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ESPEN guideline on clinical nutrition in the intensive care unit

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Abstract

Following the new ESPEN Standard Operating Procedures, the previous guidelines to provide best medical nutritional therapy to critically ill patients have been updated. These guidelines define who are the patients at risk, how to assess nutritional status of an ICU patient, how to define the amount of energy to provide, the route to choose and how to adapt according to various clinical conditions. When to start and how to progress in the administration of adequate provision of nutrients is also described. The best determination of amount and nature of carbohydrates, fat and protein are suggested. Special attention is given to glutamine and omega-3 fatty acids. Particular conditions frequently observed in intensive care such as patients with dysphagia, frail patients, multiple trauma patients, abdominal surgery, sepsis, and obesity are discussed to guide the practitioner toward the best evidence based therapy. Monitoring of this nutritional therapy is discussed in a separate document.

Key words: Intensive Care, Nutrition, Enteral, Parenteral, Guidelines, Recommendations, ESPEN

Abbreviations

ALI, acute lung injury; ARDS, adult respiratory distress syndrome; ASPEN, American Society for Parenteral and Enteral Nutrition; BMI, body mass index; CI, confidence interval; CRP, C reactive protein; CT, computerized tomography; CVVH, continuous veno-venous hemo-dia-filtration; DHA, docosahexaenoic acid; DRI, Dietary reference intakes; EE, energy expenditure; EN, enteral nutrition; EPA, eicosapentaenoic acid; ESICM, European Society of Intensive Care Medicine; ESPEN, European Society for Clinical Nutrition and Metabolism; FA, fatty acid; FFMI, Fat free mass index; GLA, gamma-linolenic acid; GLN, glutamine; GPP, good practice point; HDL, High density lipoprotein; ICU, intensive care unit; IU, international units; K,

potassium; LCT, long chain triglyceride; Mg, Magnesium; MCT, medium chain triglyceride; MNA, mini-nutrition assessment; MNA-SF, MNA-short form; MUST, malnutrition universal screening tool; NRS, nutritional risk screening; NUTRIC, nutritional risk in critically ill; P, Phosphorus; PDMS, Patient data management system; PICO, Patient Intervention Control Outcome; PN, parenteral nutrition; RCT, randomized controlled trial; REE, resting energy expenditure; RR, relative risk; SCCM, Society for Critical Care Medicine; SGA, subjective global assessment; SIGN, Scottish Intercollegiate Guidelines Network; SOFA, Sequential Organ Failure, Assessment, VO_2, oxygen consumption; VCO_2, Carbon dioxide production.

1 Introduction

The present guideline is an update and extension of the previous ESPEN guidelines on enteral nutrition (EN) and parenteral nutrition (PN) in adult critically ill patients published 2006 and 2009, respectively (1,2). Since then, the ESPEN methodology has been upgraded to the "S3 guidelines level" described elsewhere (3) resulting in rigorous evidence-based and consensus-based recommendations. The determination of the effect of nutrition alone on any possible outcome is complicated by the fact that the severity of illness and the number of comorbidities encountered among adult intensive care unit (ICU) patients is increasing (4). Furthermore, the large heterogeneity of the ICU population potentially reduces the external validity of the recommendations, which should be seen as a basis to support decisions made for each patient on an individual basis (5). For now, a gap exists between nutritional practices and the previous guidelines (6) and many available studies address only one or at most some of the specific aspects of nutritional therapy. In the current guidelines, the timing, route, dose and composition of nutrition will be discussed and recommendations will be made recognizing that acute metabolic changes as well as calorie and protein deficits play a major role in patient outcome. Since most of the previous guidelines were based on observational or retrospective data, and the fact that large prospective randomized controlled studies have since been performed and recently published, our purpose is to integrate the best and most updated knowledge from the literature analyzed by professional methodologists and critical care nutrition experts as well as by invited critical care professionals, in order to reach the best achievable recommendations. The ultimate goal is to achieve optimal nutritional support for ICU patients and to illuminate the gaps in knowledge in order to provide priorities for future clinical research.

2 Methodology

The guideline is a basic framework of evidence and expert opinions aggregated into a structured consensus process. It is a revision of the ESPEN Guideline on Enteral Nutrition: Intensive care (2006) (1) and the ESPEN Guideline on Parenteral Nutrition: Intensive care (2009) (2). The guideline update that combines EN and PN was developed by an expert group of specialists in intensive care medicine devoted to metabolism and nutrition. All members of the working group have declared their individual conflicts of interest according to the rules of the International Committee of Medical Journal Editors. Individuals employed by the nutrition and pharmaceutical industry could not participate. ESPEN reimbursed all costs incurred during the development process of the guideline, without any industry sponsoring.

Although studies from an unlimited time span were assessed, only studies published in the year 2000 or later were included in the present meta-analyses. While defining an exact cut-off is impossible, and later conduct of studies does not necessarily guarantee higher quality, we chose this approach for the reason that major relevant changes were implemented after new scientific data became available around the start of the new millennium regarding

- Composition of medical feeds
- Determination of energy demands
- Clinical trial registration for randomized controlled trials (RCTs)
- Higher quality standards requested for RCTs and reporting of results.

The new ESPEN Guideline Standard Operating Procedures (3) are inspired by the methodology of the Association of Scientific Medical Societies of Germany, the Scottish Intercollegiate Guidelines Network (SIGN) and the Centre for Evidence-based Medicine at the University of Oxford. For these guidelines, clinical questions according to the PICO system – Patient,

Intervention, Control, Outcome – are requested if possible, a systematic literature search has to be performed, including evaluation of recent other relevant guidelines, specific keywords have to be addressed (intensive care, critical care, nutrition, enteral, parenteral, oral, tube feeding, protein, calories, nutrients, macronutrients), as well as specific (not limited) topics such as surgical complications, trauma, sepsis, Extracorporeal Membrane Oxygenation or Continuous Renal Replacement Therapy, according to complexity (4) and audit findings (5). In the current guidelines, we considered it important to address the timing and route of nutrition provision together and not separately. Twenty-four PICO questions were initially defined by the authors but PICO 2 was omitted because of lack of studies and PICO 25 was added since enough literature was present (Table 1a). For didactical reasons, the numbering of the PICO questions used for the literature research has not been transferred into the numbering of the clinical questions presented below. Several PICO questions have been summarized into one clinical question, other clinical questions, not originating from PICO questions have been added based on suggestions from the working group raised during the guideline work.

To provide levels of evidence for literature selection the SIGN evidence (7) levels have been elaborated. SIGN evidence ranks the evidence from 1++ for high quality studies (meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias) to low level of evidence graded as 4 in the case of expert opinion (Table 2). For literature not included into meta-analyses (see below), evidence tables were created which are available online as Supplemental Materials. A clear and straightforward consensus procedure was adopted using voting by the experts involved in writing the manuscript during a consensus conference preceded by a web-based Delphi procedure open to ESPEN members.

During the working process the internet portal www.guideline-services.com provided access to the draft and the literature at any time exclusively for members of the guideline working group.

Revisions of the initial draft versions incorporating the points discussed were prepared by the working group and were made available to the other working groups on the internet platform for commenting and voting on (Delphi technique). The updated recommendations and the first voting were intensively discussed in a consensus conference in 2018 and accepted after revision by voting consent on the same day.

Search strategy

The PubMed and Cochrane Library databases were searched for studies and systematic reviews published between 2000 and June 2017 using a broad filter with the key words (Table 1b). Only articles published in English or with an English abstract, and studies in human adults were considered. Additionally RCTs, meta-analyses, and systematic reviews were hand-searched for studies that were missing in the initial database search. The search for literature was updated several times during the working process for the last time in August 2017. Based on assessment of abstracts, all studies considered to be appropriate were listed in the appropriate file in the internet portal and therefore were available for all members of the working group at all times.

Meta-analysis strategy

When applicable, we used meta-analytic techniques to generate pooled estimates across eligible studies. We used random-effects model and the Mantel-Haenszel method (8) to pool the results across studies included in each meta-analysis. We reported dichotomous outcomes as relative risk (RR) and 95% confidence interval (CI), and continuous outcomes as mean difference and 95%CI. We assessed statistical heterogeneity between studies using the $\chi 2$ and I^2 statistics (9). All

161 analyses were conducted using RevMan 5.3 software (10) (r Review Manager (RevMan). The
162 meta-analysis are available online as Supplemental Materials.

163

164 ***Quality of Evidence***

165 We defined quality of evidence as our confidence in the estimate of the effect to support a
166 recommendation. The quality of evidence can be high, moderate, low, or very low (see table 2).
167 We completed this process in two steps: 1) initially by assessing the quality of evidence for each
168 critical outcome addressing a specific PICO question; and 2) after assessing the quality of
169 evidence for all critical outcomes, methodologists assigned the overall quality of the body of
170 evidence.

171 We assessed the quality of evidence using the criteria described in the GRADE methodology,
172 including: risk of bias, consistency, directness, precision, risk for publication bias, presence of
173 dose-effect relationship, magnitude of effect, and assessment of the effect of plausible residual
174 confounding or bias. Generally, RCTs started at high quality of evidence. The quality of evidence
175 could subsequently be rated down based on the assessment of the GRADE categories listed
176 above.

177 We used the GRADE pro guideline development tool online software
178 (http://gdt.guidelinedevelopment.org) to generate the evidence profiles (evidence summaries).
179 The evidence profiles contain information on study design, detailed assessment of the quality of
180 evidence, relative effects of the intervention compared to the control, absolute treatment effect,
181 and the quality of evidence for each outcome, as well as the *a priori* outcome importance. In each
182 evidence profile, we provided an explicit description of the rationale behind the judgments for
183 each of the GRADE categories.

Evidence levels, grades of recommendation and consensus process

The grading system relies primarily on studies of high quality, i.e. prospective RCTs. Evidence levels were then translated into recommendations, taking into account study design and quality as well as consistency and clinical relevance (Tables 2 and 3a). The highest grade (A) is assigned to recommendations that are based on at least one RCT whereas the lowest recommendation good practice point (GPP) is based on expert opinion, reflecting the consensus view of the working group.

Some guidelines are based on level 4 (low) evidence. These guidelines reflect an attempt to make the best recommendations possible within the context of the available data and expert clinical experience. Some of the recommendations of these guidelines are based on expert opinion because randomized studies are not available, due to the ethical dilemma preventing the conduct of prospective RCTs involving malnourished patients who may be subject to further starvation as a consequence of tentative study designs or omitting an intervention with a strong physiological rationale. Recommendations are formulated in terms of a ‘strong’ or ‘conditional’, and ‘for’ or ‘against’ the intervention based on the balance of desirable and undesirable consequences of the intervention (Table 3b).

In the case of inconsistent data, the recommendations were not only based on the evidence levels of the studies but also on the judgment of the working group taking consistency, clinical relevance and validity of the evidence into account (11, 12). The recommendations were classified according to the strength of consensus within the working group in April 2018 according to Table 4 (from strong consensus to no consensus).

207 **Table 1.**

208 **a. Keywords use in PICO search**

PICO	Intervention	Control	Key words
1	Enteral nutrition	No nutrition	enteral nutrition OR enteral feeding OR tube feeding;
2	Enteral Nutrition	Oral diet	enteral nutrition OR enteral feeding OR tube feeding; AND oral diet OR oral intake
3	Enteral nutrition	Parenteral nutrition	enteral nutrition OR enteral feeding OR tube feeding; AND parenteral nutrition OR parenteral feeding
4	Enteral nutrition + Supplemental parenteral nutrition	Enteral nutrition	enteral nutrition OR enteral feeding OR tube feeding; AND parenteral nutrition OR parenteral feeding; AND supplemental
5	Parenteral nutrition	No nutrition	parenteral nutrition OR parenteral feeding
6	Postpyloric (duodenal/ jejunal) enteral nutrition	Gastric enteral nutrition	enteral nutrition OR enteral feeding OR tube feeding; AND postpyloric OR duodenal OR jejunal
7	Hypocaloric feeding/ underfeeding (below 70%)	Normocaloric (defined as 70 to 100% of EE)	nutrition OR feeding; AND hypocaloric OR underfeeding
8	Trophic feeding	Normocaloric (70 to 100%)	enteral nutrition OR enteral feeding OR tube feeding; AND trophic feeding OR trickle feeding OR minimal feeding
9	Hypercaloric (>100% of EE)	Normocaloric (defined as 70 to 100%)	nutrition OR feeding; AND hypercaloric OR intensive OR overfeeding
10	High protein (isocaloric?) (> 1.2 g/kg/d)	Low protein (isocaloric?) < 1.2 g/kg/d	nutrition OR feeding; AND protein OR amino acids
11	EPA DHA/olive	No EPA DHA/olive	nutrition OR feeding; AND eicosapentaenoic acid OR docosahexaenoic acid OR olive OR EPA OR DHA OR omega-3 fatty acids
12	Enteral glutamine	No Glutamine	enteral nutrition OR enteral feeding OR tube feeding; AND glutamine
13	Parenteral glutamine	No glutamine	parenteral nutrition OR parenteral feeding; AND glutamine

14	Supranormal antioxidants	Dietary reference intakes of antioxidants (former RDA)	Micronutrients with PN Antioxidants AND high-dose OR supranormal
15	Lipids in parenteral nutrition	No lipids for 7 days	parenteral nutrition OR parenteral feeding; AND lipids OR fatty acids
16	Prokinetics	No prokinetics	enteral nutrition OR enteral feeding OR tube feeding; AND prokinetic OR promotility OR metoclopramide OR erythromycin OR neostigmine
17	Enteral nutrition in complicated abdominal or esophageal surgery patients	No nutrition	enteral nutrition OR enteral feeding OR tube feeding; AND abdominal surgery OR esophageal surgery; NO elective
18	Enteral nutrition in complicated abdominal or esophageal surgery	Parenteral nutrition	enteral nutrition OR enteral feeding OR tube feeding; AND parenteral nutrition OR parenteral feeding; AND abdominal surgery OR esophageal surgery; NO elective
19	Parenteral nutrition in complicated abdominal or esophageal surgery	No nutrition	parenteral nutrition OR parenteral feeding; AND abdominal surgery OR esophageal surgery; NO elective
20	Gastric enteral nutrition in complicated abdominal or esophageal surgery	Postpyloric enteral nutrition	Search same as 17
21	Enteral nutrition in multiple trauma	No nutrition	enteral nutrition OR enteral feeding OR tube feeding; AND multiple trauma OR polytrauma OR severe trauma OR injury
22	Enteral nutrition in multiple trauma	Parenteral nutrition	parenteral nutrition OR parenteral feeding; AND multiple trauma OR polytrauma OR severe trauma OR injury
23	Enteral nutrition in sepsis	No nutrition	enteral nutrition OR enteral feeding OR tube feeding; AND sepsis OR septic shock
24	Enteral nutrition in sepsis	Parenteral nutrition	parenteral nutrition OR parenteral feeding; AND sepsis OR septic shock
25.	Intermittent enteral nutrition	Continuous enteral nutrition	Intermittent Or Bolus Or Continuous Or tube feeding Or enteral nutrition

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b. Databases used for searching

Publication date :	From 1st January 2000
Language	English
Databases	Pubmed, Cochrane
Filter	"human", "adult"
Publication type	Original publications, practice guidelines, recommendations, meta-analyses, systematic reviews, randomized controlled trials, observational studies
Patients	"intensive care OR critical care OR critically ill OR critical illness"
Intervention	as stated above
Control	as stated table above
Outcome	mortality, infections, Length Of Stay, long-term outcomes (Quality Of Life, ICU-Acquired Weakness and function), not included in search formulas

Table 2: Levels of evidence (3)

1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

215 **Table 3: Grades and forms of recommendations (SIGN) (3)**

a Grades of recommendation	
A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population; or A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results: or extrapolated evidence from studies rated as 1++ or 1+.
0	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2++ or 2+
GPP	Good practice points. Recommended best practice based on the clinical experience of the guideline development group

b Forms of recommendation	
Judgement	**Recommendation**
Undesirable consequences clearly outweigh desirable consequences	Strong recommendation against
Undesirable consequences probably outweigh desirable consequences	Conditional recommendation against
Balance between desirable and undesirable consequences is closely balanced or uncertain	Recommendation for research and possibly conditional recommendation for use restricted to trials
Desirable consequences probably outweigh undesirable consequences	Conditional recommendation for
Desirable consequences clearly outweigh undesirable consequences	Strong recommendation for

216

217 **Table 4: Classification of the strength of consensus (3)**

Strong consensus	Agreement of > 90 % of the participants
Consensus	Agreement of >75-90 % of the participants
Majority agreement	Agreement of >50-75 % of the participants
No consensus	Agreement of <50% of the participants

218

219

220 ***Definitions and terminologies***

221 All the definitions and terminologies used in this guideline document are in accordance with the
222 recent ESPEN terminology recommendations (13) (Figure 1).

