg and day, and did only reduce hospital LOS. In a subgroup of burned patients, glutamine pharmacotherapy reduced mortality and hospital LOS. The latter results, however, were only based on three small monocentric RCTs

(enrolling ≤45 patients each), and are, therefore, highly biased. The most recent meta-analysis on the subject included 10 RCTs (1461 critically ill patients), and could not identify relevant effects on mortality or secondary outcomes (LOS, days with MV) [349].

The current A.S.P.E.N. guideline (Recommendation F4, moderate quality of evidence) [2] speaks out against the use of an enteral glutamine pharmacotherapy, since a meta-analysis (five RCTs, 558 patients) did not reveal beneficial effects. The REDOXS trial, however, was not part of this analysis.

The Metaplus trial, which tested an enteral immunonutrition including glutamine in critically ill patients, is discussed in section 8.1.

8.4.2.2. Parenteral glutamine. A large RCT (Scandinavian Glutamine Trial, SGT) compared a parenteral administration of glutamine (0.28 g/kg and day) with placebo in 413 critically ill patients [350]. The additional intake of glutamine was without effect on the primary outcome (change in SOFA score). Patients receiving glutamine for ≥3 days (per-protocol analysis) had a significantly lower mortality in the ICU, but not after 6 months. The SGT also included ICU patients who did not have an organ dysfunction according to the inclusion criteria. Glutamine intake was independent of standard nutrition, and patients in the study mostly received a combined enteral and parenteral MNT. A major limitation of this study was its early termination because of slow patient recruitment.

Another RCT (Scottish Intensive care Glutamine or Selenium Evaluative Trial, SIGNET) enrolled 502 critically ill patients and found that parenteral glutamine did not affect infection rate, mortality and ICU LOS [351]. Limitation of this trial was the short average intervention time (5 days). In a post-hoc analysis, which selectively analyzed patients with a longer intervention period (>5 days), glutamine had no effect on infection rates.

Five recent meta-analyses focused on the potential benefits of a pharmacotherapy using parenteral glutamine, and included SIGNET and SGT into their analyses. The meta-analysis by Pasin et al. [352] included studies on enteral and parenteral glutamine pharmacotherapy; since the authors did not perform subgroup analyses, the results of this meta-analysis are not helpful to substantiate **Recommendations 48a** and **b**. The meta-analysis by Bollhalder et al. (40 RCTs, 3197 patients) showed that a pharmacotherapy using parenteral glutamine reduced infection rate and hospital LOS only in those patients whose mortality was low (<20%) [353]. Parenteral glutamine was ineffective in sicker patients (mortality >20%, 11 RCT, 1244 patients). Positive results, however, were subject to significant bias, as they were based on older studies, which had enrolled small numbers of patients, and of which methodological quality was poor [354]. The meta-analysis by Wischmeyer et al. [355] included 26 RCTs (2484 critically ill patients) and found that additional parenteral glutamine significantly reduced hospital mortality but did not alter the rate of infectious complications or ICU LOS. The Cochrane analysis published in 2015 [356] performed specific subgroup analyses and found that a parenteral glutamine pharmacotherapy (28 RCTs) significantly reduced the risk of infection as compared to placebo. The analysis, however, can be criticized for various reasons (inclusion of both critically and non-critically ill patients, inclusion of studies with a high bias, heterogeneity of the studies, low number of patients randomized (<100) in 24 of 28 studies).

Meta-analyses by Oldani et al. published in 2015 [357], and by Chen et al. published in 2014 [358] evaluated 30 RCTs (3696 critically ill patients) and 17 RCTs (3383 critically ill patients), respectively, which all had used an enteral or a parenteral glutamine pharmacotherapy. The main finding was that a parenteral glutamine pharmacotherapy significantly reduced the frequency of new infections, when patients had had an admission APACHE II score ≤15 (in the meta-analysis by Chen et al. infections rate decreased from 55.9% to 50.0% [358]).

Most recently, Stehle et al. published a meta-analysis in 2017 [359]. The authors analyzed 15 RCTs (842 highly selective critically ill patients) that had exclusively enrolled patients without hepatic or renal failure, who had been hemodynamically and metabolically stable. All patients had received glutamine-containing dipeptides in conjunction with an adequate parenteral nutrition. Glutamine dosing followed recommendations by the manufacturer (0.3–0.5 g/kg and day, maximum glutamine intake was 30% of total amino acid intake). The authors found that parenteral glutamine pharmacotherapy significantly reduced hospital mortality, frequency of infectious complications, and hospital LOS. Points of criticism of this meta-analysis were the lack of distinction between single- and multicenter studies and the very low number of patients randomized on average per study (n = 56); these limitations cause a systematic overestimation of the effect [360].

The current A.S.P.E.N. guideline (Recommendation H6, moderate quality of evidence) [2] speaks out against the routine use of a parenteral glutamine pharmacotherapy in critically ill patients. Main reasons for this recommendation were the negative results of three studies:

(i) the SIGNET trial [351], in which the intervention time may have been too short;
(ii) the REDOXS trial, which had tested a combined enteral/parenteral glutamine pharmacotherapy, and which had given very high amounts of glutamine overall [347];
(iii) the meta-analysis by Pasin et al. [352] that did not distinguish between studies on enteral and parenteral glutamine pharmacotherapy.

The current guideline of the SSC [4] also does not recommend using a parenteral or enteral glutamine pharmacotherapy (strong recommendation, moderate quality of evidence). A distinction between enteral and parenteral pharmacotherapy is not made. The authors of the SSC guideline based their recommendation on the results of seven studies:

(i) two meta-analyses by Avenell et al. published in 2006 (eight RCTs, 537 patients) [361] and in 2009 (12 RCTs, 680 patients) [362]. Both meta-analyses could not find evidence for a beneficial effect of enteral glutamine pharmacotherapy. The analysis published in 2009, however, found that glutamine reduces the frequency of infections, when given via the parenteral route;
(ii) a meta-analysis (3 RCTs, 489 patients) published by Jiang et al. in Chinese language in 2009 [363] showing that enteral glutamine was beneficial just in terms of reducing the infection rate;
(iii) a meta-analysis (14 RCTs, 751 patients) published by Nowak et al., in 2002 [364]. According to a subgroup analysis (critically ill patients), enteral glutamine did not have an effect on mortality or hospital LOS;
(iv) the negative results of the REDOXS trial (with the trial limitations discussed above);
(v) the marginal results of the SGT study by Wernerman et al. [350];
(vi) the hardly convincing results of the RCT by Grau et al. [365] showing that parenteral glutamine pharmacotherapy just reduced the frequency of new infections.

Conclusion

According to the available evidence, it appears to be justified to speak out against an enteral glutamine pharmacotherapy.

Recommendation in favor of a parenteral glutamine pharmacotherapy is more of a concern. Evidence suggesting benefits of this type of glutamine pharmacotherapy stems from the analysis of highly selected critically ill patients (those mostly requiring TPN in the absence of severe hepatic, renal, or multiple-organ failure), and from an aggregation of small, mostly monocentric studies. These limitations render our recommendation contentious. Since there is no large well-designed RCT studying the use of an exclusive parenteral glutamine pharmacotherapy, it is not possible to rule out beneficial effects in certain patient subpopulations. Candidates for a corresponding pharmacotherapy would be patients in the chronic phase of critical illness characterized by a moderate encephalopathy (GCS 13–14), a moderate circulatory failure (norepinephrine requirement <1 μg/kg min), a moderate respiratory failure (e.g., weaning while being on MV), and by the need of a prolonged TPN. Such patients usually require intensive care but mortality will be low.

We feel it would not be justified to speak out fully against the use of parenteral glutamine pharmacotherapy. This view was based on three aspects:

(i) numerous physiologic and pathophysiologic findings favoring a glutamine pharmacotherapy
(ii) a review from 2017 which aggregates all previously published meta-analyses [366]
(iii) no adverse effects were observed when glutamine was given exclusively via the parenteral route using the recommended intake (0.3–0.5 g/kg and day, maximum intake = 30% of the total amino acid intake).

8.4.3. Enteral arginine pharmacotherapy

Question Should enteral arginine be part of a pharmacotherapy in MNT?

Recommendation 49:

An enteral arginine pharmacotherapy should not be used.

Strong consensus (100%)

Commentary

Similar to glutamine, the basic amino acid arginine may also become a “conditionally essential” amino acid in critical illness. Again, however, it is unclear whether the reduced arginine availability is the cause or consequence of abnormal metabolic reactions observed after a severe disturbance of homeostasis [367]. Arginine enhances protein synthesis, stimulates lymphocyte mitogenesis and cytolytic activity of natural killer cells, and serves as a substrate for NO formation from molecular oxygen. Nitrogen release produces citrulline, the concentration of which presumably indicates mucosal integrity and function of the intestinal tract. A RCT which studied an enteral immunonutrition containing arginine, nucleotides and omega-3 fatty acids in septic patients showed that this particular diet actually increased mortality in patients with an APACHE score >20 [261]. Thus far, no RCT examined the usefulness of an exclusive enteral arginine pharmacotherapy; corresponding to the approach of the study by Galban et al. [261], two other RCTs provided patients with enteral arginine which was just part of an immunomodulatory “cocktail” [368,369].