223 **Medical nutrition therapy** is a term that encompasses oral nutritional supplements, EN and PN.
224 The two latter have traditionally been called 'artificial nutrition', but this term is suggested to be
225 replaced by medical nutrition therapy.

226 **Actual Body Weight** is the weight measured during hospitalization or reported just before the
227 hospitalization; **ideal body weight** is the weight related to the height; **adjusted body weight** is
228 applicable in the obese patient and is calculated as ideal body weight + 1/3 actual body weight.
229 Through the text, body weight is defined as preadmission "dry" weight (i.e. weight before fluid
230 resuscitation) for patients with a body mass index (BMI) up to 30 kg/m^2. For obese patients, it is
231 recommended to use an ideal body weight based on the patient's height calculated to BMI=25
232 kg/m^2. A recent study (14) proposed a more accurate evaluation of ideal body weight using BMI:
233 (weight (kg) = 2.2 x BMI + 3:5 x BMI x (height - 1:5 m)

234 **Ebb phase and Flow phase**. The different phases of critical illness are generally described as
235 'ebb' and 'flow' phase. The 'ebb' phase comprises the hyperacute early phase of *hemodynamic*
236 instability which is a reason for ICU admission, while the 'flow' phase includes a subsequent
237 period of *metabolic* instability and catabolism which can be more or less prolonged and a later
238 period of anabolism.

239 **Acute phase and Post-Acute phase** are components of the 'flow' phase. The acute phase is
240 composed of two periods: an **Early Period** defined by metabolic instability and severe increase
241 in catabolism and a **Late Period** defined by a significant muscle wasting and a stabilization of

the metabolic disturbances (see Figure 2). The **post-acute phase** follows with improvement and rehabilitation or persistent inflammatory/catabolic state and prolonged hospitalization.

Isocaloric diet is an energy administration of around the defined target.

Hypocaloric or underfeeding is an energy administration below 70% of the defined target.

Trophic feeding is a minimal administration of nutrients having beneficial effects, such as preserving intestinal epithelium, stimulating secretion of brush border enzymes, enhancing immune function, preserving epithelial tight cell junctions, and preventing bacterial translocation.

Overfeeding is energy administration of 110% above the defined target.

Low protein diet is protein administration below 0.5 g/kg/day.

3. Clinical questions with recommendations

Clinical question 1: Who should benefit from medical nutrition? Who should be considered for medical nutrition therapy?

Recommendation 1

Medical nutrition therapy shall be considered for all patients staying in the ICU, mainly for more than 48 h

Grade of Recommendation: GPP – strong consensus (100 % agreement)

Commentary

There are no studies directly addressing the effect of duration of starvation on outcome in critically ill patients. Such studies could be considered unethical as energy intake is a mainstay of survival over a longer perspective. Since previous recommendations (1, 2), a cut-off of 48 h for the initiation of early nutrition and contraindications to early EN have been better established (15). Additionally, one study showed possible benefit of a further delay of PN if EN is not possible/tolerated in non-malnourished ICU patients (16). A careful and progressive re-introduction of nutrition may limit the risk of refeeding syndrome, mainly in patients who are severely malnourished or have been in a starved state before admission (which is higher in patients with reduced food intake before or during admission) (17).

Clinical question 2: How to assess malnutrition?

Recommendation 2

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

Remark:

General clinical assessment could include anamnesis, report of unintentional weight loss or decrease in physical performance before ICU admission, physical examination, general assessment of body composition, and muscle mass and strength, if possible.

Grade of recommendation: GPP – strong consensus (100 % agreement)

Commentary

Numerous studies suggest the use of a tool to assess malnutrition in the ICU. Weight changes are difficult to evaluate in the ICU because of fluid administration and rapid wasting of lean tissues. Therefore, weight and BMI do not accurately reflect malnutrition. However, of more concern than the BMI, which might be normal despite malnutrition, is the loss of lean body mass. Loss of muscle and sarcopenia has to be detected. In obese patients, sarcopenia is frequent and constitutes a condition of malnutrition, and the larger the loss of weight or the decrease in muscle mass, the more severe the malnutrition. The concept of critical illness associated frailty has been suggested (18): frailty is strongly correlated with age and disability status as well as the burden of comorbid disease (19). Amongst critically ill patients, decrease in muscle mass, strength and endurance, as well as mobility make these patients very analogous to the typically frail, geriatric patient. The diagnosis of malnutrition is suggested by clinical observations or by complementary examinations (20).

Laboratory tools: Inflammation is usually associated with an elevated C-reactive protein (CRP) and hypoalbuminemia. Albumin and isolated pre-albumin levels are not good markers of nutritional status, low values being a response to inflammation (negative acute phase proteins). Albumin is a marker of severity of the condition and reflects the inflammatory status. In a large cohort study (6,518 patients), Mogensen et al. (21) followed survival in non-malnourished (2,123

296 patients), non-specific malnourished (3,641 patients) and protein calorie malnourished patients
297 (754 patients) and found a significant increase in 30, 90 and 365 days mortality in the non-
298 specific and protein calorie malnourished groups (14.8%, 19.5% and 29.3%, $p < 0.001$
299 respectively for the 30 days mortality).

300 Scores: Most of the tools described below have been used in the intensive care setting.
301 The subjective global assessment (SGA) includes patient history and physical examination (22).
302 In a cohort of 260 elderly ICU patients, Sheean et al. (23) compared SGA to the mini-nutrition
303 assessment (MNA) mainly dedicated to elderly patients, nutritional risk screening (NRS) 2002, a
304 score based on weight loss, BMI, decreased food intake and severity of the disease, the ESPEN
305 endorsed screening tool based on BMI, weight loss and appetite as well as acute illness, and
306 MNA-short form (MNA-SF). MNA-SF had the highest specificity, while NRS 2002 had the
307 highest sensitivity when SGA was the gold standard. The NRS 2002 validation in the ICU is still
308 pending. According to the 2015 ESPEN definition (13), patients suffering from malnutrition
309 include those with a BMI < 18.5 kg/m^2 or suffering from an unintentional weight loss > 10%
310 irrespective of time, or > 5% over the last 3 months combined with either a BMI < 20 if < 70
311 years of age, or < 22 if > 70 years of age or a fat-free mass index <15 and 17 kg/m^2 in women
312 and men, respectively. This definition has been recently replaced by the association of a
313 phenotype (weight loss %, BMI, decrease in appetite, or muscle assessment and an etiology
314 predefined (24) (Table 5). An additional score, the Clinical Frailty Score (25), ranging from 1
315 (very fit) to 7 (very frail) has been validated in the ICU and is useful mainly in elderly patients
316 (26. 27).

317 Muscle mass: Malnutrition and muscle wasting generally occur during ICU stay due to
318 the effect of catabolic hormones, an imbalance between intake and requirements but also as a
319 result of physical immobilization. Large amounts of lean body mass as well as fat mass may be

lost during a relatively short time during an ICU stay. No validated tool is available but lean body mass evaluated by ultrasound (28), computerized tomography (CT) scan (29), bioelectric impedance (30) or even stable isotopes (31) might be performed to evaluate this loss. This loss of muscle may be considered as frailty (32). Such loss in muscle is associated with a prolonged hospital stay and interferes with quality of life and functional capacity (22). Sarcopenia is defined as a decrease in muscle loss and/or function and is frequent in undernourished patients admitted to the ICU (27). Muscle function may also be assessed by various tools such as a handgrip dynamometer (33) if the patient is conscious, being an especially good prognostic factor in conscious patients with Adult Respiratory Distress Syndrome (ARDS) (34). Bioelectrical impedance can be used to assess body composition and mainly lean body mass in a stable patient not suffering from fluid compartment shifts (35). Several studies have described the advantages of bio impedance (36, 37, 38, 39) and mainly phase angle (40) in the evaluation of the prognosis of critically ill patients. However, its use is not common practice. Recently CT scan has been used in the ICU to assess lean body mass and may be a promising tool for patients undergoing abdominal CT (41). A very recent study showed that patients with low muscle mass found at admission have a higher length of stay and higher mortality (42).

Since there is no “gold standard” to define the "at risk patient" and the malnourished ICU patient, we disagree with the recent American Society for Parenteral and Enteral Nutrition (ASPEN)/Society for Critical Care Medicine (SCCM) guidelines (43) that categorize patients according to NRS 2002 (44) or nutritional risk in critically ill (NUTRIC) (45) to define their nutritional regimen (discussed further). A definition of acute critical illness-associated malnutrition still needs to be developed.

Clinical question 3: How to screen for the risk of malnutrition during hospital stay?

Statement 1

Every critically ill patient staying for more than 48 h in the ICU should be considered at risk for malnutrition.

Strong consensus (96 % agreement)

Commentary

ICU patients are admitted either from home through the emergency room/operating room or from a hospital ward after a short or long stay. Some of them are obviously malnourished due to a severe previous loss of appetite, weight loss inducing variable reduction of lean body mass and/or multiple comorbidities and they will usually receive nutritional support. That is why nutritional intervention needs to be planned carefully and considered at the same level as any other therapy supporting organ functions in the ICU. Even if the evidence regarding a clear benefit from timely and tailored nutritional intervention is scarce, minimizing (further) malnutrition along with the avoidance of overfeeding and complications of nutrition during the hospital stay should be the aim for every patient in the ICU.

No specific ICU nutritional score has been validated thus far. The existing nutritional screening tools NRS 2002 (44) and the malnutrition universal screening tool (MUST) score (46) have not been designed specifically for critically ill patients. Recently, NUTRIC, a novel risk assessment tool (45) was proposed, based on age, severity of disease reflected by the APACHE II and Sequential Organ Failure (SOFA) scores, co-morbidities, days from hospital to ICU admission, and including or not inflammation assessed by the level of interleukin 6. The final composite NUTRIC score was correlated with mortality and the expected advantage of the score was to be able to show interaction between the score and nutritional intervention regarding outcome,

366 hypothesizing that nutritional support might decrease mortality in patients with a high NUTRIC
367 score (>5). A limitation to this score is that no nutritional parameters are included. When the
368 score was compared to traditional screening tools, a large variability was observed. Recently,
369 Arabi et al. (47) failed to confirm its value in a post hoc analysis showing that among patients
370 with high and low nutritional risk, permissive underfeeding with full protein intake was
371 associated with similar outcomes as standard low feeding.

372 Furthermore, mortality is not the best outcome to assess the efficacy of a nutritional intervention
373 considering the numerous factors influencing ICU mortality. Long-term functional tests might
374 better reflect the benefit of a nutritional policy (48). In a recent systematic review studying the
375 association between malnutrition and clinical outcomes in the ICU (49), ten nutrition screening
376 tools were identified but only five were studied regarding prognostic values. The NRS 2002 had a
377 low risk of bias in two studies demonstrating malnutrition risk as an independent risk for greater
378 hospital mortality (p=0.03). It appears that among all the screening tools, NRS 2002 and MUST
379 have the strongest predictive value for mortality, and they are the easiest and quickest to
380 calculate. A recent study (50) evaluated a higher cut off (>5) of NRS 2002. However, due to the
381 lack of prospective validation of their utility for daily clinical practice and nutrition management,
382 only expert opinion can be expressed.

383 While waiting for a validated screening tool, a pragmatic approach should be considered for
384 patients at risk such as those staying in the ICU > two days, undergoing mechanical ventilation,
385 infected, underfed > 5 days, and/or presenting with a severe chronic disease. The use of a list of
386 pathologies already validated in 1999 by the European Society of Intensive Care Medicine
387 (ESICM) and ESPEN might be helpful (51).

388

Clinical question 4: When should nutrition therapy be initiated and which route should be used?

Recommendation 3

Oral diet shall be preferred over EN or PN in critically ill patients who are able to eat.

Grade of recommendation: GPP – strong consensus (100 % agreement)

Recommendation 4

If oral intake is not possible, early EN (within 48 hours) in critically ill adult patients should be performed/initiated rather than delaying EN

Grade of recommendation: B – strong consensus (100 % agreement)

Recommendation 5

If oral intake is not possible, early EN (within 48 hours) shall be performed/initiated in critically ill adult patients rather than early PN

Grade of recommendation: A – strong consensus (100 % agreement)

Recommendation 6

In case of contraindications to oral and EN, PN should be implemented within three to seven days.

Grade of recommendation: B – consensus (89 % agreement)

Recommendation 7

Early and progressive PN can be provided instead of no nutrition in case of contraindications for EN in severely malnourished patients.

Grade of Recommendation: 0 – strong consensus (95 % agreement)

Recommendation 8

To avoid overfeeding, early full EN and PN shall not be used in critically ill patients but shall be prescribed within three to seven days.

Grade of recommendation: A – strong consensus (100 % agreement)

Commentary to recommendations 3 - 8

We performed meta-analyses on EN vs no nutrition, and EN vs PN within the first 48 h after ICU admission (early phase). We did not identify studies specifically addressing nutrition during later time periods (days three to seven and beyond the first week). We did not identify any studies comparing EN to oral diet. For patients able to eat, this route should be preferred if the patient is able to cover 70% of his needs from day three to seven, without risks of vomiting or aspiration. This amount (above 70% of the needs) is considered as adequate.

In comparing early EN vs delayed EN (including six studies in ICU patients (51, 52, 53, 54, 55, 56) and four studies including non-ICU patients (57, 58, 59, 60)), and similar to an earlier meta-analysis (15), our results showed reduction of infectious complications in early EN (RR 0.76, CI 0.59, 0.97, $p<0.03$). However, this was true only when including studies that also enrolled patients outside of the ICU (see Meta-analysis I and II in Supplemental Materials). There were no

differences in other outcomes. Therefore, excluding earlier studies (before 2000) attenuates the signal that early EN may reduce infectious complications compared to delaying EN beyond 48 h. Importantly, the dosage of EN was not taken into consideration in this meta-analysis.

When comparing early EN vs early PN (including six studies in ICU patients (61, 62, 63, 64, 65, 66) and seven studies with also non-ICU patients included (67, 68, 69, 70, 71, 72, 73)) our results showed a reduction of infectious complications with EN (RR 0.50, CI 0.37, 0.67, p= 0.005), as well as shorter ICU (RR -0.73, CI -1.30, -0.16, p=0.01) and hospital stay (RR -1.23, CI -2.02, -0.45, p= 0.002; see Figure 3 and Meta-analysis II in Supplemental Materials), whereas mortality was not different.

When to start, which route to prefer and how to progress have been a matter of debate for years. Therefore recent guidelines written by ESPEN (1, 2), ASPEN/SCCM (43), the Canadian Critical Care Practice Guideline group (74) and the most recent clinical practice guidelines on early EN in critically ill patients by the ESICM working group on gastrointestinal function (15) were considered when formulating the updated ESPEN recommendations. The latter performed an extensive review of the literature, multiple meta-analyses, six web-seminars and utilized the GRADE methodology, evidence to decision framework and Delphi methodology. Since many of the authors of the current guidelines are also co-authors of the ESICM guidelines, all the authors decided to endorse respective recommendations related to early enteral feeding. Following the literature search we could agree with other guideline statements such as the recent ASPEN/SCCM guidelines (43) suggesting the "use of EN over PN in critically ill patients who require nutrition support therapy" (Evidence LOW TO VERY LOW). The Canadian Critical Care Practice Guideline guidelines (74) recommend similarly stating "when considering nutrition support for critically ill patients, we recommend the use of EN over PN in patients with an intact gastrointestinal tract." However, based on expert consensus, when a patient is determined to be at

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

We endorse contraindications as defined in ESICM guidelines (15) and suggest withholding EN in critically ill patients with uncontrolled shock, uncontrolled hypoxemia and acidosis, uncontrolled upper GI bleeding, gastric aspirate >500 ml/6 h, bowel ischemia, bowel obstruction, abdominal compartment syndrome, and high-output fistula without distal feeding access.

In a meta-analysis of studies comparing enteral and parenteral routes independent of timing, Elke et al. (75) found a dramatic reduction in ICU infections with EN as compared to PN (RR 0.64, 95 % CI 0.48, 0.87, P = 0.004, I^2 = 47 %). This difference did not occur when the calories administered by PN and EN were similar (most recent studies), suggesting that caloric overfeeding may play a role in the infectious complications of PN and therefore in the decision process regarding the route, timing and the calorie target should also be taken into account.

Taken together, timing, route and caloric/protein target should no longer be considered as three different issues, but should rather be integrated into a more comprehensive approach considering all these aspects. After defining the timing and the route, the energy/protein goal should be achieved progressively and not before the first 48 hours to avoid over-nutrition. This progression should be ordered according to a local protocol preventing sharp and too rapid increases. Full targeted medical nutrition therapy is considered to achieve more than 70% of the resting energy expenditure (REE), but not more than 100%. Key points should be aiming for 1) oral nutrition as early as possible while considering the risks of complications (e.g. aspiration); 2) early EN at a low rate and progressive increase within 48 h if oral nutrition is not possible while considering the risk of complications; this progressive increase should be ruled by local protocols; 3)

478 determination of the optimal starting point and dose of (supplemental) PN based on the risk of
479 complications from oral or EN, state of acute illness and presence of previous under/malnutrition.
480 Studies integrating all these parameters are still lacking, preventing providing a clear
481 prescription. We should avoid the provision of excessive amounts of nutrients by any route in the
482 early phase of critical illness, which is associated with relevant endogenous energy production.
483 The issue of intentional underfeeding is a matter of intense debate and is currently being
484 investigated in prospective trials comparing low and high amounts of calories and/or proteins.

485

486 ***Clinical question 5: In adult critically ill patients, does intermittent EN have an advantage over***
487 ***continuously administered EN?***

488 **Recommendation 9**

489 **Continuous rather than bolus EN should be used.**

490 **Grade of recommendation: B – strong consensus (95 % agreement)**

491 **Commentary**

492 Five studies (76, 77, 78, 79, 80) were identified and our Meta-analysis found a significant
493 reduction in diarrhea with continuous versus bolus administration (RR 0.42, CI 0.19, 0.91,
494 p=0.03), whereas no difference was identified in other outcomes (See Figure 4 and Meta-analysis
495 III in Supplemental Materials). Despite the fact that bolus administration is significantly different
496 from continuous feeding in normal volunteers, increasing significantly gastric volume and
497 superior mesenteric artery blood volume, in critically ill patients (81) these differences are not
498 always translated into clinical advantages. Four prospective small studies (77, 78, 79, 80)
499 compared bolus (intermittent) to continuous administration of EN and did not find a difference in

morbidity or mortality in small populations of ICU or trauma patients. Rhoney et al. (79) tested the tolerability of bolus gastric feeding in brain damaged patients and found large gastric residues. Tavares et al. (80) in an observational study found that continuous feeding reached the target faster, but no difference in gastrointestinal symptoms was observed between the groups. A systematic review (82) did not detect an advantage of one technique but bolus administration was associated with a lower aspiration rate and better calorie achievement. However, heterogeneity of the studies decreased the strength of the recommendation. In an ICU population fed through percutaneous endoscopic gastrostomy, bolus and continuous tube feeding achieved the same gastric volumes, insulin requirements, time to goal therapy or calorie intake (83). This limited amount of data suggest that bolus and continuous enteral feeding can achieve the same target without an increase in side effects in any of these routes. Finally, bolus feeding could provide a greater stimulus for protein synthesis (84).

Clinical question 6: In adult critically ill patients, does postpyloric EN compared to gastric EN improve outcome (reduce mortality, reduce infections)?

Recommendation 10

Gastric access should be used as the standard approach to initiate EN.

Grade of recommendation: GPP – strong consensus (100% agreement)

Recommendation 11

In patients with gastric feeding intolerance not solved with prokinetic agents, postpyloric feeding should be used.

Grade of recommendation: B – strong consensus (100 % agreement)

Recommendation 12

In patients deemed to be at high risk for aspiration, postpyloric, mainly jejunal feeding can be performed.

Grade of recommendation: GPP – strong consensus (95 % agreement)

Commentary to recommendations 10-12

Sixteen articles have been identified (85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100) Our meta- analysis (see Figure 5 and Meta-analysis IV in Supplemental Materials) shows that feeding intolerance was more prevalent in the case of gastric feeding in five studies (RR 0.16, CI 0.06, 0.45, p=0.0005). We observed a trend for less pneumonia (eleven studies) (RR 0.75, CI 0.55, 1.03, p=0.07) in patients treated with postpyloric feeding and no differences in mortality (12 studies), diarrhea (seven studies) or ICU length of stay.

The ASPEN/SCCM (43) recommend that "the level of infusion should be diverted lower in the GI tract in those critically ill patients at high risk for aspiration or those who have shown intolerance to gastric EN". A recent Cochrane analysis (101) suggested placing a postpyloric tube in patients according to the local possibilities. Postpyloric EN has been associated with a decrease in ventilator acquired pneumonia in several earlier meta-analyses, but this benefit did not translate into decreases in length of ventilation, ICU or hospital stay, or mortality (102, 103). Importantly, various postpyloric locations (duodenal and jejunal) were not differentiated, despite the known different effects on gastrointestinal and pancreatic secretions as well as differing risks of duodenogastric reflux (102.). As postpyloric tube placement requires expertise, is commonly

associated with some time delay, and is considered less physiologic compared to gastric EN, the routine use of the postpyloric route is currently not justified. Moreover, postpyloric feeding could possibly be harmful in cases of GI motility problems distal to the stomach. Taken together, we suggest using gastric access as a standard and implementing postpyloric access in the case of intolerance to gastric feeding due to gastroparesis. Patients with a very high risk of aspiration may benefit from early postpyloric EN. We recommend postpyloric feeding in patients with a high risk for aspiration. According to ASPEN recommendations (41), patients at increased risk for aspiration may be identified by a number of factors, including inability to protect the airway, mechanical ventilation, age >70 years, reduced level of consciousness, poor oral care, inadequate nurse:patient ratio, supine positioning, neurologic deficits, gastroesophageal reflux, transport out of the ICU, and use of bolus intermittent EN (104). The Canadian Critical Care Practice Guideline guidelines (74) confirm this approach: "Strategies to Optimize Delivery and Minimize Risks of EN: Small Bowel Feeding vs. Gastric. Based on eleven level 2 studies, small bowel feeding compared to gastric feeding may be associated with a reduction in pneumonia in critically ill patients."

Clinical question 7: In adult critically ill patients, does the administration of prokinetics improve outcome (reduce mortality, reduce infections)?

<u>Recommendation 13</u>

In critically ill patients with gastric feeding intolerance, intravenous erythromycin should be used as a first line prokinetic therapy.

Grade of recommendation: B – strong consensus (100% agreement)

Recommendation 14

Alternatively, intravenous metoclopramide or a combination of metoclopramide and erythromycin can be used as a prokinetic therapy.

Grade of recommendation: 0 – strong consensus (100 % agreement)

Commentary to recommendations 13 and 14

Six studies have been identified (105, 106, 107, 108, 109, 110). According to our meta-analysis (see Meta-analysis V in Supplemental Materials), prokinetic use is associated with a trend towards better enteral feeding tolerance (RR 0.65, CI 0.37, 1.14, p=0.14). This is significant for intravenous erythromycin (usually at dosages of 100-250 mg 3 times a day) (RR 0.58, CI 0.34, 0.98, p=0.04) for two to four days but not for other prokinetics like metoclopramide (at usual doses of 10 mg two to three times a day). The incidence of pneumonia was not affected with the use of prokinetics, but only one study with intravenous erythromycin reported this outcome. Effectiveness of erythromycin or other prokinetics is decreased to one third after 72 hours (111) and should be discontinued after three days.

The measurement of gastric residual volume (GRV) for the **assessment** of gastrointestinal dysfunction is common and may help to identify intolerance to EN during initiation and progression of EN. However, **monitoring** of established EN with continued measurements of GRV may not be necessary (112). We suggest that enteral feeding should be delayed when GRV is > 500 mL/6 hours. In this situation, and if examination of the abdomen does not suggest an acute abdominal complication, application of prokinetics should be considered. ASPEN/SCCM (43) and the Surviving Sepsis initiative (113) recommend the use of prokinetics metoclopramide (10 mg three times a day) and erythromycin (3-7 mg/kg/day) in the case of feeding intolerance (weak recommendation, low quality of evidence for the surviving sepsis initiative, and for

ASPEN/SCCM) (43). Both drugs have also been shown to be efficacious for elevated gastric residuals in an earlier meta-analysis not limited to critically ill patients (114). Both agents have been associated with QT prolongation, and a predisposition to cardiac arrhythmias, but large series have only reported few adverse effects such as seizures in neurological patients. The BLESS trial (115) has shown modification in the microbiota of non-cystic fibrosis bronchectasis patients receiving erythromycin for 48 months. No such effects have been described after 48 hours. Our meta-analysis based on six studies finds a significant advantage to erythromycin and its use should be encouraged for 24 to 48 hours, since it promotes gastric motility, and if a large (> 500 mL) GRV still persists, the use of post-pyloric feeding should be considered over withholding EN, unless a new abdominal complication (obstruction, perforation, severe distension…) is suspected (see Meta-analysis V in Supplemental Materials).

Clinical question 8: How to define the energy expenditure (EE)?

The exact amount of calories to administer to critically ill patients is difficult to define and varies over time. To approach a fair recommendation, several parameters must be considered:

- The nutritional status of the patient prior to admission: lean, normal weight, overweight or obese, suffering from significant weight loss before admission, and the number of days of hospitalization before ICU admission and/or in the ICU

- The endogenous nutrient production and autophagy (116, 117)

- The energy balance of the patient during ICU hospitalization (118, 119)

- The time elapsed and energy balance since hospital admission

- The occurrence of refeeding syndrome (or at least hypophosphatemia) at the time of feeding

Recommendation 15

In critically ill mechanically ventilated patients, EE should be determined by using indirect calorimetry.

Grade of recommendation: B – strong consensus (95 % agreement)

Statement 2

If calorimetry is not available, using VO_2 (oxygen consumption) from pulmonary arterial catheter or VCO_2 (carbon dioxide production) derived from the ventilator will give a better evaluation on EE than predictive equations.

Consensus (82 % agreement)

Commentary to recommendation 15 and statement 2

The weakness of predictive equations and the use of indirect calorimetry have been subject to multiple evaluations and recommendations from ESPEN (2) and ASPEN (43), both preferring the use of indirect calorimetry to evaluate ICU patient needs (rated a very weak recommendation by ASPEN). The predictive equations are associated with significant inaccuracy (up to 60%), leading to over or under evaluation of the needs and inducing over or underfeeding (120). Numerous meta-analyses have demonstrated the poor value of predictive equations (121, 122), variability that is increased because body weight remains a value difficult to accurately assess (123). If indirect calorimetry is not available, calculation of REE from VCO_2 only obtained from ventilators (REE = VCO_2 x 8.19) has been demonstrated to be more accurate than equations (124) but less than indirect calorimetry (125). VO_2 calculated from pulmonary artery catheter can

also be used. In the absence of indirect calorimetry, VO_2 or VCO_2 measurements, use of simple weight-based equations (such as 20-25 kcal/kg/d) (1, 2, 43): the simplest option may be preferred.

Clinical question 9: In critically ill patients for whom caloric needs are measured using indirect calorimetry or estimated using predictive equations, should isocaloric or hypocaloric nutrition be used?

Recommendation 16

If indirect calorimetry is used, isocaloric nutrition rather than hypocaloric nutrition can be progressively implemented after the early phase of acute illness

Grade of recommendation: 0 – strong consensus (95 % agreement)

Recommendation 17

Hypocaloric nutrition (not exceeding 70% of EE) should be administered in the early phase of acute illness.

Grade of recommendation: B – strong consensus (100 % agreement)

Recommendation 18

After day 3, caloric delivery can be increased up to 80-100% of measured EE.

Grade of recommendation: 0 – strong consensus (95 % agreement)

Commentary to recommendations 16 - 18

Our meta-analysis (see Figure 6 and Meta-Analysis VI in Supplemental Materials) focused only on studies using indirect calorimetry found a trend (RR 1.28, CI 0.98, 1.67, p=0.07) to improved short term mortality when using indirect calorimetry as a calorie target, but there were no significant differences in long term mortality, infection or length of stay. Four RCTs have based their energy targets on indirect calorimetry. The pilot TICACOS study (126) showed that such a strategy was associated with an improvement in 60 day survival in the per protocol study, but also to an increase in length of ventilation, infections and length of stay related to the calorie overload and positive energy balance due to non-nutritional energy intakes. Petros et al. (127) showed a reduction in the infection rate in the study group. Heiddeger et al. (128) measured EE at day 3 and adapted the calorie intake accordingly, comparing supplemental PN from day four to an EN only group. The intervention group had a lower late nosocomial infection rate after day 9. The recent EAT-ICU study compared the goal-directed group, receiving the EE measured with indirect calorimetry as a caloric target to reach within 24 hours to patients receiving standard therapy. The study group also received protein according to urinary nitrogen loss. No advantages or harm was observed in terms of functional outcome, morbidity, or mortality in this RCT (129).

A larger database analysis suggested that calorie intake is associated with significantly improved survival when it is close to measured EE (130) or between 70 and 100% of the repeatedly measured resting energy expenditure (131). Undernutrition or over-nutrition is deleterious to outcome according to these large observational studies. A recent meta-analysis revealed that the effect of different energy intake levels on clinical outcome as suggested by observational studies is probably over estimated (132). Moreover, such observational studies are prone to intrinsic bias. This is one of the reasons why several experts and co-authors of the actual paper decided not to base recommendations regarding ICU nutrition on observational studies as better outcome (less severe illness) may result in better energy provision and vice versa (43).