Arginine may trigger negative hemodynamic effects particularly in sepsis by an increased NO availability. A very small mechanistic study (8 patients), however, could not demonstrate such a detrimental effect in patients presenting with hemodynamic shock [370]. A tracer study by Ligthart-Melis et al. [371] found that glutamine was the precursor of 70% of the arginine synthesized *de novo* in the body [372,373]. After absorption, enteral glutamine is a precursor for renal arginine synthesis.

Currently, an enteral arginine intake <30 g per day (provided together with other substrates) is considered safe in hemodynamically stable septic patients. This maximum dose also applies to parenteral administration, although only a few studies have examined effects and side effects of different parenteral dosages of arginine [367,374].

Since there are only insufficient data on the usefulness of an enteral arginine pharmacotherapy, and due to potential adverse effects on the outcome of septic patients, we speak out against such a pharmacotherapy. This recommendation is in line with corresponding recommendations of the A.S.P.E.N. and SSC guidelines (2016) [2,4].

Although there is a lack of high-quality studies to give a sufficiently detailed answer to the question, the author group considers a “Should” recommendation to be justified.

8.4.4. Parenteral branched-chain amino acid pharmacotherapy

Question: Should parenteral branched-chain amino acids be part of a pharmacotherapy in MNT?

Recommendation 50:

A parenteral branched-chain amino acid pharmacotherapy should not be used routinely.

Consensus (84%)

Commentary

Branched-chain amino acids (valine, leucine and isoleucine) are proteinogenic essential amino acids. Five older RCTs largely having a small sample size (n < 100) compared a total parenteral nutrition enriched with branched-chain amino acids, with a standard TPN [375–379]. There were no significant differences in mortality or rates of infectious complications. Due to insufficient evidence, critically ill patients should not receive amino acid solutions enriched with branched-chain amino acids.

The current S3-guideline of the DGEM in cooperation with the GESKES, the AKE, and the DGVS “*Clinical Nutrition in Gastroenterology (Part 1) – Liver*” [202], however, recommends using enteral diets and parenteral solutions enriched with branched-chain amino acids in those patients, who have an hepatic dysfunction combined with a high-grade encephalopathy (grade A recommendation, strong consensus).

8.4.5. Dosage of parenteral amino acids

Question: How much parenteral amino acids should a critically ill patient receive during parenteral nutrition?

Recommendation 51:

Amino acid intake should be controlled by individual metabolic tolerance and by protein intake/targets recommended for each phase of critical illness (section 6.3). To calculate amino acid intake from protein intake, protein intake should be multiplied by the factor 1.2.

Strong consensus (100%)

Commentary

There are no clinical data indicating a precise maximum dose for amino acid intake. By measuring changes of plasma urea concentration and nitrogen balance, some authors argue that intakes ≤3 g amino acids/kg per day would be safe [380]. On the other hand, a *post hoc* analysis of a large RCT in critically ill children suggested that even standard amounts of parenteral amino acids may already worsen clinical outcomes [135]. Furthermore, urea concentration and nitrogen balance are no established prognostic variables. Thus, we are unable to define a maximum dose for amino acid intake, especially for patients in the acute phase.

There are some clinical data helping to define a minimum dose for amino acid intake. A meta-analysis by Tian et al. [58] showed that intakes <0.65 g protein/kg ideal body weight and day in the acute phase increased the frequency of infections (compared with intakes >0.85 g protein/kg ideal body weight and day) regardless of calorie intake. However, analyzed studies did not control amino acid intake by individual substrate tolerance. When there are no clinical signs of severe substrate intolerance (section 6.2.3), average amino acid intake should not be < 1 g/kg of actual body weight and day.

To calculate (parenteral) amino acid intake, it is necessary to multiply protein intake by the factor 1.2. Based on the weight unit, solutions with free amino acids contain ~17% less protein equivalent than formed protein [124].

Although there is a lack of high-quality studies to give a sufficiently detailed answer to the question, the author group considers a "Should" recommendation to be justified. Recommendations regarding protein intakes in the different phases of critical illness are presented in section 6.3, **Recommendations 14–18**.

8.4.6. Caloric carbohydrate: amino acid ratio during parenteral nutrition

Question: Which caloric carbohydrate: amino acid ratio should be used in parenteral nutrition?

Recommendation 52a:

The caloric carbohydrate: amino acid ratio (energy percent, E–%) should not be greater than 75 E–%: 25 E–% in the acute phase.

Strong consensus (94%)

Recommendation 52b:

An exclusive parenteral amino-acid intake (without concomitant glucose intake) should be avoided unless it is used to compensate for selective losses during RRT (section 7.3).

Strong consensus (100%)

Commentary

We speak out against a carbohydrate-based parenteral nutrition (expert consensus). The caloric carbohydrate: amino acid ratio (energy percent, E–%) during parenteral nutrition should not be greater than 75 E–%: 25 E–% in the acute phase, particularly in those patients whose expected mortality is <10%, and who do not have severe organ failure.

A high carbohydrate intake may require an insulin infusion to control glucose concentration. When combined with an insufficient amino acid intake, and if the disturbance of homeostasis has not been severe, this scenario may cause an endogenous amino acid deficit resulting from insulin-induced anti-catabolic effects in skeletal muscle tissue [151,381–383].

Clinical studies could prove the existence of such a mechanism [384,385]. These studies compared a caloric carbohydrate:amino acid ratio <67 E–%: 33 E–% with an exclusive carbohydrate intake (caloric carbohydrate: amino acid ratio 100 E–%: 0 E–%). The latter regimen caused a disproportionate change of the rate of muscle protein synthesis and breakdown. This mismatch led to a pronounced deficiency of essential endogenous amino acids and – in the absence of an exogenous intake - to a subsequent decrease in the rate of hepatic protein synthesis.

There is evidence that such an amino acid deficit is of clinical relevance especially in non-muscle tissues [386], and particularly in leukocytes, in which function and antiinfectious defense mechanisms will be impaired [387].

A RCT in high risk surgical patients compared a moderately hypocaloric enteral nutrition (~15 kcal/kg per day) with a mildly hypocaloric parenteral nutrition (20 kcal/kg and day, caloric carbohydrate: amino acid ratio 75 E–%: 25 E–%) [388]. The high caloric carbohydrate: amino acid ratio was associated with an increased morbidity. Morbidity, however, was lower when the caloric carbohydrate: amino acid ratio had been 60 E–%: 40 E–% [389]. In the EPaNIC trial patients in the intervention group had a calorie intake with an approximate caloric carbohydrate:amino acid ratio of 82 E–%: 18 E–%. This unfavorable ratio (in combination with an intensive insulin therapy) may have contributed to the worse outcome in the intervention group [134,250]. A comparable mismatch between parenteral carbohydrate/amino acid intake and endogenous amino acid release may have also contributed to the negative outcomes observed in other clinical studies testing an intensive insulin therapy [390,391].

It should be noted, however, that all of the above studies only included patients with a comparatively low mortality risk (≤10%) (Table 11). In patients with a higher mortality risk and with a catabolic rate which is presumably less sensitive to insulin, high caloric carbohydrate: amino acid ratios are presumably less detrimental [251] (Table 11).

Mechanistic studies conducted in the recovery phase indicate that an exclusive parenteral amino acid intake is not beneficial because anti-catabolic effects will be minimal, and associated with a higher risk for an amino acid excess (due to the persisting release of endogenous amino acids) [392,393].

Although there is a lack of high-quality studies to give a sufficiently detailed answer to the question, especially for the target group, the author group considers a "Should" recommendation to be justified.

9. Micronutrient intake

9.1. Daily needs

Question: Should a patient receive micronutrients during enteral nutrition?

Table 11
Controlled studies on the effect of the parenteral caloric carbohydrate: amino acid ratio on clinical outcomes of critically ill patients.

Author	Number of patients	Patients	Design	Calorie intake during the acute phase	Parenteral caloric carbohydrate: amino acid ratio	Effect on ICU-/hospital length of stay	Effect on Morbidity	Effect on Mortality
Casaer et al., 2011 [250]	4640	Mainly cardiac surgery ICU patients (mortality ≈ 10%)	SPN for 7 days *vs.* volitional/ enteral	22 *vs.* 13 kcal/kg and day	4.5:1	↑	↑	Ø
Van Barneveld et al., 2016 [388]	123	Postoperative, rectal cancer (advanced/recurrent) (mortality 0%)	PN *vs.* EN for 5 days	20 *vs.* 15 kcal/kg and day	3:1	Ø	↑ (Anastomotic leakage)	Ø
Doig et al., 2013 [251]	1372	ICU patients with contraindication for EN (mortality ≈22%)	SPN for 7 days *vs.* standard therapy	15 *vs.* 11 kcal/kg and day	2.8:1	Ø	Ø	Ø
Perinel J et al., 2016 [389]	204	Postoperative, pancreatic cancer (mortality ≈10%)	PN *vs.* EN for 10 days	26 *vs.* 15 kcal/kg and day	1.5:1	Ø	↓ (Pancreatic fistulae)	↓

Ø: no difference; ↑: increased or extended; ↓: decreased; EN: enteral nutrition; ICU: intensive care unit; PN: parenteral nutrition; SPN: supplemental parenteral nutrition.