If there is consensus stating that overfeeding should be avoided, it remains difficult to define which calorie targets should be proposed in the different phases of critical illness. Actual EE should not be the target during the first 72 hours of acute critical illness. Early full feeding causes overfeeding as it adds to the endogenous energy production which amounts to 500 to 1400 kcal/day (116). The assessment of the endogenous nutrient production would be very helpful (albeit not possible until now) in order to correct for and so prevent overnutrition and deleterious effects such as increased length of stay, ventilation duration and infection rates, if exogenous nutrients are administered on top of this endogenous production (133). Early full feeding also increases the risk of refeeding (see Recommendation 57). On the other hand, a too low intake, below 50%, may lead to severe calorie debt and empty the energy reserves, reduce lean body mass and may increase infectious complications (118, 119). Recently the analysis of a large data base including 1,171 patients with indirect calorimetry data (131) confirmed that under- and overfeeding were both deleterious, and that the optimal amount appeared to be between 70 and 100% of measured EE. Prospective randomized studies comparing the delivery of 70-80% of the measured EE to another regimen may improve our knowledge.

<u>Recommendation 19</u>

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

Grade of recommendation B – strong consensus (95 % agreement)

Commentary

Twelve studies using predictive equations (16, 46, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144) in addition to observational studies were analyzed trying to find the optimal level of calories to administer to ICU patients. If predictive equations are used to target energy prescription, we suggest using hypocaloric nutrition (up to 70% estimated needs), over isocaloric nutrition (70% or greater of estimated needs), in the early phase of acute illness (RR 0.92, 0.86, 0.99, p=0.02).

Unfortunately, also for this question, identified studies did not allow to address different time periods. Two initially separate PICO questions have been analyzed together due to difficulties in their separation, so that “trophic” nutrition was integrated in the “hypocaloric”. No clear benefit of hypocaloric vs isocaloric nutrition was observed in any of the studied outcomes. In the recent decade, various studies have compared energy intake based on predictive equations to reduced calorie intake achieving even trophic enteral feeding. These studies (134, 138) and the meta-analysis derived from them (144, 145, 146) concluded that there was no difference between normocaloric versus hypocaloric diets in critically ill patients. In another meta-analysis, Marik and Hooper (132) reported a lower hospital mortality for permissive underfeeding as compared with standard normocaloric feeding. The Braunschweig study (136) found an increase in mortality in the group of patients receiving calories close to the prescribed recommended energy intake, without an explanation of the cause of death, except a likely refeeding syndrome (147). This underlines the importance of the timing in addition to the goal and the route in the interpretation of the studies. Some studies administer full medical nutrition therapy from day one or two (early phase) (EAT-ICU (129), NUTRIREA-2 (66), CALORIES (65)) while others are starting only after three to four days or even later. From all these studies, the ideal amount of calories cannot be determined. Large observational series including hundreds to thousands of patients have observed that the optimal calorie load associated with the best survival is around

80% of predicted energy needs (148), whereas too low or too high calorie intake is associated with increased mortality (5). Other observational studies suggested no relation between intake and outcome or better outcome with lower energy intakes (149, 150, 151). However, in all these studies, calorie delivery was lower than recommended/prescribed or the studies were not targeted to this parameter. It has to be stressed that negative energy balance has been shown to be associated with poor outcome (117, 118) and is one of the main physiological concepts guiding nutrition prescription. This energy deficit is associated with protein catabolism and loss of both lean body mass as well as fat mass that has been associated with poor outcome. Thus, at a certain time, caloric delivery should likely match expended energy. Optimal timing likely differs between patients and is not settled yet.

Clinical question 10: When should we apply/implement supplemental PN?

Recommendation 20

In patients who do not tolerate full dose EN during the first week in the ICU, the safety and benefits of initiating PN should be weighed on a case-by-case basis.

Grade of recommendation: GPP – strong consensus (96.30 % agreement)

Recommendation 21

PN should not be started until all strategies to maximize EN tolerance have been attempted.

Grade of recommendation: GPP – strong consensus (95 % agreement)

Commentary to recommendations 20 and 21

Despite the fact that RCTs are available, the studies are so different that we decided not to perform a meta-analysis. It has been suggested that when the level of energy needs provided by EN is below 60% three days after ICU admission, supplementary PN should be initiated to reach a maximum of 100% of the energy needs (measured by indirect calorimetry whenever possible) (ESPEN 2009: Supplementary PN should be initiated in critically ill patients when energy needs are not covered with EN within three days after admission) (2). Although early enteral feeding is recommended in most cases (15) (see specific section), the calorie and protein targets are difficult to achieve in many situations. Numerous observational studies have pointed out the deleterious effects of negative energy balance (118, 119) and there is no debate regarding the need for supplementing PN to EN in the case of prolonged nutritional deficit. However, the best timing to prescribe supplemental PN remains debated. The ESPEN 2009 guidelines (2) stated that all patients receiving less than their targeted enteral feeding after two days should be considered for supplementary PN.

Casaer et al. (16) observed that early (supplemental or exclusive) PN is associated with increased morbidity including prolonged ICU dependency and mechanical ventilation, and increased infection rate and need for renal replacement therapy. These findings may be related to the specific study protocol, the patients' characteristics and the large amount of calories administered guided by predictive equations instead of indirect calorimetry. However, results of this study revealed the potential harm of nutritional intervention aiming at full, possibly overestimated calorie targets during the acute phase of critical illness. The primary outcomes of the smaller studies comparing early PN with other modalities did not differ between groups (152, 153). These divergent findings could result from the differences in sample size, amount of nutrients provided, or could reflect the limited impact of nutrition on global outcomes used for other purposes. In addition, it is not known whether usage of calorimetry would have resulted in

different targets and different outcomes in the EPaNIC study. The optimal time point for supplemental PN aiming to achieve full caloric needs is not clear, but is suggested to be between days four and seven (128, 154).

As a result, ASPEN/SCCM (43) recommend that in patients with either a low or high nutritional risk, the use of supplemental PN should be considered only after seven to ten days if they are unable to meet >60% of energy and protein requirements by the enteral route alone. This statement is based on the evaluation that initiating supplemental PN on top of EN prior to day 7-10 after ICU admission does not improve clinical outcome and even may have detrimental consequences. Notably, we are not aware of any studies either starting late PN beyond day eight or comparing the effects of starting late PN between day four to seven versus eight to ten.

Some of the other studies addressing supplemental PN (128, 154, 155) did not show similar findings to the EPaNIC study. Moreover, the Calories study (65) and NUTRIREA-2 (66), although not studying supplemental PN but comparing early PN with early EN, demonstrated that the route of nutritional support was not associated with the occurrence of infectious complications as far as the amount of nutrient provided was limited (In the NUTRIREA-2 study (66), an increase in bowel ischemia was observed in the enteral group). It was suggested that early observations of increased infectious morbidity may have been related to the calorie load (overfeeding) more than being a consequence of the administration of supplemental PN (16). Finally the EAT-ICU study (129) associating supplemental PN with enteral feeding from the early stage of admission in order to reach a target defined by indirect calorimetry, did not find any harm or advantage in terms of morbidity, long term function or mortality. The role of supplemental PN remains to be defined in terms of timing, amount and composition.

Clinical question 11: In adult critically ill patients, does high protein intake compared to low protein intake improve outcome (reduce mortality, reduce infections)?

Recommendation 22

During critical illness, 1.3 g/kg protein equivalents per day can be delivered progressively

Grade of recommendation: 0 – strong consensus (91 % agreement)

Statement 3

Physical activity may improve the beneficial effects of nutritional therapy.

Consensus (86 % agreement)

Commentary to recommendation 22 and statement 3

Muscle comprises the largest protein pool in the body. Critical illness is associated with marked proteolysis and muscle loss (up to 1 kg per day) that is associated with ICU acquired weakness (31). A higher protein intake and physical activity might be needed to overcome anabolic resistance associated with older ager and critical illness (184).

Energy and protein requirements may not change in a parallel way and should be considered separately. While a too large energy delivery could lead to overfeeding and refeeding, and may therefore be deleterious, increased protein delivery may be of benefit in critically ill patients. It has been observed (5) that in daily practice the amount of protein provided to most ICU patients is less than the loss, and is related to technical difficulties and commercial product composition not adequately enriched with proteins in comparison to the calorie content (156). In addition, 100 g of protein hydrolysate produces only 83 g of amino acids (157). Recently products with a higher protein to energy ratio have become available. The previous ESPEN guidelines (2)

recommended administering 1.2 to 1.5 g/kg/d protein based on three studies showing improvement in nitrogen balance (158, 159, 160).

Observational studies have demonstrated the benefits of high protein delivery. Leverve et al. showed that only patients receiving a large amino acid load and able to have a positive amino acid flux in their legs survived (161). Weijs et al. (162) studying 886 patients showed that ICU patients with 1.2 to 1.5 g/kg/d delivered protein had reduced 28-day mortality. Allingstrup et al. (163) showed a step-wise dose-dependent improvement in survival when protein delivery was higher. Nicolo (164) in 2,824 patients showed an improvement in survival if patients received more than 80% of their protein target. Compher et al. (165) showed that the odds of death decreased by 6.6% with each 10% increase in protein intake. Rooyackers (166) combining several labelled amino acid and protein isotope studies, demonstrated that additional protein was associated with a better net protein balance. In a retrospective study, Song et al. (167) showed a significant improvement in ICU outcomes of ventilated critically ill patients receiving > 90% of target protein intake. Looijaard et al. (168) showed that sarcopenic ICU patients benefit more from protein intake > 1.2 g/kg per day. Finally Zusman et al. (131) showed significantly higher survival when protein was administered > 1.3 g/kg/d, resulting in a gain of 1% survival for each 1 g of protein.

However, RCTs are less conclusive. The Nephro-Protect study (169) with higher amino acid administration in the intervention arm resulted only in improving the creatinine clearance of patients on day 4, while not affecting clinical endpoints. Older studies administrating high protein (170) in patients suffering from acute renal failure only found renal improvement. Scheinkestel et al. (171) also administered increasing doses of protein in patients suffering from acute renal failure. They confirmed an improvement in nitrogen balance with higher protein intake and found that nitrogen balance was associated with an improvement in outcome, but not protein intake.

839 The more recent Ferrie study (172) included 119 patients receiving 0.8 or 1.2 g/kg parenteral
840 amino acids as part of their nutritional regimen. They found that the patients receiving the higher
841 amount of amino acids had less fatigue, greater forearm muscle thickness on ultrasound and
842 better nitrogen balance, but no difference in mortality or length of stay. Interpretation of the study
843 was also complicated by a higher incidence of death in the high amino acid arm which may have
844 created an artefact in muscle force in survivors as additional analyses provided by the authors
845 have suggested. In a small study, Rugeles et al. (140) compared hyperproteic (1.4 g/kg/d)
846 hypocaloric vs isocaloric (0.76 g/kg/day protein) EN and only found a difference in the SOFA
847 scores. In another study (141), this group administered 1.7 g/kg/d of protein with normocaloric
848 and hypocaloric regimens and did not find any significant differences between the 2 groups. A
849 meta-analysis of these randomized studies was not performed since they focused on different
850 populations and had no uniform end point.

851 The Top Up study (142) did not find any difference in outcome between those achieving protein
852 target versus controls. The EAT ICU study (129) compared high protein intake administered
853 according to nitrogen excretion from day one to standard administration and did not find any
854 difference in six minute walk test (primary objective) or other parameters related to morbidity or
855 mortality. Of note, this study provided full energy from day 1. In addition, the post hoc analysis
856 of EPaNIC (173, 174) studies suggested that early administration of amino acids (mainly at day
857 3) was associated with a later live discharge from the ICU, questioning the indication of
858 administrating amino acids in the early stay in the ICU (175). On the other hand, Doig et al (154)
859 showed benefit (reduction of ventilation time and improved strength) when administering 1
860 g/kg/day protein.

861 The optimal timing of protein intake is also unclear. While Weijs et al. (130) retrospectively
862 found that early protein intake of ≥ 1.2 g/kg/day at day four was associated with better survival in

non-overfed non-septic patients and Zusman et al. (176) showed a significant survival advantage for early protein administration reaching 1 g/kg/day at day three versus late protein administration, another retrospective study (177) found that a larger amount of protein administered in during day three to five was associated with higher mortality, while an overall higher protein intake was associated with lower mortality.

None of these studies is comparable to the others in terms of patient selection, calorie and protein intake, timing and route of administration. They underline the need for well conducted RCTs to answer the question of protein administration in the ICU. However, it is possible that similar to caloric targets, optimal protein targets change over time in the ICU and that a high protein intake is only beneficial if not associated with overfeeding.

Exercise has been suggested in several studies (178, 179) to be effective in preventing anabolic resistance (180), reducing morbidity and improving the level of activity. However, some divergent results have also been published (181, 182, 183). Administration of increased protein intake together with increased physical activity should be further explored and seems to be promising (184).

Clinical question 12: What are the optimal combinations of carbohydrates and fat during EN and PN?

<u>Recommendation 23</u>

The amount of glucose (PN) or carbohydrates (EN) administered to ICU patients should not exceed 5 mg/kg/min.

Grade of recommendation: GPP – strong consensus (100 % agreement)

Recommendation 24

The administration of intravenous lipid emulsions should be generally a part of PN.

Grade of recommendation: GPP- strong consensus (100 % agreement)

Recommendation 25

Intravenous lipid (including non-nutritional lipid sources) should not exceed 1.5 g lipids / kg /day and should be adapted to individual tolerance.

Grade of recommendation: GPP – strong consensus (100% agreement)

Commentary to recommendations 23 - 25

The optimal nutritional composition of macronutrients is defined by minimal requirements and upper limits. For carbohydrates the upper limit should be 5 mg/kg body weight/min: For intravenous lipids the upper recommendation is 1 g/kg body weight/day with a tolerance up to 1.5 g/kg/day. Administration in excess can lead to waste, storage or even toxicity. In normal volunteers (185), the *de novo* lipogenesis induced by overfeeding of isoenergetic amounts of diets rich in fat or carbohydrate was not significantly different.

Carbohydrates are the preferential substrate for production of energy, but in critical illness, insulin resistance and hyperglycemia are common secondary to stress (186). A minimal requirement has been proposed in previous guidelines (2) based on a society recommendation (187). This evaluation is weak as has been stated: ‘carbohydrate could be theoretically eliminated from the diet, but it is probably safe(r) to give 150 g/day: This may be explained by organ preference on glucose such as the brain (100-120 g/day), red blood cells, immune cells, renal

907 medulla and all the transparent tissues of the eyes (2). The exact optimal carbohydrate amount to
908 administer is difficult to determine. Critical illness alters enteral nutrient absorption (188).
909 Endogenous glucose production is increased and does not decrease when nutrients and insulin are
910 administered as compared with healthy conditions (189). Excessive glucose based energy
911 provision is associated with hyperglycemia, enhanced CO_2 production, enhanced lipogenesis,
912 increased insulin requirements and no advantage in protein sparing in comparison with a lipid
913 based energy provision (116). The use of diabetic-specific enteral formula in ICU patients
914 suffering from Type 2 Diabetes Mellitus seems to improve the glucose profile (190, 191) and
915 may have clinical and economic impact (192).The hyperglycemia related to PN enriched in
916 dextrose requires higher doses of insulin (193). The recommended glucose administration should
917 not exceed 5 mg/kg/min (2, 194).

918 **Lipids.** Essential fatty acids (FA) were previously recommended at a dose of 8 g/day, but recent
919 studies have shown that pediatric patients receiving pure fish oil lipid emulsions did not develop
920 essential FA deficiency after months (195): of note the fish oil lipid emulsion contain 20% of
921 other FA which is probably the reason for this good tolerance. Fat can be administered enterally
922 or parenterally and as for carbohydrates, the exact amount required is unknown. Fat absorption is
923 impaired in critically illness (196). Lipid metabolism is modified in critical illness and low
924 plasma triglyceride levels and high plasma (HDL) cholesterol levels are associated with
925 improved survival (197). The optimal glucose/lipid ratio has been evaluated in terms of
926 improving nitrogen balance with a high ratio suggested (198). However, administration of
927 marked amounts of carbohydrates and lipids can lead to hyperglycemia and liver function test
928 abnormalities while high fat administration can lead to lipid overload, and especially unsaturated
929 fat to impaired lung function and immune suppression (199). Close monitoring of triglycerides
930 and liver function tests may guide the clinician for the best ratio (200).

Special attention should be paid if propofol is administered, since it is a source of FA. This lipid solution contains 1.1 kcal/mL and can provide a large calorie load over and above nutritional support (201, 202). Electronic patient data management systems (PDMS) help to recognize this calorie overload. Citrate use in continuous veno-venous hemo-dia-filtration (CVVH) is also associated with increased carbohydrate load and should be taken into account as a non-nutritional calorie intake (202).

Regarding the FA composition of the lipid emulsions, the recent expert recommendations indicated that a blend of FAs should be considered, including medium chain triglycerides (MCTs), n-9 monounsaturated FAs, and n-3 polyunsaturated FAs. At this stage, the evidence for n-3 FA-enriched emulsions in non-surgical ICU patients is not sufficient to recommend it as a standalone (203).

Clinical question 13: Should we use additional enteral / parenteral glutamine (GLN) in the ICU?

Recommendation 26

In patients with burns > 20% body surface area, additional enteral doses of GLN (0.3-0.5 g/kg/d) should be administered for 10-15 days as soon as EN is commenced.

Grade of recommendation: B – strong consensus (95 % agreement)

Recommendation 27

In critically ill trauma, additional EN doses of GLN (0.2-0.3 g/kg/d) can be administered for the first five days with EN. In case of complicated wound healing it can be administered for a longer period of ten to 15 days.

Grade of recommendation: 0 – strong consensus (91 % agreement)

Recommendation 28

In ICU patients except burn and trauma patients, additional enteral GLN should not be administered.

Grade of recommendation: B – strong consensus (92.31 % agreement)

Commentary to recommendations 26 - 28

The amino acid GLN is a normal component of proteins, representing around 8% of all amino acids, and is present in standard commercial enteral feeds. GLN for parenteral use has been available since 1994, after its synthesis by Fürst and Stehle (204). For stability reasons, it was not present in standard PN (205).

GLN transports nitrogen between cells and/or organs and serves as a metabolic fuel in rapidly proliferating cells (204). Under physiological conditions, sufficient endogenous GLN stores are maintained by both daily nutritional intake (80 g of mixed protein contains approximately 10 g GLN) and by endogenous synthesis (skeletal muscle and liver) (204).

Plasma GLN levels have repeatedly been shown to be low during critical illness, and low values to be associated with poor outcome (206, 207, 208). However, not all critically ill patients are GLN depleted. Rodas et al. (208) showed a U-shaped association between plasma GLN levels and outcome. Most patients with very high plasma GLN concentrations suffered acute liver

973 failure (204). As GLN is one of the most potent gluconeogenic and ureogenic amino acids, liver
974 failure reduces the normal removal of ammonia produced from GLN metabolism. In the
975 REDOXS trial (209), some patients exhibited high levels of plasma GLN (210, 211).

976 In major burns, studies include limited number of patients: nevertheless, the existing randomized
977 trials have repeatedly demonstrated that GLN (and its precursor ornithine α-ketoglutarate) have
978 beneficial effects in major burn injuries, reducing infectious complications (mainly gram negative
979 infections) and also mortality (212). This has been confirmed in the latest meta-analysis (213,
980 214), and is included in the specific ESPEN burn guidelines (215). A well conducted meta-
981 analysis including four trials (155 patients) with intention to treat analysis concluded that GLN
982 supplementation was associated with a significant reduction of infectious complications, and of
983 mortality due to bacteremia (216). The most recent randomized trial was published in 2014 (217)
984 confirmed the reduction of infectious complications in 60 patients. This higher requirement is
985 explained by exudative losses: analysis of burn exudates shows that GLN is lost in larger
986 amounts than any other amino acid (218).

987 The efficiency of enteral GLN on infection reduction was also suggested in major trauma (219).
988 A RCT in 20 trauma patients with delayed wound healing, showed that oral antioxidant and GLN
989 containing supplements reduced time to wound closure (22 days versus 35: p=0.01). In the
990 control patients a decline of plasma GLN was observed, while it was modestly increased in those
991 having received 20 g GLN per day for 14 days. Finally, enteral GLN has also proven to improve
992 body composition and in particular lean body mass in a group of 44 head and neck cancer
993 patients randomized to receive a GLN supplement (30 g daily) for four weeks (220). The authors
994 observed a significant Improvement of fat-free mass, serum albumin, and quality of life scores
995 postoperatively (220).

During continuous renal replacement therapy, losses of about 1.2 g GLN/day are observed (221). These patients might be candidates for enteral complementation.

In other critically ill patients, the MetaPlus trial (222) showed no advantage in terms of infection of a feeding solution containing additional enteral GLN. Of note none of the groups received the planned high dose protein resulting in a mean delivery of 0.9 g/kg/day. Meta-analysis showed that enteral GLN reduces increased gut permeability significantly but does not reduce mortality (223, 224).

Recommendation 29

In unstable and complex ICU patients, particularly in those suffering from liver and renal failure, parenteral GLN -dipeptide shall not be administered.

Grade of recommendation: A – strong consensus (92.31 % agreement)

Commentary

A previous meta-analysis including studies published after 2000 was available and therefore a new meta-analysis was not performed. Since the 1990s, many studies have been conducted in critically ill patients, mostly using GLN together with EN or PN at nutritional doses (0.2 to 0.3 g/kg/d of GLN); these trials have shown benefits in terms of infectious complication reduction, lower mortality (225, 226, 227) and reduction of hospital costs (228). The results were consistent through several meta-analyses (229, 230) and have been recently confirmed in an analysis including RCTs performed after 2000, using GLN as part of nutrition support. The only negative trial in terms of absence of effect was attributed to the delivery of a dose of GLN lower than recommended (231).

When analyzed together (232) most single center studies observed improved survival while some multicenter studies did not confirm this finding, reaching no significant results in the overall population (mortality of 29% for those receiving GLN and 28% for the control group). The positive trials used GLN as part of global nutrition in stabilized patients. On the other hand, the administration of combined enteral and parenteral GLN (233) in doses higher than recommended in severely ill patients with multi-organ failure was associated with a higher mortality. The REDOXS study (209), designed as a 2 x 2 factorial trial, generated concerns for a number of reasons, including the fact that the randomization resulted in higher severity with more organ failures in the GLN groups, largely explaining the higher mortality (234). Finally, Stehle et al. (235) in a meta-analysis including only stable patients showed an advantage to administering GLN. Of note, there are no data on long term administration of GLN, most trials having used additional GLN for less than 14 days.

The positive impact of parenteral GLN on cost has been clearly demonstrated. In an Italian multicenter ICU population (236), Pradelli et al. estimated the potential cost-effectiveness of parenteral GLN in a multicenter ICU population based on the expected clinical benefit as reported in RCTs evaluating parenteral GLN. They found a 4991 € cost reduction compared to PN-without GLN. Of note, the analysis was updated in 2015, confirming the previously published data (237). There are no cost-efficiency data for GLN addition to EN, except for a study in 68 very-low-birth-weight infants (238), in whom GLN resulted in cost reduction. Knowing that high plasma GLN may occur in the early phase, blind administration may not be safe. Point-of-care devices are not yet available, being in the development phase.

Clinical question 14: Should we use enteral / parenteral EPA/DHA?

Recommendation 30

High doses of omega-3-enriched EN formula should not be given by bolus administration.

Grade of recommendation: B – strong consensus (91 % agreement)

Recommendation 31

EN enriched with omega-3 FA within nutritional doses can be administered.

Grade of recommendation: 0 – strong consensus (95 % agreement)

Recommendation 32

High doses omega-3 enriched enteral formulas should not be given on a routine basis.

Grade of recommendation: B – consensus (90 % agreement)

Commentary to recommendations 30 - 32

We identified eight studies (239, 240, 241, 242, 243, 244, 245, 246) addressing this question; in four of them antioxidants were also given. A meta-analysis did not reveal any benefit (see Meta-analysis VII in Supplemental Materials), but there was a trend towards increase in PO_2/FiO_2 with intervention (RR 22.59, CI -0.88, 46.05, p=0.06). However, because it may change quickly and is dependent on ventilator settings, fluid status, body position etc. PO_2/FiO_2 is probably not the best outcome variable.

Calder et al. (203) recently summarized the various formulae available and their described effects in various conditions related to intensive care. The International Society for the Study of FA and Lipids recommends a daily intake of 500 mg of eicosapentaenoic acid (EPA) + docosahexaenoic

acid (DHA) for healthy humans (247), three to seven times this dose could be considered a high dose in ICU patients. Enteral formulae enriched in borage oil and/or omega-3 FA have been administered in patients suffering from ARDS, acute lung injury (ALI) and sepsis with positive effects regarding length of stay, length of ventilation and even mortality (239, 240, 245, 248). These four studies used the same study and control formulae. Santacruz et al. (249) analyzed the effects of enriched formulae according to the lipid composition of the control group. A multicenter study comparing the formula enriched in EPA, gamma-linolenic acid (GLA; from borage oil) and antioxidants to a regular formula could only find an advantage in terms of length of ventilation (250). Our meta-analysis (see Meta-analysis VII in Supplemental Materials) found a trend for advantage in oxygenation for enteral formulae enriched in EPA, GLA and antioxidants while other outcomes were unchanged. Other studies administered omega-3 FA and borage oil as an additive, rather than as a component of the formula (243) and in the Rice et al. study (244), in combination with a very low daily protein intake (far from recommendations and lower than in the control group), leading to no advantage or even increased risk associated with higher omega-3 FA administration. Aggregating all the studies without taking into account the amount of omega-3 FA or whether they are given as bolus or continuous administration, does not yield any advantage for any formula (250). Glenn and Wischmeyer (251) analyzed separately the studies administering omega-3 FA as a bolus or in a continuous manner and found that continuous administration improved length of stay and length of ventilation; in contrast, bolus administration had no advantage. The pre-emptive administration of the same formula administered in the first 3 studies in severe, ventilated, multiple trauma patients did not find any advantage (245). In this study, the membrane content of EPA and DHA was very low at baseline and was hardly corrected with omega-3 and borage oil administration, suggesting that we do not know the exact amount of omega-3 FA to administer to this category of patients. In the post-hoc

analysis of the MetaPlus study (252), administrating GLN, EPA/DHA and antioxidants to critically ill patients, only the change from baseline to day 4 of EPA + DHA/long chain triglyceride (LCT) ratio was statistically significantly associated with six month mortality (hazard ratio 1.18, 95% ci 1.02-1.35, P=0.021) suggesting a harmful effect of these nutrients in medical ICU patients. It has to be noted that this harmful effect was not observed in the previous studies on patients in ALI or ARDS.

Recommendation 33

Parenteral lipid emulsions enriched with EPA + DHA (Fish oil dose 0.1-0.2 g/kg/d) can be provided in patients receiving PN.

Grade of recommendation: 0 – strong consensus (100 % agreement)

Commentary

We did not perform new meta-analyses, since previous meta-analyses including studies from year 2000 and later are available. From previous and recent recommendations (2, 42), it is clear that the use of intravenous fat emulsions based solely on a soybean oil rich in 18 carbon omega-6 FA should be avoided due to their likely pro-inflammatory effects. Comparative studies of administrating lipid emulsions daily or not at all did not show any deleterious effects and as in the previous ESPEN guidelines (2), we recommend not to delay administration and provide intravenous lipid emulsions daily (253). Alternative lipid emulsions have become available, including sources that incorporate olive oil, fish oil, and coconut oil (MCTs) in various combinations. Meta-analyses have shown an advantage to lipid emulsions enriched in fish oil or olive oil (254). Dai et al showed a better survival as well as a shorter length of stay (255). Olive oil also had an advantage over soybean oil in terms of LOS (256, 257). However, Umpierrez et al. (258) did not find any difference in terms of morbidity and mortality between olive oil and

soybean oil. Prospective randomized studies including surgical patients admitted in the ICU for a period of their hospitalization have shown less morbidity in the fish oil group compared to other lipid emulsions (259, 260, 261, 262, 263, 264). Grau et al. in a multicenter prospective randomized double blind study, showed a significant decrease in infection rate using a lipid emulsion with long chain triglycerides (LCT; soybean oil), MCT and fish oil compared to an emulsion with LCT/MCT alone (265). A review of numerous meta-analyses (266) comparing these new lipid emulsions with one-another and with soybean oil-based lipid emulsions is available, summarizing many prospective comparative studies. Those of Palmer et al. (267), Chen et al. (268), Pradelli et al. (269), Manzanares et al. (270) and Zhu et al. (271) showed a decrease in length of stay, while Manzanares et al. (270) and Zhu et al. (271) also showed a decrease in infections. Fish oil has been administered in septic patients showing improvement in morbidity (272, 273, 274). Tao et al. (275) found a reduction in mechanical ventilation days in septic patients receiving fish oil enriched intravenous lipid emulsion, but the studies showed heterogeneity and had low sample size. Lu et al (274) and Manzanares et al. (270) reported similar findings in other meta-analyses. Kreymann et al. (277) recently analyzed the effects of additional EPA/DHA compared to LCT and LCT/MCT in critically ill patients and found a significant improvement in the infection rate. However, many of the studies suffered from high bias and low level of evidence. The ASPEN (43) and Surviving Sepsis Recommendations (113) do not acknowledge any advantage to new lipid emulsions.

Clinical question 15: Should we use parenteral micronutrients and antioxidants in critically ill patients?

Micronutrients, i.e. trace elements and vitamins, have numerous functions that they generally exert in combination: they are essential for the metabolism of carbohydrates, proteins and lipids

(i.e. nutrition), for immunity and antioxidant defense, for endocrine function, and for DNA synthesis, gene repair and cell signaling. The present recommendations are limited to the nutritional and antioxidant aspects.

Recommendation 34

To enable substrate metabolism, micronutrients (i.e. trace elements and vitamins) should be provided daily with PN.

Grade of recommendation: B – strong consensus (100 % agreement)

Commentary

Providing micronutrients to include the full range of trace elements and vitamins is an integral part of nutritional support as stated in the 2009 guidelines (2). Parenteral and enteral feeding preparations differ in that commercially available PN solutions contain no micronutrients for stability reasons: this requires their separate prescription (2). There are no studies regarding PN with or without micronutrients, but these studies would be unethical. This lack of evidence does not allow us to give strong recommendations, but trials would be considered unethical.

Several micronutrients are severely depleted during the inflammatory response, and hence difficult to interpret. Recent evidence tends to show that persistently low zinc concentrations might become an important biomarker in sepsis (278).