Recommendation 53:

A patient should receive vitamins and trace elements, if enteral nutrition cannot meet daily needs, and if supplemental parenteral nutrition is required to ensure the desired calorie and protein intake according to the disease phase and individual metabolic tolerance.

Strong consensus (100%)

Commentary

The amount of vitamins and trace elements contained in standard enteral formulas meets recommended daily needs, when a patient's daily intake is $\geq$ 750 mL (2 kcal/mL) or $\geq$ 1500 mL (1 kcal/mL). Therefore, during step-up of enteral calorie intake in the acute phase, clinicians should give additional vitamins and trace elements starting with the beginning of MNT and ending on that day on which a patient tolerates the minimum enteral intake stated above.

Reference values for daily needs of healthy adult subjects have been published by German–Austrian–Swiss (D–A–CH) Nutrition Societies [394] and WHO [395], respectively.

Although there is a lack of high-quality studies to give a sufficiently detailed answer to the question, especially for the target group, the author group considers a "Should" recommendation to be justified.

Question: Should a patient receive micronutrients during parenteral nutrition?

Recommendation 54:

During partial, exclusive or total parenteral nutrition, patients shall always receive vitamins and trace elements.

Strong consensus (100%)

Commentary

For adult critically ill patients, daily parenteral need of vitamins and trace elements follows recommendations made for healthy, non-malnourished adults [396]; because of a lack of data, there are no consistent recommendations valid for the target group of this guideline. Quantitative differences exist between recommendations made by North American institutions ("FDA Requirements for Marketing") [397] and by nutrition societies of German speaking countries [394]. The latter societies proposed a higher daily parenteral need assuming that the hyper-metabolic state (trauma, sepsis) increases the requirement for vitamins and trace elements [396]. Requirement may increase further in burns patients because of exudative losses from open wounds [398], and in patients during mechanical RRT. For the latter patients, the S1 guideline of the DGEM [144] recommends providing daily twice as much parenteral water-soluble vitamins as in patients not requiring a RRT.

It should be noted that some commercially available combination products do not contain vitamin K (cofactor for the synthesis of coagulation factors II, VII, IX and X [prothrombin complex], and for protein C and S). When such products are used, patients should receive vitamin K separately depending on the targets of the anticoagulation therapy. Many vitamins are sensitive to light and oxygen. Therefore, users should protect vitamin preparations from light, and should keep administration times short (30–60 min) [396]. For technical reasons, small amounts of vitamin K are also contained in fat emulsions. Even TPN, however, cannot entirely meet daily vitamin K needs; consequently, provisioning of vitamin K shall be a part of TPN.

Although there is a lack of high-quality studies to give a sufficiently detailed answer to the question, especially for the target group, the author group considers a "shall" recommendation to be justified.

9.2. Pharmacotherapy

The author group defines a high-dose enteral or parenteral administration of vitamins and trace elements as pharmacotherapy characterized by an intake, which is higher than that recommended for covering daily needs of healthy adults (section 9.1). Baseline intake shall prevent a micronutrient deficiency or its aggravation, respectively; pharmacotherapy with these micronutrients, however, tries to reduce oxidative stress, improve immunologic competence, and prevent organ dysfunction, respectively [399].

9.2.1. Selenium

Question: Should patients receive a pharmacotherapy with selenium?

Recommendation 55:

Patients shall not receive a pharmacotherapy with selenium.

Strong consensus (93.75%)

Commentary

Selenium is an essential trace element required as a cofactor by > 25 seleno-proteins which are involved in immune and endocrine pathways mostly stimulating antioxidant reactions. Selenium-containing enzymes (including glutathione-peroxidase) are part of the body's antioxidant protection system responsible for the neutralization of oxygen and nitrogen radicals at the cellular level. Selenium concentrations in plasma correlate inversely with severity of sepsis and clinical outcome of septic patients [400,401]. Because of selenium's high biologic importance, numerous scientists widely promoted a corresponding pharmacotherapy in recent years, and several RCTs were conducted in critically ill patients to establish beneficial effects. These RCTs administered selenium via the enteral or parenteral route using a monotherapy or a combination therapy including other micronutrients.

The multicenter selenium in Intensive Care (SIC) RCT randomized 249 patients with severe sepsis/septic shock, and compared a parenteral administration of 2000 μg sodium selenite (given on day 1) + 1000 μg per day during the next 14 days, with placebo [402]. Compared to placebo, this pharmacotherapy increased whole blood selenium concentration and glutathione peroxidase activity significantly. Still, the intention-to-treat analysis could not demonstrate a significant effect on the primary outcome (28-day mortality) or on secondary outcomes. Only the per-protocol analysis (n = 189) showed that selenium significantly reduced 28-day mortality (odds ratio (OR) 0.56, 95%CI 0.32–1.00, P = 0.049). A subgroup analysis suggested that patients presenting with an APACHE III score >102 and with failure of $\geq$3 organs may benefit the most from a pharmacotherapy with selenium.

A RCT by Forceville et al. [403] examined the effect of a parenteral pharmacotherapy with selenium in 60 patients with severe sepsis. The authors gave 4000 μg sodium selenite on the first day of the study followed by 1000 μg per day for $\leq$9 days. Pharmacotherapy with selenium did not affect any of the outcomes (extent of septic shock, mortality, ICU LOS and frequency of adverse events). Another RCT included only 35 septic patients, but provided patients with more selenium during the acute phase (2000 μg/2 h bolus on day 1 of the study followed by a continuous infusion of 1600 μg per day until day 10). This pharmacotherapy significantly reduced SOFA scores and the frequency of VAPs [404].

The SIGNET study did not give a bolus, but administered 500 μg of parenteral sodium selenite daily. The intention-to-treat analysis could not detect a selenium effect on the frequency of infectious complications, 6-month mortality or on other clinical outcomes, such as the SOFA score and ICU LOS. Selenium, however, reduced the frequency of infectious complications in those patients who had received selenium for more than 5 days [351]. The REDOXS trial administered 500 μg of parenteral sodium selenite and 300 μg of enteral sodium selenite per day in patients with multiple-organ failure (without initially giving a bolus, but combining enteral selenium with other enteral antioxidants); the study showed no benefit in terms of patient outcomes [347].

Two meta-analyses published in 2013 found that a parenteral, exclusive pharmacotherapy with selenium reduced the mortality of

severely septic patients [405,406]. The authors identified beneficial effects particularly in those patients who had initially received a selenium bolus, and whose daily selenium dose had been ≥1000 μg for more than seven days.

An updated Cochrane analysis published in 2015 included 16 RCTs (2084 critically ill patients); 13 studies demonstrated a beneficial effect of selenium (sodium selenite or organic selenium), but simultaneously had a high risk for a bias [407]. Selenium did not affect infection rates, duration of MV and ICU LOS.

The SISPCT study was published in 2016, and tested a pharmacotherapy with selenium in 1089 septic patients (1000 μg/30 min bolus on day 1 of the study followed by a continuous infusion of 1000 μg per day, maximum therapy duration was 21 days) (2 × 2 factorial trial). Even this prolonged pharmacotherapy affected neither primary outcome (28-day mortality) nor secondary clinical outcomes [408]. Interestingly, however, less patients in the selenium group needed a RRT, and their hospital LOS was shorter. On the contrary, pharmacotherapy with selenium increased mortality in those patients whose antibiotic therapy had not been controlled by procalcitonin concentrations.

An updated meta-analysis (21 RCTs, 4044 patients) by Manzanares et al. showed that, overall, a selenium pharmacotherapy had no effect on mortality or morbidity (including infection rate) irrespective of the selenium dose [409]. In non-septic patients, however, selenium pharmacotherapy significantly lowered the rate of nosocomial infections. This subgroup, however, included all patients of the REDOXS trial in which 60% of the patients had been suffering from sepsis thereby fulfilling the inclusion criterion "shock". Consequently, a large portion of patients in the above, non-septic subgroup was in fact septic contradicting the selection criterion "non-septic". Consequently, results of this subgroup analysis neither support nor deny the usefulness of a selenium pharmacotherapy in non-septic patients.

The A.S.P.E.N. guideline, which analyzed studies published before 2014, could not make a recommendation on the usefulness of a selenium pharmacotherapy in sepsis due to conflicting studies (Recommendation N3, moderate quality of evidence) [2]. In its own meta-analysis (9 RCTs), A.S.P.E.N. found no therapeutic benefit for a pharmacotherapy including selenium, zinc or antioxidants; A.S.P.E.N., however, did not perform subgroup analyses. The SSC guideline [4] recommended that patients with sepsis/septic shock should not receive a selenium pharmacotherapy due to a lack of therapeutic benefit (strong recommendation, moderate quality of evidence). SSC based the recommendation on the results of its own meta-analysis evaluating 10 RCTs (including the SISPCT trial). Again, this meta-analysis did not differentiate between subgroups.

Conclusion

In light of the available evidence, the author group considers a "Shall not" recommendation to be justified.

9.2.2. Zinc, alpha tocopherol, and vitamins A, C and D

Question: Should patients receive a pharmacotherapy with zinc, alpha-tocopherol, vitamins A and C, or with a combination of those?

Recommendation 56a:

Patients should not receive routinely a pharmacotherapy with zinc, alpha-tocopherol, vitamins A and C, or with a combination of those.