Similarly, we recommend the repletion of micronutrients, in conditions of chronic and acute deficiency. Continuous renal replacement therapy for more than two weeks is a new cause of acute micronutrient deficiencies and particularly of severe copper deficiency that may explain life-threatening complications in patients requiring this therapy (279).

Recommendation 35

Antioxidants as high dose monotherapy should not be administered without proven deficiency.

Grade of recommendation: B – strong consensus (96 % agreement)

Commentary

Oxidative stress, defined as an imbalance between increased reactive oxygen and nitrogen species and endogenous antioxidant mechanisms, is observed in severe critical care conditions requiring mechanical ventilation (280), such as septic shock, severe pancreatitis, ARDS, major burns and trauma: this is associated with oxidative damage to proteins and lipids (281). The antioxidant micronutrients, and in particular copper, selenium, zinc, and vitamins E and C belong to the primary antioxidant defenses: their circulating levels are decreased below reference ranges in these conditions (282, 283, 284, 285) in association with intense inflammation.

On the basis of the analysis of 15 RCTs (286), showing a significant reduction of infectious complications and of mortality, the 2016 ASPEN guidelines (43) recommend the provision of a combination of antioxidant micronutrients “in safe doses” (i.e. 5-10 times Dietary reference intakes =DRI). A European randomized trial which was not included in this analysis suggests that the clinical effect of a combination of antioxidants is already apparent after five days of administration (287). This short term support of the endogenous antioxidant system should not be confused with the daily nutritional doses of trace elements and vitamins required along with PN (2). Doses exceeding ten times the DRI should not be used in clinical settings without proven severe deficiency.

The number of trials testing the enteral administration of antioxidant micronutrients is limited. Howe et al. showed in a RCT in 72 patients on mechanical ventilation that delivering an enteral

combination of 1g vitamin C and 1000 international units (IU) vitamin E resulted in a reduction of length of mechanical ventilation with no impact on length of stay or mortality (288).

Regarding high dose intervention, selenium and vitamin C will be commented upon separately as their mechanisms of action differ: Se supports the activity of the glutathione peroxidase family of antioxidant enzymes, while vitamin C primarily acts on the endothelium and microcirculation (284, 289).

Selenium: Low serum Se is associated with intense inflammation, organ failures and poor outcome in children and adults (290). High dose Se therapy (1000-4000 µg) has been investigated in conditions of septic shock. A meta-analysis including nine trials and 792 patients with sepsis investigated the safety of Se supplementation and observed an important heterogeneity (291): the authors concluded that in sepsis, Se doses higher than daily requirements may reduce mortality. The absence of an effect of Se supplementation in the REDOXS trial (209) might have been due to the adequacy of the Se status in the North American population compared to the European population who are Se borderline deficient (292). Manzanares et al. (293), in a meta-analysis, did not find any clinical outcome improvement in mono or combined therapy, with or without loading and with or without sepsis. High dose Se monotherapy has recently been shown to be inefficient in reducing mortality in an important German cohort (294). As the kidney excretes Se, doses in excess of DRI should be avoided in case of renal failure.

Ascorbic acid (vitamin C): Critically ill patients exhibit low circulating ascorbic acid concentrations (286). A low plasma concentration is associated with inflammation, severity of organ failure and mortality. Preclinical studies show that high-dose vitamin C can prevent or restore microcirculatory flow impairment by inhibiting activation of nicotinamide adenine dinucleotide phosphate-oxidase and inducible nitric oxide synthase (289, 295). Ascorbate also

prevents thrombin-induced platelet aggregation and platelet surface P-selectin expression, thus preventing micro thrombi formation (289). It additionally restores vascular responsiveness to vasoconstrictors, preserves the endothelial barrier by maintaining cyclic guanylate phosphatase and occluding phosphorylation and preventing apoptosis (296). Finally, high-dose vitamin C can augment antibacterial defenses (282).

In major burns, the early phase of resuscitation is characterized by massive capillary leak and endothelial dysfunction causing shock and organ failure. Resuscitation of burn victims with high-dose ascorbic acid (66 mg/kg/hour for 24 h) was reported in 2000 (296) and later (297, 298) to reduce fluid intakes. Further trials are ongoing (299): in 24 patients randomized to vitamin C doses of 50-200 mg/kg/kg or placebo, no adverse safety events were observed in ascorbic acid-infused patients. These patients exhibited prompt reductions in SOFA scores (absent in placebo patients), along with a significant reduction of the inflammation biomarkers (C-reactive protein and procalcitonin). Recently, Marik et al. suggested that administration of high doses vitamin C, thiamine and hydrocortisone decreased mortality and prevented the occurrence of multiple organ failure in severe sepsis and septic shock (285). Indeed, under acidotic conditions in sepsis, ascorbate promotes dissolution of microthrombi in capillaries, thereby contributing to resolving microcirculatory alterations.

Clinical question 16: Should additional vitamin D be used in critically ill patients?

Recommendation 36

In critically ill patients with measured low plasma levels (25-hydroxy-vitamin D < 12.5 ng/ml, or 50 nmol/l) vitamin D3 can be supplemented.

Grade of recommendation: GPP- consensus (86 % agreement)

Recommendation 37

In critically ill patients with measured low plasma levels (25-hydroxy-vitamin D < 12.5 ng/ml, or 50 nmol/l) a high dose of vitamin D3 (500,000 UI) as a single dose can be administered within a week after admission.

Grade of recommendation: 0 – consensus (86 % agreement)

Commentary to recommendations 36 and 37

Vitamin D3 can be synthesized in sufficient amounts by the human body so long as there is exposure to sunlight and good liver and renal function. Vitamin D3 has a nuclear receptor and a large number of genes are under direct or indirect control of this vitamin. Hypovitaminosis D is common in the general population, with a seasonal occurrence, while low plasma concentrations of vitamin D have been repeatedly shown in critically ill patients. In the latter patients, deficiency has been associated with poor outcome (300), including excess mortality, longer length of stay, higher sepsis incidence, and longer mechanical ventilation (301).

Seven randomized supplementation trials including 716 critically ill adult patients have been performed: they have shown beneficial effects, with mortality reduction when compared to placebo (302, 303) with follow up to six months after intervention. No side effects have been observed. The trial doses have varied between 200,000 and 540,000 units administered by the enteral, intramuscular or intravenous routes. These doses are far in excess of the daily recommended intakes (RDI) doses of 600 IU/day, and are based on the demonstration that using the RDI doses leads to prolonged normalization time (304): a loading therapy is required (305,306). Nutritional doses should be administered to all ICU patients but have been proven not

to correct the low plasma concentrations. At this stage though, a single high dose (500,000 IU) can be administered in the first week and seems safe in patients with deficiency.

Clinical question 17: Nutritional therapy in special conditions

The following three recommendations are based on previous recommendations published by the European Society of Intensive Medicine (ESCIM) (15).

Recommendation 38

EN should be delayed

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

Grade of recommendation: B – strong consensus (100 % agreement)

Recommendation 39

Low dose EN should be administered

- **in patients receiving therapeutic hypothermia and increasing the dose after rewarming;**

- **in patients with intra-abdominal hypertension without abdominal compartment syndrome, whereas temporary reduction or discontinuation of EN should be considered when intra-abdominal pressure values further increase under EN; and**
- **in patients with acute liver failure when acute, immediately life-threatening metabolic derangements are controlled with or without liver support strategies, independent on grade of encephalopathy.**

Grade of recommendation: B – strong consensus (95.65 % agreement)

Recommendation 40

Early EN should be performed

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

Grade of recommendation: B – strong consensus (95.83 % agreement)

Commentary to recommendations 38-40

We endorse the ESICM guidelines that formulated 17 recommendations favoring initiation of early EN (within 48 hours of ICU admission) and seven recommendations favoring delaying EN (15), as summarized in our recommendations 34-36. In meta-analyses performed for the ESICM

guidelines, early EN reduced infectious complications in unselected critically ill patients, in patients with severe acute pancreatitis, and after GI surgery, whereas no evidence of superiority for early PN or delayed EN over early EN was detected in any of the sub-questions. However, all issued recommendations were weak due to the low quality of evidence, with most of them finally based on expert opinion (15).

Clinical question 18: Special conditions not included in the ESICM recommendations

i. Non intubated patients

Recommendations 41

In non-intubated patients not reaching the energy target with an oral diet, oral nutritional supplements should be considered first and then EN.

Grade of recommendation: GPP – strong consensus (96 % agreement)

Recommendations 42

In non-intubated patients with dysphagia, texture-adapted food can be considered. If swallowing is proven unsafe, EN should be administered.

Grade of recommendation: GPP – strong consensus (94 % agreement)

Recommendations 43

In non-intubated patients with dysphagia and a very high aspiration risk, postpyloric EN or, if not possible, temporary PN during swallowing training with removed nasoenteral tube can be performed.

Grade of recommendation: GPP – strong consensus (92 % agreement)

Commentary to recommendations 41 - 43

Oral intake is frequently prescribed in the intensive care setting varying from 25 to 45% of the patients in the first four days, but does not reach the energy or protein requirements according to the Nutrition Day ICU survey (5). This population includes patients admitted for monitoring, patients receiving non-invasive ventilation and post intubation/ tracheostomy patients.

Non-ventilated patients: Reeves et al. (307) described the energy and protein intakes of patients with ARDS receiving non-invasive ventilation. From this small observational study, it is concluded that oral intake was inadequate, mainly with increasing time on non-invasive ventilation, and earlier during their hospital admission. In total 78% of the patients met less than 80% of the requirements. Of 150 patients who required non-invasive ventilation for more than 48 hours, 107 were incapable of oral intake and received enteral feeding which was associated with increased airway complications and median non-invasive ventilation duration (308). Patients requiring high-flow oxygen via nasal cannula were deemed medically appropriate to resume oral alimentation (78% out of 50 patients), while 22% continued nil per os. The authors recommended referring the patients recognized to have swallowing issues for swallowing evaluation, in order to prevent oral nutrition complications (39).

Oral intake is impaired **after extubation** and a high incidence of swallowing dysfunction has been described (between 10 to 67.5%, with a mean around 50%, despite different timing and methods assessing the dysphagia) (310). This post-extubation swallowing disorder could be

prolonged for to up to 21 days mainly in the elderly and after prolonged intubation. Thus, at 21 days post-extubation, 24% of older patients were feeding tube dependent (311). Recently, 29% of 446 ICU patients had prolonged post-extubation swallowing disorder at discharge and some post-extubation swallowing disorder has been shown 4 months after discharge (312). The same authors who described the tools to diagnose post-extubation swallowing disorder, also suggest the use of thickening food to increase oral intake. However, this approach has not been validated in the ICU (312). In a four year follow up by Kruser and Prescott (313) the time to self-reported recovery of swallowing function was three months, but 25% of patients took more than six months to recover. After one week, none of the 50 patients studied by Peterson et al. (314) exceeded 50% of daily requirements and were prescribed a therapeutic diet.

After tracheostomy, a cohort study showed that the majority of the patients returned to oral intake, but the time to commencement of oral intake was correlated with increased time to decannulation and increased time to decannulation correlated with increased hospital length of stay (315). Supplemental PN has not been extensively studied in this population.

ii. Frail patients

Frail patients can be diagnosed at admission as well as during the ICU stay. Frailty is a clinical syndrome in which 3 or more of the following criteria occur: 1. Unintentional weight loss, 2. Self-reported exhaustion, 3. Weakness (by grip strength), 4. Slow walking speed and 5. Low physical activity (316). Specific criteria diagnosing frailty during ICU stay are not available. Poor appetite and nutritional intake (316, 317) may be evident. Frailty is more frequent in the elderly population (50% in patients older than 80 years) and is associated with increased mortality. It is different from malnutrition, as demonstrated in a systematic review assessing malnutrition and frailty: in 5447 older patients from ten studies, 2.3% were malnourished (according to Mini-

Nutritional Assessment) while 19.1 % were frail. 68% of the malnourished were frail while only 8.4% of the frail were malnourished (318). For those surviving, loss of autonomy and increased length of recovery is expected. Physical function can be impaired for a prolonged time (more than 4 years). In a recent systematic review (319) including ten observational studies enrolling a total of 3030 patients (927 frail and 2103 fit patients), frailty was associated with higher hospital mortality (RR 1.71; 95% CI 1.43, 2.05; $p < 0.00001$; $I^2 = 32\%$] and long-term mortality (RR 1.53; 95% CI 1.40, 1.68; $p < 0.00001$; $I^2 = 0\%$). The pooled prevalence of frailty was 30% (95% CI 29–32%). Frail patients were less likely to be discharged home than fit patients (RR 0.59; 95% CI 0.49, 0.71; $p < 0.00001$; $I^2 = 12\%$). Frailty occurrence was also decreased in patients fed with EN enriched with the omega-3 FA EPA (320). In patients receiving > 1 g/kg per day protein as 20% of the calories, frailty was less common. An ESPEN expert working group (321) recommend 1.2 to 1.5 g protein/kg/day in older people who are malnourished or at risk of malnutrition because they have acute or chronic illness, with even high protein intake for individuals with severe illness or injury".

Clinical question 19: In adult critically ill patients with sepsis, does EN compared to no nutrition improve outcome (reduce mortality, reduce infections)?

Clinical question 20: In adult critically ill patients with sepsis, does EN compared to PN improve outcome (reduce mortality, reduce infections)?

The clinical questions 19 and 20 are both answered by the following Recommendation 44.

<u>Recommendation 44</u>

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

If contraindicated, EN should be replaced or supplemented by progressive PN.

Grade of recommendation: GPP – strong consensus (94 % agreement)

Commentary

A meta-analysis on enteral versus no nutrition was not feasible due to paucity of related studies. The stress-related increased metabolic needs observed during sepsis have been well quantified and are likely to promote malnutrition, or aggravate pre-existing malnutrition, at the time of admission to the ICU. Knowing that malnutrition is associated with impaired clinical outcomes, it is likely that no nutrition is deleterious or at least less favorable for long term outcome than nutrition support. Elke et al. (322) confirmed this opinion in a secondary analysis of a large nutrition database including 2,270 patients with sepsis, pneumonia and with an ICU stay > three days. Increased amounts of calories and protein per day were associated with a decrease in 60 day mortality and an increase in ventilation-free days. The surviving sepsis campaign guidelines do not recommend full EN and suggests administering low-dose enteral feeding in the 1st week of ICU stay giving an evidence grade of 2B. However, this statement is based on studies not aimed at septic patients.

A meta-analysis was not possible due the paucity of studies on this question (enteral versus parenteral nutrition). The respective value of EN and PN should be discussed separately for patients with sepsis from those with septic shock, since shock may jeopardize intestinal perfusion during enteral feeding. Patients with sepsis on EN are likely to be underfed, due to their poor gastrointestinal tolerance to liquids and feeds. Such a condition is associated with the development of a progressively increasing energy debt, representing the difference between energy need and intake, strongly correlated with complications and/or reduced survival (89, 91, 323, 324). Unfortunately, recent studies showed that the use of EN often provides about half of

the measured energy expended over the first week in the ICU, a condition associated with an increased complication rate proportional to the deficit incurred over the ICU stay (325). Only one outcome study in septic patients compared “early” EN with energy target reached by the 3rd day after admission with “late” EN (no nutrition until day 3 after ICU admission) and found no difference (survival or infection rate) (326). A number of physiologic advantages are associated with the use of EN, such as the preservation of gut integrity and intestinal permeability, as well as a down modulation of the inflammatory response and of insulin resistance (193). Two studies (327, 328) have compared the respective effect of hypocaloric or trophic EN (about 70% of the predicted energy target), versus full EN (≥ 80% of the predicted energy target) and found no differences in terms of survival. On the other hand, PN generally allows to fully cover the nutritional needs even during the first days of the ICU stay. However, the full provision of energy needs during the first three to four days after ICU admission may not be desirable, as there is an intense endogenous production of energy substrate during the first days of disease/trauma-related stress (329) and because refeeding may play a role. This was also the conclusions of the EPaniC study including more than 1000 septic patients (16). On this basis, a pragmatic approach remains to consider EN as the first choice for nutrition support during the first three to four days after ICU admission in order to avoid overfeeding, a condition shown to be deleterious. For those patients for whom EN is not feasible or is insufficient after three days, PN should be prescribed up to approximatively half of the predicted or measured energy needs and EN prescribed as soon as the clinical condition permits. In addition, protein administration has been recommended in higher doses in critically ill patients. Weijs et al. reported that septic patients did not improve outcome when receiving increased (1.2 g/kg/d) protein intake compared to non-septic patients (130, 330), but they found no harm either.

Septic shock

In patients with septic shock receiving vasopressors or inotropes, no evidence-based answer can be proposed as no interventional studies have been reported to date. On a pathophysiological basis, intolerance to EN in patients with uncontrolled shock is likely to be very high. In fact, impaired splanchnic perfusion related to shock can potentially be further aggravated by EN administration as digestion represents an extra workload theoretically capable of leading to bowel ischemia or necrosis (331). The use of EN during the first 48 h after admission in patients with uncontrolled shock was shown to be less favorable in terms of survival than its delayed use (48 h after admission) in patients with successful resuscitation and stable hemodynamic parameters (332). In the recent NUTRIREA-2 study (66), 61% in the enteral group and 64% in the parenteral group suffered from septic shock. No difference between the groups was noted in terms of mortality. Nevertheless there were significantly more digestive complications in the early EN group, indicating that full feeding during shock is to be avoided, and that in fact PN may be the safer route in some patient groups. ESICM (15) as well as our guidelines (recommendation 38) recommend to delay the introduction of EN in such cases.

As the study results remain conflicting, a pragmatic approach may be considered in patients with sepsis: a fraction (20-50%) of a full nutrition support should be initiated as early as possible to "open" the enteral route, then the amount of feeds should be progressively increased according to the GI tolerance in order to achieve optimal nutrition support once patients have overcome the hemodynamic alterations related to sepsis, i.e. a few days after admission. For those patients with sepsis for whom EN is not feasible for prolonged periods (e.g. bowel discontinuity, etc.), PN should be prescribed after successful resuscitation up to approximatively half of the predicted or measured energy needs and EN prescribed as soon as the clinical condition permits.

Clinical question 21: Critically ill patients with surgical complications after abdominal or esophageal surgery

Recommendation 45

In patients after abdominal or esophageal surgery, early EN can be preferred over delayed EN.

Grade of recommendation: 0 – strong consensus (96 % agreement)

Recommendation 46

In critically ill patients with surgical complications after abdominal or esophageal surgery and unable to eat orally, EN (rather than PN) should be preferred unless discontinuity or obstruction of GI tract, or abdominal compartment syndrome is present.

Grade of recommendation: GPP – strong consensus (96 % agreement)

Recommendation 47

In the case of an unrepaired anastomotic leak, internal or external fistula, a feeding access distal to the defect should be aimed for to administer EN.

Grade of recommendation: GPP – strong consensus (95.83 % agreement)

Recommendation 48

In the case of an unrepaired anastomotic leak, internal or external fistula, or if distal feeding access is not achieved, EN should be withheld and PN may be commenced.

Grade of recommendation: GPP – strong consensus (100 % agreement)

Recommendation 49

In case of high output stoma or fistula, the appropriateness of chyme reinfusion or enteroclysis should be evaluated and performed if adequate.

Grade of recommendation: GPP – strong consensus (100 % agreement)

Commentary to recommendations 45 - 49

We performed a meta-analysis of EN vs no nutrition within the first 48 h, which did not reveal clear benefit of EN in this subgroup of patients, but a trend towards fewer infectious complications was observed (RR 0.47, CI 0.20, 1.07, p= 0.07). Two studies addressing early EN vs early PN in elective upper GI surgery were identified (333, 334, 335) (see Meta-analysis VIII in Supplemental Materials).

We did not identify any RCTs on abdominal trauma surgery nor (complicated) abdominal aortic surgery published since year 2000. Earlier studies have been summarized in recent guidelines (15).

In a sub-group analysis of the EPaNIC study, early and late PN was compared in complicated pulmonary/esophageal and abdomino-pelvic surgery patients. Reduced infection rates in late vs early PN were observed (29.9% vs. 40.2%, p=0.01) with no difference in any mortality outcomes, whereas all these patients received virtually no EN during the seven study days (16). The latter finding should most likely be interpreted as a harmful effect of early full feeding, also demonstrated in several other recent studies.

We did not identify any RCTs comparing gastric vs postpyloric EN in patients after complicated abdominal surgery.

We did not identify any studies focusing on the impact of different routes in periods of the ICU stay beyond “early”.

Without evidence, but based on common reasoning and pathophysiological considerations, surgical complications leading to gastrointestinal contents leaking into the abdominal cavity should always lead to withholding/stopping EN. At the time of developing such complications, patients usually have developed considerable energy deficits. Therefore, PN should be considered early after re-surgery if such a problem clearly cannot be solved within the next days, but started at a slow infusion rate. Enteral feeding access distal to the leak should be aimed for in these cases. Small bowel ischemia associated with early (in some cases aggressive) EN via surgical jejunostomy has been reported in several case reports (336, 337). In these cases, close monitoring of abdominal symptoms is required, and only continuous administration and slow build-up of EN via jejunostomy is advocated.

Importantly, the presence of an intestinal anastomosis or re-anastomosis without leakage should not delay EN.

Esophageal surgery commonly results in the loss of the lower esophageal sphincter function and is therefore associated with a significantly increased risk of aspiration. Therefore many centers use “nil per mouth” strategy with EN via a surgical jejunostomy. We identified two RCTs addressing early EN via surgical jejunostomy in patients after esophageal surgery (in one case, the study group included other upper gastrointestinal surgery patients, not limited to esophageal surgery (338)), suggesting potentially beneficial effects on the inflammatory state when compared with early PN and lower infection rates when compared with delayed EN (339). One larger retrospective study comparing early EN via surgical jejunostomy vs early PN resulted in less life-threatening complications and a shorter postoperative hospital stay (340).

In many cases of complicated abdominal surgery, patient tolerance to EN is impaired. Furthermore, depending on surgery, maldigestion and/or malabsorption may occur. Therefore, (supplemental) PN should be considered timely to avoid prolonged nutritional deficits. In specific situations with high-output stoma or fistula, chyme reinfusion or entero/fistuloclysis should be considered (341).

Clinical question 22: How should head trauma patients be fed?

Recommendation 50

Trauma patients should preferentially receive early EN instead early PN.

Grade of recommendation: B – strong consensus (96 % agreement)

Commentary

Our meta-analysis including three studies (342, 343, 344) showed a decrease in length of stay (RR -0.47, CI -7.57, -1.71, p=0.002), a trend for decrease in mortality (RR 0.69, CI 0.39, 1.23, p=0.21), but no difference in incidence of pneumonia when early EN was administered. (see Meta-analysis IX in Supplemental Materials).

Most trauma patients are not malnourished on admission (6% SGA C), but may become malnourished during ICU stay (increase in SGA B) (345). These patients at risk may be missed by the NUTRIC score since a significant loss of muscle mass occurs and is correlated with length of hospitalization and three month function level (346). Most of the patients (233) are underfed (receiving 58% of the energy requirements, and 53% of the protein requirements). After discharge, the nutrition deficit persists (346). Kompan et al. (342) compared early EN through a nasogastric tube to early PN followed by EN in multiple trauma patients and found a significant

decrease in pneumonia and LOS, but not in hospital stay and mortality. Justo Meirelles at al. (343), in moderate traumatic brain injury, compared EN to PN after resuscitation and did not show any significant outcome difference. Fan et al. (344) compared 3 groups: early EN, early PN and EN followed by supplemental PN. Mortality, complication were decreased significantly and nutritional status and clinical outcomes were improved in the early EN + supplemental PN group. An earlier meta-analysis (349) showed that early EN was associated with reduced mortality. Higher protein intake reaching 1.5 to 2 g/kg/day may be considered in this population, since there are large protein losses (20-30 g/L) (350).

Clinical question 23: How should obese patients be fed?

Recommendation 51

An iso-caloric high protein diet can be administered to obese patients, preferentially guided by indirect calorimetry measurements and urinary nitrogen losses.

Grade of recommendation: 0 – consensus (89 % agreement)

Recommendation 52:

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

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

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

If urinary nitrogen losses or lean body mass determination are not available, protein intake can be 1.3 g/kg "adjusted body weight" /d.

Grade of recommendation: GPP – consensus (89 % agreement)

Commentary to recommendations 51 and 52

Overweight and obese patients have become more prevalent in ICUs in parallel with increasing prevalence in the population (351). Reported recommendations (43) are based on randomized trials of hypocaloric intake performed more than 20 years ago in less than 50 patients and models based on observational data and summarized by Dickerson et al. (350). The BMI cutoff for lower energy provision and high protein supply was mostly 30 kg/m^2. Overweight patients have not been addressed. Obese patients are only slightly more prevalent in the ICU than in the hospital and in the related populations. There is a large variability in the prevalence between countries with more than 39% and 37% obese (BMI>30 kg/m^2) present in the US ICUs and hospital wards, 22% and 19% in Europe, 17% and 14% in South America and 10% and 7% in the Asian and Pacific region based on data from the Nutrition Day project (6, 351). Such large differences can be explained by different stages of the obesity epidemic but also by differences in genetic background and ethnicity. Moreover the cutoffs for overweight and obese need to be adapted to the ethnic background.

Hypocaloric nutrition is usually considered when energy supply is <70% of calculated energy needs based on ideal body weight. In hypocaloric nutrition a weight loss of 2-3 kg per week is considered acceptable. No systematic research on safe limits for weight loss in overweight and obese ICU patients has been reported. Additionally, hypocaloric medical nutrition therapy appears to be the rule on many ICUs (6).

We recommend the measurement of energy consumption with indirect calorimetry and urinary nitrogen loss to guide energy requirements and protein needs, since predictive equations are inaccurate. Obese patients defined on the basis of BMI are a heterogeneous group of patients. High BMI may be associated with an extremely trained muscle mass as in body builder at one end of the spectrum and sarcopenic obese with an even lower muscle mass than would be expected from height at the other end. The muscle mass of obese patients will be highly dependent on their level of activity. Age is a further factor to be considered. Muscle mass typically is maximal between 25-35 years of age and decreases thereafter. Thus, in an older person with the same body weight, a lower muscle mass is likely to be present.

If indirect calorimetry is not available and nitrogen excretion not measured, we suggest the use of ideal body weight as reference weight in overweight and obese patients. Many guidelines propose specific cutoffs at BMI 30, 40 and 50 kg/m^2 where standard nutrition formulas are replaced by alternative formula for energy and protein needs. With increasing BMI, the proportion of tissues with lower energy consumption and lower protein turnover decrease. Thus we propose to decrease energy provision where BMI indicates overweight or obesity. The reference (adjusted) body weight should then change from actual body weight to ideal body weight at a BMI > 25 kg/m^2. Probably using as ideal body weight: 0.9 x height in cm -100 (male) (or -106 (female)) is sufficiently precise giving the overall uncertainties. Such an approach would completely ignore the metabolic demand of adipose tissue and muscle. Adipose tissue utilizes 4.5 kcal/kg/day and muscle 13 kcal/kg/day. (352). The proportion of muscle within the excess weight of an obese individual might be roughly 10%. A pragmatic approach is to add 20-25% of the excess weight (actual body weight-ideal body weight) to ideal body weight for all calculations of energy requirements.

Several authors advocate a controlled undernutrition of obese subjects while providing a relatively larger dose of protein between 2-2.5 g/kg/day (ideal body weight as reference) (353). An observed 2.7 kg weight loss per week was considered to be advantageous when nitrogen balance could be achieved. It remains unclear whether overweight and obese critically ill patients have a higher nitrogen loss than patients with a normal BMI when adjusted for actual lean body mass.

Additional metabolic derangements such as decreased glucose tolerance, altered lipid metabolism, lack of micronutrients and decreased gut motility will need specific attention (354). Recommendations on early EN, gastrointestinal tolerance and progressive increase in nutrition over several days apply similarly to overweight and obese patients as to all other ICU patients.

Clinical question 24: How should nutrition therapy be monitored during the ICU stay?

The issue of monitoring is generally not addressed in nutrition guidelines, even though it is the main step to achieve success with any therapy. In an attempt to decrease the gap between the prescribed quantities and those actually delivered, particularly with EN, we propose standard operating procedures developed in a separate document (200). The main goals of monitoring of nutrition therapy in the ICU are:

a) To assure that optimal nutritional support is planned and provided as prescribed regarding energy, protein and micronutrient targets,

b) To prevent or detect any possible complication,

c) To monitor response to feeding and detect refeeding, and

d) to detect micronutrient deficiencies in patient categories at risk.

Clinical question 25: Which laboratory parameters should be monitored?

Studies comparing measurement of laboratory parameters versus not measuring are not available. However, no study is required to show that laboratory parameters are important to prevent or detect severe complications such as refeeding syndrome or liver dysfunction related to nutrition, as well as to assist in the achievement of normoglycemia and normal electrolyte values. The importance of phosphate, potassium and magnesium monitoring when initiating feeding in critically ill patients is stressed. Therefore most laboratory recommendations will remain supported by a low level of evidence. We highlight the importance of monitoring glucose and preventing refeeding syndrome in this guideline. The other monitoring recommendations are discussed in a separate article (200).

i. Glucose

Recommendation 53

Blood glucose should be measured initially (after ICU admission or after artificial nutrition initiation) and at least every 4 hours, for the first two days in general.

Grade of recommendation: GPP – strong consensus (93 % agreement)

Recommendation 54

Insulin shall be administered, when glucose levels exceed 10 mmol/L.

Grade of recommendation: A – strong consensus (93 % agreement)

Commentary to recommendations 53 and 54

The issue of stress-related hyperglycemia has been a matter of intense debate for 2 decades. The ideal blood glucose target appears elusive when factors linked to the patient (e.g. presence of previous diabetes, of a neurological impairment), to the treatment (amount and route of calories provided) and to the time from injury are not well defined. A number of observational studies confirmed a strong association between severe hyperglycemia (> 180 mg/dl, 10 mmol/l) (355), marked glycemic variability (coefficient of variation > 20%) (356, 357), mild hypoglycemia (< 70 mg/dl, 3.9 mmol/l) (358) and increased mortality. However the prospective trials remain inconclusive, owing to differences in practices and to the difficulties in achieving safe and effective glycemic control. The glycemic target associated with the best adjusted outcome ranges from 80-150 to 140-180 mg/dl (7.8-10 mmol/l), which is different from the blood glucose levels actually achieved (359).

Therefore, current recommendations suggest starting insulin therapy when blood glucose exceeds 150 (347) or 180 mg/dl (10 mmol/l) (360). Blood glucose control is essential, and should target a concentration of 6-8 mmol/l which has been shown to be associated with improved outcome (361, 362, 363, 364, 365, 366). Even though the supporting evidence is weak, there is no rationale to support another target blood glucose level. The monitoring of blood glucose is discussed in a separate article focused on monitoring (200).