Strong consensus (93.75%)

Recommendation 56b:

Patients may receive a pharmacotherapy with vitamin D, when they have a severe vitamin D deficiency (25 [OH] D ≤ 30 nmol/L corresponding to ≤12 ng/mL).

Consensus (81.25%)

Commentary

9.2.2.1. Zinc. Critically ill patients commonly demonstrate reduced plasma levels of zinc [410]. Plasma Zinc concentrations are lower in septic than in non-septic patients. It is unclear whether low Zinc concentrations are indicative of an acute-phase response, a relative Zinc deficit, or a limited availability. Besides altering zinc plasma concentrations, critical illness may also affect serum zinc-binding capacity, which decreases in septic patients; simultaneously, concentrations of free intracellular Zinc in immune cells are low. Apparently, however, the Zinc surplus resulting from the reduced serum zinc-binding capacity cannot counter the low intracellular concentrations thereby contributing to an immune dysfunction. Possibly, zinc redistribution is part of an exaggerated secondary reaction, and a Zinc pharmacotherapy, which is adjusted to the individual zinc-binding capacity, may help critically ill septic patients to improve their immune status.

A pilot RCT of 56 critically ill patients suggested benefits of a zinc pharmacotherapy in terms of reducing immunosuppression and prevention of secondary infections [411]. A small meta-analysis (four RCTs, 140 patients), however, could not demonstrate that a Zinc pharmacotherapy reduced mortality or shortened ICU LOS of critically ill patients [412]. Hence, benefits of a zinc pharmacotherapy remain uncertain.

9.2.2.2. Alpha-tocopherol. TPN routinely provides patients with certain amounts of alpha-tocopherol of which the concentration, however, varies between 16 and 505 mmol/L in individual fat emulsions depending on storage time and type of lipid; addition of alpha-tocopherol to fat emulsions shall counteract the risk of of long-chain fatty acid peroxidation [413]. Alpha-tocopherol concentrations may decrease in patients with ARDS [414] and with septic shock [415], and a parenteral alpha-tocopherol pharmacotherapy may normalize these abnormal concentrations [416,417]. Clinical efficacy is controversial. Bartels et al. [416] showed that a parenteral administration of 3 × 600 IU alpha-tocopherol daily before a hepatic operation shortened postoperative ICU LOS (but not HLOS). Lassnigg et al. [417] combined a pre-with a post-operative pharmacotherapy, which, however, did not improve clinical outcomes after cardiac operation.

9.2.2.3. Vitamin C. Vitamin C (ascorbic acid) possesses several pleiotropic functions; potential benefits include direct, non-enzymatic effects (scavenging of free radicals), anti-inflammatory effects and protective effects on endothelial function; ascorbic acid is a cofactor for the biosynthesis of various molecules (collagen, norepinephrine) and may facilitate adrenal cortisol secretion [409,418]. Independent from the type of disturbance of homeostasis, the majority of critically ill patients demonstrate an increased metabolic clearance of vitamin C causing a reduction of plasma vitamin C concentrations [419]. Several concepts are available to perform a vitamin C pharmacotherapy in critically ill patients, but they vary depending on whether ascorbic acid concentration is known [420] or unknown [421].

Only a few small RCTs could demonstrate benefits related to an exclusive vitamin C pharmacotherapy. In patients with sepsis and organ failure, an ascorbic acid pharmacotherapy (50 mg/kg per day) reduced SOFA scores and 28-day mortality without affecting ICU LOS [422]. Correspondingly, Zabet et al. showed that a more intensive parenteral ascorbic acid pharmacotherapy (4 × 25 mg/kg per day for 72 h) decreased catecholamine requirement in patients with septic shock [423]. A retrospective analysis of 40 burns patients found that a parenteral administration of ascorbic acid (66 mg/kg per day) was associated with reduced fluid needs and increased diuresis [424]. A RCT gave 2 g of oral ascorbic acid before

and 1 g after operation to 209 cardiac surgery patients. This pharmacotherapy did not alter ICU LOS, but shortened hospital LOS by two days [425]. A meta-analysis by Hu et al. evaluated eight RCT (1060 cardiac surgery patients) [426] and found that perioperative oral administration of ascorbic acid decreased the risk of atrial fibrillation.

A few monocentric RCTs tested an ascorbic acid pharmacotherapy together with the application of other antioxidants. Nathens et al. [427] showed that a pharmacotherapy combining parenteral ascorbic acid (3 × 1 g, i.v.) with enteral alpha-tocopherol (3 × 1000 IU) reduced the frequency of a severe multiple-organ failure and shortened ICU LOS. A retrospective observational before/after study examined the potential benefits of one week of an enteral−parenteral pharmacotherapy, which combined ascorbic acid (3 × 1 g) with alpha-tocopherol (3 × 1000 IU) and selenium (1 × 200 μg) in several thousand patients after a severe trauma injury. Implementation of this pharmacotherapy was associated with reduced mortality [429], rates of abdominal compartment syndromes, and duration of MV [428].

The REDOXS trial, however, could not confirm these benefits. This trial randomized 1200 critically ill patients with ≥2 organ dysfunctions (section 8.4.2.); in the antioxidant study arm patients received 500 μg of parenteral and 300 μg of enteral selenium, combined with 20 mg of enteral zinc, 10 mg of beta-carotene, 500 mg of alpha-tocopherol and 1500 mg of ascorbic acid. This combined pharmacotherapy did not alter 28-day mortality or other clinical outcomes [347].

Marik et al. conducted a retrospective before-after study in 94 patients with sepsis or septic shock [430]. The study found that there was an association between a 4-day parenteral application of vitamin C (1.5 g every 6 h) together with hydrocortisone and thiamine, and a reduced catecholamine need, SOFA score, and hospital mortality. It is unclear which of the individual compounds was responsible for the association, or whether just the combination of different compounds was important for this observation. Due to the design of the study, however, results are only hypothesis generating and await confirmation by larger RCTs.

9.2.2.4. Vitamin A. Vitamin A is the general term for fat-soluble retinoids and carotenoids. Alpha-, beta- and gamma-carotene are retinol precursors, of which beta-carotene is the most important. Reduced concentrations of retinol were identified in 65% of critically ill patients, and that of beta-carotene in 73% [431]. Goode et al. [415] measured plasma concentrations of retinol and beta-carotene in 16 patients with severe sepsis or septic shock (Sepsis-1 definition). The mean plasma retinol concentration was 26.5 ± 19.3 μg/dL compared with 73.5 ± 18.3 μg/dL in healthy subjects. Additionally, 13 (81%) patients had retinol values below the lower limit of the reference range (<37.0 μg/dL). Plasma beta-carotene concentrations were undetectable (<15 μg/L) in eight (50%) patients, and below the reference range in the remaining patients. Perioperative pharmacotherapy providing 5000 IU of enteral retinol per day for 21 days shortened ICU LOS and reduced mortality in a small monocentric study in cardiac surgery patients [432].

9.2.2.5. Vitamin D. The prevalence of vitamin D deficiency in healthy Europeans is about 40% [434]. A prospective observational study in Australia showed that vitamin D insufficiency (25 nmol/L ≤ 25-OH-D ≤ 50 nmol/L) and deficiency (25-OH-D < 25 nmol/L) occurs in 54 and 24% of critically ill patients, respectively, and is accompanied by reduced 1,25-dihydroxy vitamin D concentrations and protein binding to vitamin D [433,438]. Similar results were obtained in patients with severe sepsis or septic shock (Sepsis-1 definition) [440]. Mortality and the risk of bacteremia correlate inversely with 25-OH-D concentrations measured at or before hospital admission [435−437]. In 610 patients with severe sepsis or septic shock (Sepsis-1 definition), however, no such correlation could be found [440].

A pharmacotherapy providing 250,000 IU or 500,000 IU of enteral vitamin D per day shortened HLOS in 31 mechanically ventilated patients [439]. A large RCT ("VitDal-ICU" study, 492 critically ill adult white patients with vitamin D deficiency) gave oral/enteral vitamin D3 or placebo once at a dose of 540,000 IU followed by monthly maintenance doses of 90,000 IU for 5 months. Vitamin D pharmacotherapy did not reduce hospital length of stay, hospital mortality, or 6-month mortality. Lower hospital mortality was observed in the severe vitamin D deficiency subgroup (25-OH-D ≤12 ng/mL), but this finding should be considered hypothesis generating [441].

Recent meta-analyses by Langlois et al. and Weng et al. could not identify a survival benefit or other clinical benefits of a vitamin D pharmacotherapy given to critically ill patients [442,443], whereas the meta-analysis by Putzu et al. (seven studies, 716 critically ill patients) did identify such benefits [445]. Results of the latter meta-analysis, however, are biased because vitamin D doses of the analyzed studies varied widely, and the analysis combined many small studies significantly increasing the risk of a systematic overestimation of the effect. The meta-analysis by Weng et al. was criticized for not including all available published trials and for not pooling effect estimates with different follow-up, thereby losing the precision and information size of the effect estimate [444].

Conclusion

Due to conflicting studies, the A.S.P.E.N. guideline could not make a recommendation regarding a pharmacotherapy providing selenium, zinc and antioxidants to septic patients (Recommendation N3, moderate quality of evidence) [2]. A.S.P.E.N., however, suggested that a combination of antioxidant vitamins and trace minerals in doses reported to be safe in critically ill patients be provided to those patients who require a specific MNT (Recommendation F3, low quality of evidence). A meta-analysis conducted by A.S.P.E.N. (15 studies, 586 patients) demonstrated that a combination of vitamins and trace elements reduced mortality, but left unchanged ICU LOS and morbidity (infection rate and duration of MV) [2].

The A.S.P.E.N. author group criticizes in its commentary that dose, route and duration of micronutrient pharmacotherapy is not sufficiently standardized. For micronutrients zinc, alpha-tocopherol, or vitamins A, and C, the current evidence is insufficient to make recommendations in favor of a (high-dose) pharmacotherapy that exceeds the doses recommended to cover the daily needs of healthy individuals as outlined in section 9.1.

Clinicians may use a vitamin D pharmacotherapy to normalize concentrations in patients presenting with a severe vitamin D deficiency (25-OH-D ≤30 nmol/L, corresponding to ≤12 ng/mL). Since there is no evidence of adverse effects, critically ill patients may receive up to 10,000 IU of enteral or parenteral vitamin D per day [446].

9.2.3. Thiamine (vitamin B1)

Question: Should patients receive a pharmacotherapy with thiamine?

Recommendation 57:

Patients may receive a pharmacotherapy with thiamine, when there is clinical evidence of thiamine deficiency (e.g., in patients having a history of chronic alcohol abuse).

Strong consensus (100%)

Commentary

Thiamine is a precursor of thiamine pyrophosphate; it is an essential coenzyme of several decarboxylases involved in energy producing pathways of glucose metabolism. Thiamine deficiency (defined as a whole blood thiamine concentration < 71−185 nmol/L, or < 24−62.5 mg/L, or by a reduced erythrocyte transketolase

activity) is common in patients suffering from chronic alcohol abuse [447]. Thiamine deficiency can lead to congestive heart failure, neurologic symptoms (wet or dry Beriberi, Wernicke's encephalopathy) and lactic acidosis [448]. In a bicentric RCT in 88 patients with septic shock, a pharmacotherapy with thiamine (2 × 200 mg of parenteral thiamin per day) reduced lactate concentrations and possibly improved survival in a subgroup of patients with established thiamine deficiency [449]. Apart from anaphylactic reactions, thiamine does not cause acute, toxic adverse reactions.

Exact dose and duration of a thiamine pharmacotherapy is unclear. A systematic review suggested that a short-term thiamine pharmacotherapy (3 × 200–500 mg of parenteral thiamin, given on the first day of intensive care) be provided to critically ill patients having a history of chronic alcohol abuse and/or clinical evidence of thiamine deficiency (encephalopathy) [450]. Two review articles recommended that patients having clinical evidence of a thiamine deficiency should receive 100–300 mg of parenteral thiamine per day for the first three days after ICU admission [446,448]. Pharmacotherapy in the absence of thiamine deficiency does not appear to be beneficial as demonstrated by the RCT by Donnino et al. [449].

10. Monitoring

Monitoring and control of calorie and protein intake by individual metabolic tolerance is addressed in section 6.2.2, **Recommendations 9b and 9c**, in section 6.2.3, and in section 6.3.2, **Recommendation 14c**. Fig. 3 and 4 show a practice-oriented concept for the individual control of substrate intake according to maximum daily insulin requirements and phosphate concentration. To monitor specific aspects of MNT in critically ill patients, readers may consult the S3 guideline *"Monitoring of Artificial Nutrition: Specific Aspects"* of the DGEM, GESKES and AKE [110]. The author group considers the recommendations made in this S3 guideline still valid, since an updated literature search did not reveal a need for modification.

11. Specific patient groups

11.1. Preliminary remarks

Individual sections of this guideline focused on specific aspects of MNT in critically ill patients presenting with malnutrition or receiving mechanical RRT. With regard to organ-specific aspects of MNT in critical care, readers may consult specific, current S3 guidelines of the DGEM (www.dgem.de/leitlinien).

In the following sections, we address specific aspects of MNT in obese critically ill patients and in patients needing extracorporeal techniques for cardiac or pulmonary support, respectively, or mechanical cardiac assist devices. The author group found it useful to make specific recommendations for the latter patient subgroups because of the increasing use of extracorporeal support techniques.

Due to the paucity of data, however, the author group felt that it would not be expedient to make separate recommendations for critically ill patients with pre-existing diabetes mellitus, burns or after a severe trauma injury. This opinion differed from that of other medical societies.

For example, the current guidelines of the International Society for Burn Injuries (ISBI) [451] and of ESPEN [398] recommend that calculation of energy needs in burn patients should consider the percentage of burned body surface area, when indirect calorimetry is unavailable. Furthermore, protein intake should be significantly higher in burn patients (up to 3 g/kg and day) than in other critically ill patients.

However, there is no large RCT suggesting that control of MNT according to such specific equations would improve clinical outcomes in this specific patient group. The recommendations on protein intake in burns are based on two very old RCTs, which showed that a high protein intake improved nitrogen balance in 36 adult burn patients [452], and mortality in 18 children [453]. The A.S.P.E.N. guideline [2] suggests - in line with their recommendations for non-burn patients - early enteral nutrition in burns patients (Recommendations M4a, b and d, expert consensus). In recommendation M4c (expert consensus), the A.S.P.E.N. guideline also suggests that patients with burn injury should receive protein in the range of 1.5–2 g/kg and day. As rationale, however, A.S.P.E.N., only quotes one pathophysiological study published in 1983, which included six patients in the chronic phase after acute burn injury [139]; otherwise, the guideline just refers to the above-mentioned ESPEN guideline [398].

We considered the scientific evidence and the rationale given by the aforementioned guidelines of ESPEN and A.S.P.E.N. insufficient to make specific recommendations for these specific patient groups.

11.2. Obesity/bariatric surgery

With the exception of the recommendations made below, recommendations (and their differences to the recommendations of

Table 12
Studies on hypocaloric, high-protein MNT in obese critically ill patients.

Author	Number of patients	Design	Body weight	Characteristics of patients	Route of nutrient delivery	Nutritional regimen	Results
Choban et al., 1997 [456]	16 *vs.* 14	Prospective randomized	BMI 35	Postoperative: fistulae; trauma (13 critically ill patients, 17 non-critically ill patients)	Parenteral	2 g amino acids/kg IBW and day + 11 *vs.* 21 kcal carbohydrate + fat/kg actual BW and day	N balance comparable
Burge et al., 1994 [455]	9 *vs.* 7	Prospective randomized	BMI 34	Postoperative: Fistulae/ enteritis/pancreatitis	Parenteral	2 g amino acids/kg IBW and day +50% *vs.* 100% of measured energy expenditure (15 *vs.* 30 kcal carbohydrates + fat/kg IBW and day)	N balance comparable
Dickerson et al., 1986 [461]	13	Prospective observational	208% IBW	Postoperative: Fistulae/ abscess/anastomotic leakage	Parenteral	2 g amino acids/kg IBW and day + 50% measured energy expenditure (14 kcal carbohydrates/kg IBW and day)	N equilibrium, complete recovery
Dickerson et al., 2002 [457]	40	Retrospective observational	BMI 38	Surgical ICU patients	Enteral	18 vs 25 kcal/kg adapted BW and day (of which 2 g protein/kg IBW and day) (28 *vs.* 12 patients)	N balance comparable, hypocaloric group: shorter ICU LOS, reduced duration of antimicrobial therapy

BMI: Body Mass Index; BW: body weight; IBW: ideal body weight; ICU: intensive care unit; LOS: length of stay; N: nitrogen.

other societies, e.g., A.S.P.E.N. [2]) concerning critically ill obese patients (including those after a bariatric procedure) are the same as those made above for non-obese critically ill patients.

Question: How should critically ill obese patients be fed?

Recommendation 58:

Critically ill obese patients (BMI $\geq$30 kg/m^2) should receive a hypocaloric diet ensuring a high protein intake.

Strong consensus (91%)

Commentary

Hypocaloric MNT including a high protein intake is intended to minimize muscle catabolism while avoiding metabolic side effects and improving insulin resistance. In theory, secondary acceleration of endogenous fat oxidation should reduce body fat mass and replace protein as source of energy thereby saving body protein [454]. This hypothesis, however, was only studied by two small RCTs (n = 16 and n = 33) and by two small retrospective/prospective observational studies (n = 13 and n = 40) in critically and non-critically ill patients (Table 12). The two RCTs [455,456], both published by the same scientist, suggested that such a hypocaloric high-protein diet (providing 50% of the measured energy expenditure) was as affective as a standard eucaloric diet in terms of sparing nitrogen.

Observational studies could not identify metabolic or clinical disadvantages of such a hypocaloric high-protein MNT. A retrospective study of 40 critically ill obese patients compared a hypocaloric, high-protein diet (providing 2 g protein/kg ideal body weight and day) with a eucaloric standard diet (18 *vs*. 25 kcal/kg adapted body weight and day) [adapted body weight = (actual body weight − ideal body weight) × 0.25 + ideal body weight] [457]. In the unadjusted analysis, patients receiving the hypocaloric, high-protein diet had a significantly shorter ICU LOS and duration of MV, and more antibiotic-free days (Table 12).

A large multicenter observational study that did not explicitly test a hypocaloric, high-protein MNT found for patients with BMI >35 kg/m^2 that protein intake correlated inversely with mortality and duration of MV [96]. Although there are no large RCTs, the current A.S.P.E.N. guideline [2] suggests that high-protein hypocaloric feeding be implemented in the care of obese ICU patients (Recommendation Q4, expert consensus). This recommendation was based on recommendations made by the preceding A.S.P.E.N. guideline (2013) [458], and on results of the above observational study by Alberda et al. [96]. Recommendations of the 2013 A.S.P.E.N. guideline (low quality of evidence) were based on six studies. One of them was a trial just comparing older with younger obese critically ill patients (MNT was identical); another study just included non-critically ill obese patients after bariatric operations. Results of the study by Alberda et al. [96] were biased due to the observational study design, and were, at the very most, hypothesis generating (section 2.4.2).

Despite significant uncertainties, the majority of experts believe that a hypocaloric, high-protein diet increases insulin sensitivity, improves glycemic control, ameliorates protein catabolism and reduces loss of lean body mass [459,460].

Although there is a lack of high-quality studies to give a sufficiently detailed answer to the question, the author group considers a “Should” recommendation to be justified.

Question:

Which method should be used to determine energy expenditure in obese critically ill patients?

Recommendation 59a:

Indirect calorimetry should be used to determine the energy expenditure in obese critically ill patients (BMI $\geq$30 kg/m^2).

Strong consensus (100%)

Question:

What is the calorie target of obese critically ill patients?

Recommendation 59b:

The calorie target should be at 60% of the measured energy expenditure.

Strong consensus (100%)

Recommendation 60:

When calorimetry is unavailable, calorie target of obese critically ill patients (BMI $\geq$30 kg/m^2) should be estimated at 11–14 kcal/kg *actual* body weight and day (BMI 30–50 kg/m^2), or at 22–25 kcal/kg *ideal* body weight and day (BMI >50 kg/m^2).

Strong consensus (100%)

Commentary

Indirect calorimetry should be used to determine the energy expenditure in obese critically ill patients **Recommendation 5a**, section 6.1 for non-obese patients). When calorimetry is unavailable, energy expenditure of obese critically ill patients can be estimated using body weight-based equations. Reference for these equations is the *actual* body weight for patients with BMI 30–50 kg/m^2, and *ideal* body weight for patients with BMI >50 kg/m^2.

The rationale for these recommendations is a study by Mogensen et al. [462] who showed that approximation of energy expenditure in obese critically ill patients was possible by using these weight references. The “ideal body weight” is referred to a normal BMI of 22, and is defined as: ideal body weight (kg) = 48.4 + 77.0 × (height − 1.50 m) [122].

These recommendations are consistent with the current recommendations of the 2016 A.S.P.E.N. guideline (Recommendation Q5, expert consensus) [2]. Since A.S.P.E.N. and the study by Mogensen et al. [462] both refer to the ideal body weight for patients with BMI >50 kg/m^2, no other reference weight is recommended for this patient subgroup.

The calorie target respects the idea of a hypocaloric high-protein MNT for obese critically ill patients (**Recommendation 58**) and should be at 60% of the measured energy expenditure (in non-obese critically ill patients, it is at 100% of the energy expenditure).

When using body weight-based equations, and for patients with BMI 30–50 kg/m^2, 11–14 kcal/*actual* body weight and day (i.e. the caloric target) correspond to 60–70% of measured energy expenditure. For patients with BMI >50 kg/m^2, 60–70% of measured energy expenditure correspond to 22–25 kcal/*ideal* body weight and day. The rationale for these recommendations is again the study by Mogensen et al. [462]. Individual calorie intake (% of the target), however, depends on the phase of the disease and on individual metabolic tolerance (section 6.2.3 for non-obese critically ill patients).

The 2016 A.S.P.E.N. guideline recommends that for all classes of obesity, the target of the EN regimen should not exceed 65–70% of energy expenditure (Recommendation Q5, expert consensus) [2]. A similar recommendation was made by the 2013 A.S.P.E.N. guideline “*Nutrition Support of Hospitalized Adult Patients with Obesity*” [458] which also states that - when indirect calorimetry is unavailable - formulas to calculate 60% of energy expenditure may use the actual body weight (14 kcal/kg actual weight and day) for all obese patients.

Although there is a lack of high-quality studies to answer the question in detail, the author group considers a “Should” recommendation to be justified (**Recommendations 59a and 59b**).

Question: How is the protein target defined in obese critically ill patients?

Recommendation 61:

Usually, in obese critically ill patients (BMI $\geq$30 kg/m^2) the target of protein or amino acid intake in the acute phase should be at 1.5 g protein (or at 1.8 g amino acids)/kg *ideal* body weight and day.

Strong consensus (94%)

Commentary

In obese critically ill patients, the protein target should be at 1.5 g/kg ideal body weight and day respecting the idea of a hypocaloric high-protein MNT (**Recommendation 58**). The ideal body weight (kg) is defined by: 48.4 + 77.0 × (height − 1.50 m) [122]. Individual protein intake (% of target), however, depends on the phase of the disease and on individual metabolic tolerance (section 6.3.2 for non-obese critically ill patients).

A single member of the author group did not share the majority opinion expressed in **Recommendations 61**. A therapeutic alternative pushed forward by this member was to refer protein intake to the measured or estimated lean body mass (instead of referring it to ideal body weight). The majority of the members of the author group did not accepted this therapeutic alternative, which was only based on data from healthy volunteers [121], and which would have required complex adjustments to age and gender. Therefore, we did not include this alternative as a recommendation.

Our recommendations on protein intake in obese critically ill patients differ significantly from that made by the current A.S.P.E.N. guideline [2]. A.S.P.E.N. suggested that protein should be provided in a range from 2.0 g/kg ideal body weight and day for patients with BMI 30–40 kg/m^2 up to 2.5 g/kg ideal body weight and day for patients with BMI ≥40 kg/m^2 (Recommendation Q5, expert consensus). Rationale for this recommendation was an observational study and two small RCTs; one of them, however, only compared older with younger obese critically ill patients (but not different protein intakes), whereas the other had a questionable outcome variable (nitrogen balance). The recommendation on protein intake of the current A.S.P.E.N. guideline also differs from the corresponding recommendation in the 2013 A.S.P.E.N. guideline "*Nutrition Support of Hospitalized Adult Patients with Obesity*" [458]. In this older guideline, A.S.P.E.N. recommended that critically ill obese patients should have a daily protein intake of 1.2 g/kg actual body weight or of 2–2.5 g/kg ideal body weight; the exact level of protein intake should be controlled by nitrogen balance. In current guideline, however, A.S.P.E.N. did not report the reasons why they changed the contents of this older recommendation.

It was the opinion of the author group that the aggressive protein intake advocated by the A.S.P.E.N. guideline for obese critically ill patients was just as open to criticism as were corresponding recommendations for non-obese critically ill patients (section 6.3.2). Evidence regarding benefits or harms of protein intake in the acute phase of critical illness is still weak, and is even weaker for obese critically ill patients. For those patients, no study has tested effects of different protein intakes on clinical outcomes yet (Table 12).

Administration of high amounts of protein/amino acids is not possible by using commercially available products. In clinical practice, clinicians must add specific enteral and parenteral supplements (protein or amino acid concentrates) to standard MNT.

Although there is a lack of high-quality studies to to give a sufficiently detailed answer to the question in detail, the author group considers a "Should" recommendation to be justified.

Question: How much parenteral glucose or fat should an obese critically ill patient receive?

Recommendation 62a:

Glucose is the preferred carbohydrate, and intake should respect primarily the 60% calorie target, the phase of the disease and individual metabolic tolerance.

Strong consensus (97%)

Recommendation 62b:

Fat intake should respect primarily the 60% calorie target, the phase of the disease and individual metabolic tolerance. Linoleic acid and alpha-linolenic acid content of the individual fat emulsion should also control parenteral fat intake.

Strong consensus (93%)

Commentary

We recommend, based on expert consensus, that obese critically ill patients should have a maximum intake of 2.5 g glucose/kg actual body weight and day when BMI is 30–50 kg/m^2, and a maximum intake of 5 g glucose/kg ideal body weight and day when BMI is > 50 kg/m^2 respecting the hypocaloric nature of the diet.

Basis for the weight-adjusted maxima of glucose intake were the maxima recommended for non-obese critically ill patients (sections 6.1 and 8.2.2). We transformed the latter maxima by adjusting them to the maximum of calorie intake recommended for obese critically ill patients (11–14 kcal/kg actual body weight and day, when BMI is 30–50 kg/m^2, or 22–25 kcal/kg ideal body weight per day when BMI is > 50 kg/m^2). By a proportional adaption, we obtained intake maxima for obese critically ill patients (**Recommendation 60**).

We used the same approach to calculate maxima of fat intake. Based on expert consensus, we recommended that obese critically ill patients should have a maximum intake of 0.9 g fat/kg actual body weight and day when BMI is 30–50 kg/m^2, and a maximum intake of 1.5 g fat/kg ideal body weight and day when BMI is > 50 kg/m^2.

To formulate the minimum of fat intake, we acknowledged that obese critically ill patients presumably have an increased requirement of essential fatty acids.

To meet minimum fat requirements, the A.S.P.E.N. guideline (2004) [286] recommended that at least 2–4% of total calorie intake should be linoleic acid, and 0.25–0.5% α-linolenic acid; linoleic acid and α-linolenic acid intake should not be less than 5.4 g and 0.75 g/kg and day, respectively [328]. Daily fat intake should also respect product-specific linoleic acid and α-linolenic acid content of the fat emulsion.

Although there is a lack of high-quality quality studies to to give a sufficiently detailed answer to the question, the author group considers a "Should" recommendation to be justified.

Question: Should obese critically ill patients be placed on specific enteral formulations?

Recommendation 63:

Obese critically ill patients should receive enteral formulations with low calorie density (<2 kcal/mL) and reduced caloric carbohydrate/fat:protein ratio.

Consensus (87%)

Commentary

This recommendation corresponds to that made by the 2016 A.S.P.E.N. guideline (Recommendation Q6, expert consensus) [2]; rationale for this recommendation were merely technical reasons. Only a reduced caloric carbohydrate/fat:protein ratio allows clinicians to provide obese critically ill patients with a hypocaloric, high-protein enteral diet in clinical practice. Use of standard enteral formulations would require additional (and, thus, expensive), separate protein/amino acid supplementation.

Although there is a lack of high-quality studies to answer the question in detail, the author group considers a "Should" recommendation to be justified.

Question: Should patients with a history of bariatric surgery or other potentially malabsorptive disorders receive a pharmacotherapy with micronutrients?

Recommendation 64:

Critically ill patients with a history of bariatric surgery shall receive a pharmacotherapy with thiamine together with

commercially available preparations of vitamins, minerals, and trace elements to treat micronutrient deficiency (section 9.1**, Recommendations 53** and **54**).

Strong consensus (100%)

Commentary

Patients with a history of bariatric surgery are at a particular high risk of thiamine deficiency; these patients should receive a pharmacotherapy with thiamine before starting MNT, together with preparations of vitamins, minerals, and trace elements to treat micronutrient deficiency [2,460,463]. Recommendations of the 2016 A.S.P.E.N. guideline (Recommendation Q8, expert consensus) [2] and of the older 2013 A.S.P.E.N. guideline [458] are identical with our recommendation. Rationale of the older A.S.P.E.N. recommendation, however, were 22 observational studies and two RCTs, all showing a micronutrient deficiency after bariatric surgery. In addition, readers may consult specific guidelines addressing this topic [458,464].

Although there is a lack of high-quality studies to answer the question in detail, the author group considers a "Shall" recommendation to be justified.

11.3. Extracorporeal cardiovascular support systems/implanted ventricular-assist devices

With the exception of the recommendations made below, recommendations concerning critically ill patients with extracorporeal pulmonary support (veno-venous extracorporeal membrane oxygenation (vv-ECMO) or cardiac and pulmonary support (veno-arterial extracorporeal membrane oxygenation = va-ECMO, "extracorporeal life support" = ECLS), or with implanted ventricular-assist devices (VAD) are the same as those made above for patients not needing such devices.

11.3.1. vv-/va-ECMO

Cardiovascular support systems such as vv-/va-ECMO and micro-axial-assisted support systems are increasingly in use to treat refractory lung injury, cardiogenic shock, or combinations of these diseases [465]. Only a small number of studies addressed specific problems encountered during MNT in those patients. Data are sparse concerning the effects of such extracorporeal supportive devices on the function of organs not being the primary target. This deficit includes bowel function, and utilization or metabolism of exogenous substrates [466].

Furthermore, there are no guidelines or detailed recommendations addressing MNT in this subpopulation of adult critically ill patients. The Extracorporeal Life Support Organization (ELSO) guideline barely notes that "with all critically ill patients, full caloric and protein nutritional support is essential" [467]. In 2010, A.S.P.E.N. published a guideline on MNT in neonates with ECMO [468]. Since these patients are not part of the target group defined for this guideline, we did not consider this specific guideline for the recommendations described below.

Question: Which method should be used to determine energy expenditure in critically ill patients with vv-/va-ECMO?

Recommendation 65:

According to **Recommendations 5b** and/or **60,** a body weight-based formula should be used primarily to determine energy expenditure/calorie target in patients with vv-/va-ECMO. Indirect calorimetry should not be used.

Strong consensus (100%)

Commentary

Methodically, measurement of energy expenditure in patients receiving vv-/va-ECMO by indirect calorimetry is difficult because CO_2 is removed *via* the extracorporeal membrane; thus, CO_2 production is not correctly reflected by the spirometry unit of the calorimeter. Small exploratory studies tried to circumvent this problem by modifying technical aspects of calorimetry thereby improving its use in patients with vv-/va-ECMO; a prospective validation of these modifications by clinical studies of adequate size, however, is still pending [469,470].

The "Measuring Energy Expenditure in ECMO Patients (MEEP)" protocol combines measurements by indirect calorimetry (via pulmonary function) with blood-gas samples taken from the inflow and outflow tract of the oxygenator to determine O_2 and CO_2 content [470]. The exchange of gas in the membrane was calculated as the product of the difference in gas content and the vv-ECMO blood flow passing through the membrane, as measured by the device itself. Total O_2 uptake and CO_2 elimination were used in the equation of Weir to calculate energy expenditure. A particularly important aspect is high CO_2 content observed in patients needing a high gas flow for therapy; these patients most likely have a greater substrate turnover and energy expenditure. A prospective validation of this hypothesis by clinical studies, however, is still pending.

Considering the weak evidence, energy expenditure of patients receiving vv-/va-ECMO should be determined primarily by using the body weight-related formula as described above for non-obese critically ill patients (**Recommendation 5b**, section 6.1) and obese critically ill patients (**Recommendation 60**, section 11.2).

Although there is a lack of high-quality studies to answer the question in detail, the author group considers a "Should" recommendation to be justified.

Question: Which route (enteral or parenteral) should be used for nutrient delivery in patients receiving vv-/va-ECMO?

Recommendation 66:

In critically ill patients with VV-/va-ECMO, but without signs of severe intestinal dysfunction and/or hemodynamic instability, enteral nutrition may be used in all phases of the disease (section 7.2.1, **Recommendations 23** and **24**).

Strong consensus (100%)

Commentary

Retrospective studies with a small sample size ($n < 100$) [471,472], and case reports [473] showed that early enteral nutrition is possible and compatible with vv-/va-ECMO when individual metabolic tolerance is closely monitored. The enteral route of substrate delivery is not recommended for patients with an increased risk of intestinal complications (e.g. ischemia, bleeding). Ridley et al. evaluated MNT standards in 107 critically ill patients receiving vv-/va-ECMO, by a multicenter prospective observational study conducted in Australia and New Zealand [474]. The authors showed that the enteral route was the preferred route of nutrient supply in these patients; enteral nutrition, however, was interrupted on 53% of the days of the study. Most common reasons for interruption were non-specific diagnostic measures and a high gastric residual volume.

Although evidence is weak up to now (lack of RCTs), we feel that the enteral route can be used in all disease phases for delivering nutrients to patients receiving vv-/va-ECMO who do not have clinical signs of severe intestinal dysfunction and/or hemodynamic instability (section 7.2.1). Enteral MNT in these patients, however, requires a tight control of gastrointestinal tolerance and an individual monitoring/control of calorie and protein intake (section 6.2.2, **Recommendations 9b** and **9c**, section 6.2.3 and section 6.3.2, **Recommendation 14c**). Furthermore, enteral MNT should respect the increased bleeding risk due to the obligatory anticoagulation during vv-/va-ECMO. ESICM [3] formulated an identical recommendation concerning the use of enteral MNT in patients receiving vv-/va-ECMO (Question 6, evidence level 2D).

Question: How much fat should a critically ill patient needing vv-/va-ECMO receive during parenteral nutrition, and how should fat be administered?

Recommendation 67a:

Patients with vv-/va-ECMO and a simultaneous parenteral MNT may receive parenteral lipids according to **Recommendations 45a–d** (section 8.3.3). During infusion of the lipid emulsion the function of the membrane oxygenator should be closely monitored (oxygenator clotting).

Strong consensus (97%)

Recommendation 67b:

During parenteral nutrition, patients with vv-/va-ECMO should have a continuous infusion of lipid emulsions for 12–24 h (no bolus application) (section 8.3.3, **Recommendation 45b**). Lipid emulsions should not be infused directly into the ECMO circuit, but through a remote central venous line.

Strong consensus (97%)

Commentary

Individual case reports suggested that infusion of lipid-containing emulsions in patients receiving vv-/va-ECMO may lead to device-associated complications such as layering out of the emulsion from blood, agglutination, formation of blood clots, oxygenator clotting and premature dysfunction. Two systematic reviews examined the frequency of such adverse events. A review by Hayes et al. [322] identified a single case report [475] and one RCT [476]. In the case report, infusion of 0.2 mL/kg min (100 mL) of a 20% lipid emulsion for four hours (used as rescue therapy for intoxication) was associated with the need to replace the oxygenator membrane three times. The RCT included nine neonates receiving vv-ECMO who required intravenous nutrition. Patients received 1–3 g (5–15 ml)/kg per day of 20% lipid emulsion into either the ECMO circuit or via separate intravenous line [476]. Adverse effects occurred more frequently with administration into the ECMO circuit, particularly in areas of stasis.

Another review by Lee et al. [477] identified a survey conducted in 94 centers [478]. When infusing lipids (0.5–3 g/kg body weight and day), 11 centers reported agglutination of the emulsion, and two centers formation of blood clots or dysfunction of the membrane oxygenator. Lee et al. also detected nine case reports, which had rapidly infused lipid emulsions to treat drug intoxications (rescue therapy). According to two case reports there were no mechanical complications within the ECMO circuit; the remaining seven case reports did not provide information on specific complications of intravenous lipid administration.

The evidence regarding device-associated complications by infusion of lipid emulsions (as rescue therapy) is weak; therefore, based on expert consensus, the author group recommends that critically ill patients needing vv-/va-ECMO and a simultaneous parenteral MNT, may receive parenteral lipid emulsions

Table 13
Studies evaluating different tools to assess nutrition status in patients before VAD implantation.

Author	Number of patients	Tool	Malnourished (%)	Comments
Butler et al., 2005 [487]	222	BMI	None	No significant relationship between BMI and cardiac index or frequency of infectious, neurologic or respiratory complications or bleeding complications
Lietz et al., 2007 [488]	280	Albumin concentration	44*	Increased 90-day mortality after LVAD implantation in patients with serum albumin ≤3.3 g/dL.
Musci et al., 2008 [489]	590	BMI	None	Patients with BMI ≤20 and ≥ 35 kg/m^2 had an increased postoperative mortality and risk of multiple-organ failure. Patients with BMI 20–24 kg/m^2 had an increased risk of dying from sepsis. Patients with BMI 30–34 kg/m^2 had an increased risk of dying from stroke. Patients with BMI <20 and >35 kg/m^2 had the highest postoperative mortality.
Mano et al., 2009 [490]	64	BMI	34[a]	Patients with the lowest BMI (<16 kg/m^2) had the highest mortality. A stepwise increase in BMI (<16, 16–18.4 and ≥ 18.5 kg/m^2) was associated with a 38% reduction of mortality.
Aggarwal 2013 [481]	154	MNA	90	MNA could detect risk of malnutrition before clinical effects became evident (early detection of subclinical signs); MNA scores were an independent predictor of overall mortality after adjustment for serum albumin and hemoglobin concentration.
Kato et al., 2013 [491]	272	Albumin concentration	46	Preoperative hypoalbuminemia (<3.5 g/dL) was an independent predictor of postoperative mortality in patients undergoing LVAD implantation.
Weitzel et al., 2013 [492]	24	Substrates of the citrate cycle, amino acid and creatine concentration	24	Cardiac cachexia and dysfunction caused a substrate shift in cardiac metabolism. LVAD implantation restored abnormal cardiac metabolic function.
Emani et al., 2013 [493]	896	BMI, albumin concentration, pre-albumin concentration	48	Clinical course after LVAD implantation varied depending on nutrition status and BMI. Cachectic patients gained more weight after implantation than did overweight individuals. In all patients, albumin concentrations increased after LVAD implantation; the effect was particularly pronounced in cachectic patients.
Yost et al., 2014 [494]	162	MNA short-form (MNA-SF)	77–90.1	MNA-SF score was a strong predictor of survival. MNA-SF allowed – compared to other screening tools – a faster assessment of nutrition status in patients with acute heart failure who were awaiting VAD implantation or heart transplantation.
Yost et al., 2015 [495]	98	Preoperative measurement of resting energy expenditure	None	Indirect calorimetry allowed measuring resting energy expenditure in VAD patients; energy expenditure of VAD patients was comparable to that of patients with left-ventricular heart failure.
Yost et al., 2018 [482]	288	PNI[b]	98.9	PNI scores correlated with the hospital LOS and 1-year survival after VAD implantation.

BMI: Body Mass Index; LVAD: left ventricular assist device; MNA: Mini Nutritional Assessment; PNI: Prognostic Nutritional Index * Percentage of patients with albumin levels ≤3.3 g/dL.

[a] Patients with BMI <16 kg/m^2.

[b] PNI = (10 × serum albumin [g/dL]) + (0.005 × lymphocyte count) [481]. PNI <40 was predictive of a shorter survival in patients.

(**Recommendations 45a–d** in section 8.3.3). However, close monitoring of specific complications, such as clot formation in the membrane oxygenator or layering out of the emulsion from blood with consecutive oxygenator dysfunction, is mandatory.

Although there is a lack of high-quality studies to answer the specific question in detail, the author group considers a "Should not" recommendation concerning **Recommendation 67b**, and a "Should" recommendation concerning **Recommendation 67a** to be justified.

11.3.2. Implanted ventricular assist devices (VAD)

VAD implantation – into the left ventricle (LVAD), right ventricle (RVAD), or both ventricles (BiVAD) – represents an option for a surgical (heart failure) therapy of patients with end-stage congestive heart failure. Indications of VAD implantation include a bridge to transplant or to recovery, or a permanent support until death [479].

Varying indications of VAD, and different stages of VAD therapy are associated with specific consequences for MNT. These consequences are particularly relevant during the acute phase after VAD implantation, when secondary, severe complications have to be treated often leading to critical illness and a prolonged ICU LOS [480].

Question: How should nutrition status be assessed in critically ill patients with VAD upon ICU admission?

Recommendation 68:

In addition to the criteria for disease-specific malnutrition proposed by the DGEM, the Prognostic Nutritional Index (PNI) or the Mini Nutritional Assessment (MNA) may be used at the time of ICU admission to assess the nutrition status of critically ill patients with VAD.

Strong consensus (100%)

Commentary

Frequency of malnutrition is >90% in patients suffering from congestive heart failure who are treated by an implanted VAD [481,482]. Malnutrition increases the perioperative mortality of these patients (up to 12.2%); simplified scoring systems, however, allow the identification of such high-risk patients.

About 10% of patients suffering from chronic congestive heart failure present with cardiac cachexia defined by significant weight loss >7.5% during >6 months. Cardiac cachexia is caused by inadequate food intake, malabsorption and increased nutrient loss, and is associated with specific risks [483,484].

An observational study including 288 patients post VAD implantation found that a preoperative PNI <30 was associated with prolonged hospital LOS and reduced 1-year survival. PNI was calculated as (10 × serum albumin (g/dL)) + (0.005 × lymphocyte count) [482]. Another prospective observational study evaluated various malnutrition screening tools (MNA, Malnutrition Universal Screening Tool (MUST), NRS and SGA) in 1193 patients awaiting cardiac surgery. The only tools, which allowed predicting postoperative complications, were MNA and MUST [486]. Originally, however, MNA was designed to assess nutrition status of older patients [485], and MUST of adult outpatients [42]. Furthermore, validation of these scores for predicting mortality and morbidity of critically ill patients with VAD, and evidence for the use of these scores to control MNT in these patients is still pending (section 4).

Table 13 presents an overview of studies, which examined use of various tools to assess nutrition status in patients with VAD. These studies, however, were not explicitly conducted in patients who presented with the clinical characteristics as we had defined them for the target group of this guideline. For these patients, who are at a high risk of malnutrition, we recommended to assess nutrition status at the time of ICU admission (section 4, **Recommendation 2**). Although evidence is weak (lack of prospective validation studies), the author group feels that clinicians may use (i) the criteria presented above to define malnutrition (**Recommendation 2**), and (ii) PNI or MNA to assess nutrition status of critically ill patients with VAD.

Question: What are the peculiarities of enteral or parenteral MNT in critically ill patients with VAD?

Recommendation 69:

Critically ill patients with VAD may be fed according to the recommendations made for the general target group of this guideline.

Strong consensus (97%)

Commentary

An observational study recorded gastrointestinal function (endoscopy, barium swallow, gastric emptying) in 27 patients after VAD implantation [496]. In the acute phase after implantation, patients reported early satiety and/or increased nausea during volitional intake/enteral nutrition; furthermore, esophageal transit time and gastric emptying time was prolonged, but improved subsequently.

Patients after VAD implantation need a therapeutic anticoagulation. This therapy increases (i) the risk of local bleeding complications when establishing an enteral (or parenteral) access site, and (ii) the risk of spontaneous gastrointestinal bleeding which interferes with volitional intake/enteral nutrition; these risks make it more difficult to reach recommended calorie and protein intake/targets [497,498]. According to several case reports, however, endoscopic PEG tube placement is feasible and safe in patients after VAD implantation, if specific indications/contraindications are strictly respected [499,500].

To evaluate the use of parenteral MNT, a retrospective study analyzed the association between the duration of PN and clinical outcomes in 43 patients after VAD implantation. The authors found that a prolonged PN (>7 days) was not associated with a worse morbidity (frequency of thrombosis, stroke or infection), a longer ICU LOS or HLOS, or with shorter survival time [501]. Another retrospective study included 300 patients after VAD implantation. This study, however, found that use of PN (instead of EN) was an independent risk factor for developing a fungal VAD infection; VAD infection was associated with a mortality rate of 91% [502]. Due to the observational design, on cannot separate causality from mere association, and there is a high risk of indication bias in this study (section 2.4.2).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2019.05.002.

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