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

The process of glycemic control encompasses multiple steps (367):

- Blood draw: preferentially central venous or arterial. Avoid capillary pricks in critically ill patients

- Glucose meter: the point-of-care devices are not validated for use in the critically ill, as several sources of interference are likely. The use of blood gas analyzer or central laboratory analyzers (hexokinase-based) is essential
- Insulin: intravenous and continuous in case of ongoing nutrition support (enteral or parenteral) using an electric syringe
- Insulin algorithm: dynamic scale rather than sliding scales

How to avoid hypo- and hyperglycemia during nutrition support?

Severe hyperglycemia, mild hypoglycemia and high glycemic variability should be avoided, as a result of the strong and consistent associations reported from cohort studies between each of these domains of dysglycemia and adjusted mortality and morbidity. The use of a low limit of the target range > 90 mg/dl and of dynamic scales to titrate the infusion of insulin appear as reasonable strategies that will need to be adapted to the local environment. Avoiding the intravenous infusion of large amounts of glucose (>3-4 mg/kg/min) is probably also recommendable.

Commonly, hyperglycemia can be managed with increased insulin doses, but adequacy of carbohydrate administration should always be considered when high insulin needs (exceeding 6 U/hr) persist for more than 24 hours. Rarely, a temporary reduction of feeding may be considered. These provided limits are arbitrary and not based on evidence, therefore an individual approach to differentiate possible reasons for high insulin needs (caloric delivery, infection, steroids etc.) and interpretation of trends is required.

ii. Electrolytes

Recommendation 55

Electrolytes (potassium, magnesium, phosphate) should be measured at least once daily for the first week.

Grade recommendation: GPP – strong consensus (92 % agreement)

Recommendation 56

In patients with refeeding hypophosphatemia (<0.65 mmol/l or a drop of >0.16 mmol/l), electrolytes should be measured 2-3 times a days and supplemented if needed.

Grade recommendation: GPP – strong consensus (100 % agreement)

Recommendation 57

In patients with refeeding hypophosphatemia energy supply should be restricted for 48 h and then gradually increased.

Grade recommendation: B – strong consensus (100 % agreement)

Commentary to recommendations 55 - 57

Refeeding syndrome can be defined as the potentially fatal shifts in fluids and electrolytes that may occur in malnourished patients receiving artificial refeeding. Each case of refeeding syndrome – a potentially lethal state (368) - has to be detected early to prevent complications (369). Therefore, assessment of nutritional status at admission is needed with a schedule for the measurement of electrolytes, including phosphate. Studies measuring laboratory parameters vs not measuring are not available. However, laboratory parameters are important to prevent or detect severe complications like refeeding syndrome or liver dysfunction related to nutrition, as

well as to assist in the achievement of normoglycemia and normal electrolyte values. Repeated measurements of P, K and Mg during initiation of feeding in critically ill patients are important to detect development of refeeding syndrome, especially because among critically ill patients electrolyte disturbances upon refeeding are not limited to patients with overt malnutrition. The occurrence of refeeding hypophosphatemia may be conceived as a warning signal. In a RCT, Doig et al. showed that protocoled caloric restriction for 48 hours in patients developing hypophosphatemia upon refeeding improved survival despite similar phosphate supplementation in both groups (143).

Slow progressions to energy target during the first 72 hours, also called caloric restriction, should be considered to facilitate control of electrolyte disturbances if refeeding syndrome is anticipated or detected (370). Importantly, whereas potassium is commonly measured in critically ill patients, measurements of phosphate are less common. Undetected rapid development of severe hypophosphatemia may lead to death after initiation of feeding as patients admitted to ICU are often malnourished either before or during admission to the hospital (86). Missed electrolyte disturbances might explain the dramatic increase in early mortality associated with intensive feeding in the INTACT trial including patients with ALI and not fed for 6-8 days prior to the intervention (136, 147). A recent early calorie restriction study showed that electrolyte alterations were less likely to occur with a cautious introduction of feeding (371). This was confirmed by a retrospective study (372).

4. Conclusions.

Medical nutrition therapy of the critically ill patient remains a challenge. Numerous published trials however have allowed us to improve the evaluation of the needs of patients throughout their ICU stay, integrating with better understanding of the physiology. The absence of studies focused on the early or prolonged stay does not allow us to fine tune the prescription of nutrition in these conditions. ICU patients are a heterogeneous group and a unique recommendation for every patient and situation cannot be suggested. Each diagnosis, each period of time (early, post resuscitated, stabilized, long stay), and any concurrent complications must be taken into consideration. Nevertheless, these guidelines based on the best current knowledge and evidence provide a set of nutritional recommendations in the most frequent clinical situations encountered in daily practice in the ICU.

1751 Table 5. Thresholds for severity grading of malnutrition into Stage 1 (Moderate) and Stage 2
1752 (Severe) malnutrition according to the recent ESPEN GLIM recommendations (23).

	Phenotype Criteria			**Etiology Criteria**	
	Weight Loss (%)	**Body Mass Index (kg/m^2)**	**Muscle Mass**[a]	**Food Intake, malabsorption or GI symptoms**	**Disease burden/ Inflammation**
Stage 1/ Moderate Malnutrition (Requires 1 phenotypic and 1 etiologic criterion)	5-10% within the past 6 mo, or 10-20% beyond 6 mo	<20 if <70 yr, <22 if ≥70 yr Asia:<18.5 if <70 yr, <20 if ≥70 yr	Mild to moderate deficit (per validated assessment methods – see below)	Any reduction of intake below ER for >2 weeks, or moderate mal-absorption/GI symptoms[b]	Acute disease/ injury[d], or chronic disease-related[e]
Stage 2/ Severe Malnutrition (Requires 1 phenotypic and 1	>10% within the past 6 mo, or >20% beyond 6	<18.5 if <70 yr, <20 if ≥70 yr Asia: TBD	Severe deficit (per validated assessment methods – see below)	≤50% intake of ER for >1 week, or severe mal-absorption/GI symptoms[c]	Acute disease/ injury[d], or chronic disease-related[e]

etiologic criterion)	mo				

GI=gastro-intestinal, ER=energy requirements, yr=year, mo=month

a For example fat free mass index (FFMI, kg/m^2) by dual-energy absorptiometry or corresponding standards using other body composition methods like bioelectrical impedance analysis (BIA), CT or MRI. When not available or by regional preference, physical exam or standard anthropometric measures like mid-arm muscle or calf circumferences may be used. Thresholds for reduced muscle mass need to be adapted to race (Asia). Functional assessments like hand-grip strength may be used as a supportive measure.

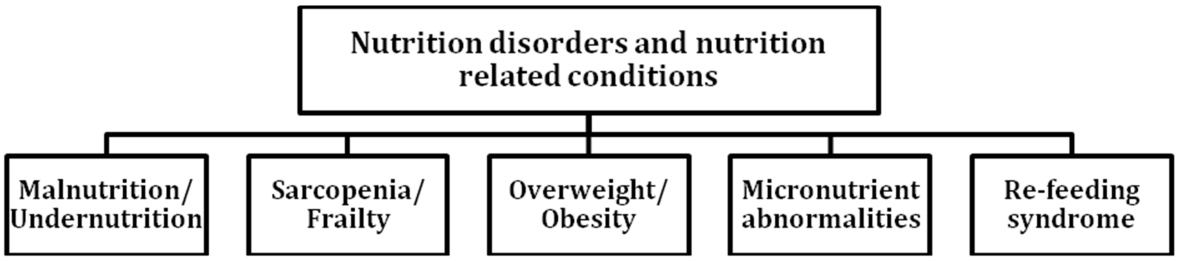
b Gastrointestinal symptoms of moderate degree – dysphagia, nausea, vomiting, diarrhea, constipation or abdominal pain.

c Gastrointestinal symptoms of severe degree – dysphagia, nausea, vomiting, diarrhea, constipation or abdominal pain.

d Acute disease/injury-related with severe inflammation. For example major infection, burns, trauma or closed head injury.

e Chronic disease-related with chronic or recurrent mild to moderate inflammation. For example malignant disease, chronic obstructive pulmonary disease, congestive heart failure, chronic renal disease or any disease with chronic or recurrent Inflammation. CRP may be used as a supportive laboratory measure.

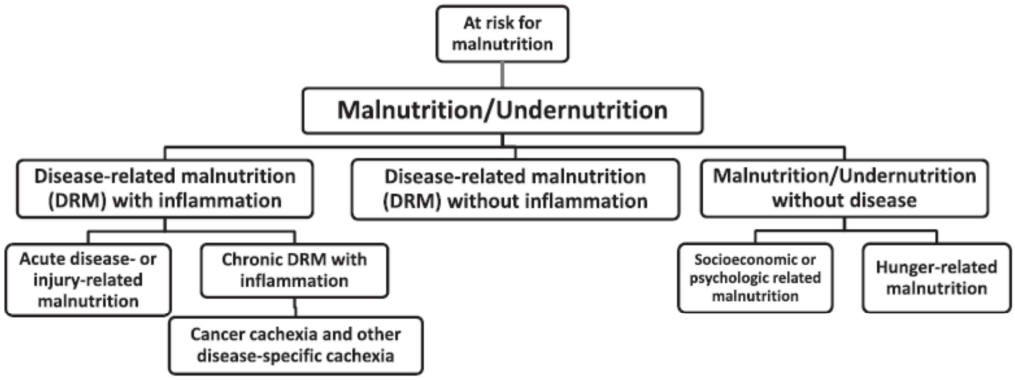
1772 Figure 1 A: Overview of nutrition disorders and nutrition-related conditions (13).



1773

1774 Fig 1 B: Diagnosis tree of malnutrition; from at risk for malnutrition, basic definition of

1775 malnutrition to etiology-based diagnoses



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1777 From Cederholm et al. (20) with permission.

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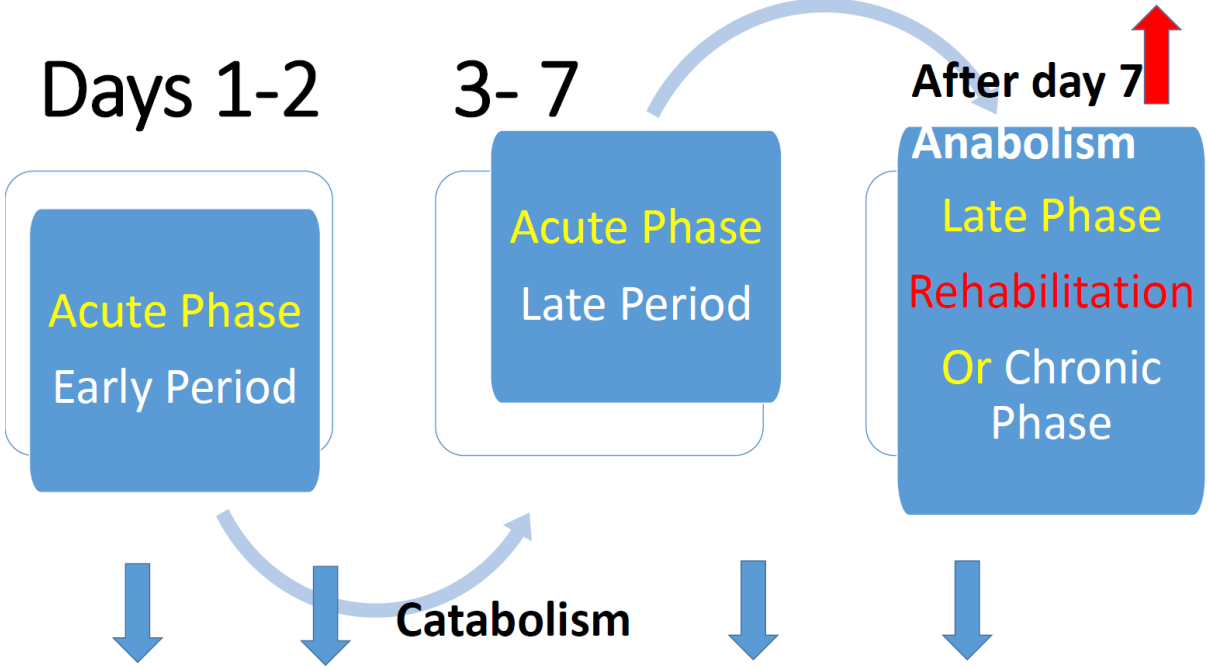
Figure 2: Description of the acute and late phases following infection/stress/injury. After injury, the acute phase is composed of an early and a late period. Then the post-acute phase can be progressing to convalescence and rehabilitation or chronicity and Prolonged Inflammatory and Catabolic Syndrome (PICS).



1787 **Figure 3. Meta-analysis of studies comparing infection complications in patients receiving**

1788 **early enteral or parenteral nutrition (Meta-analysis II).**

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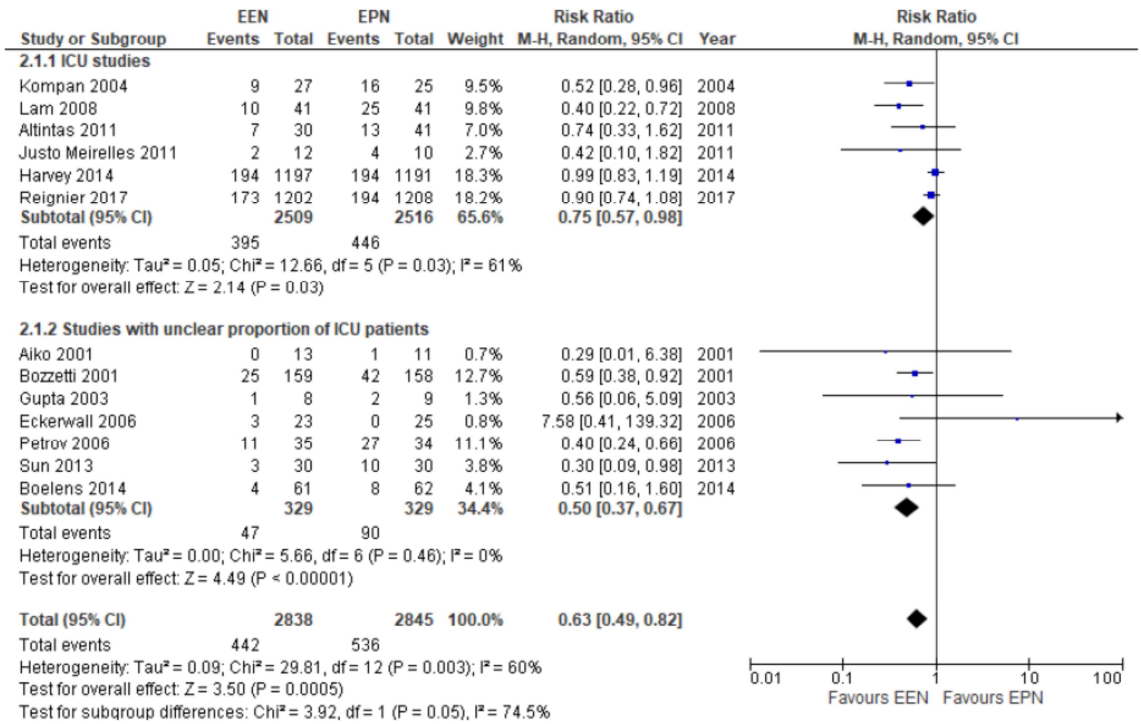

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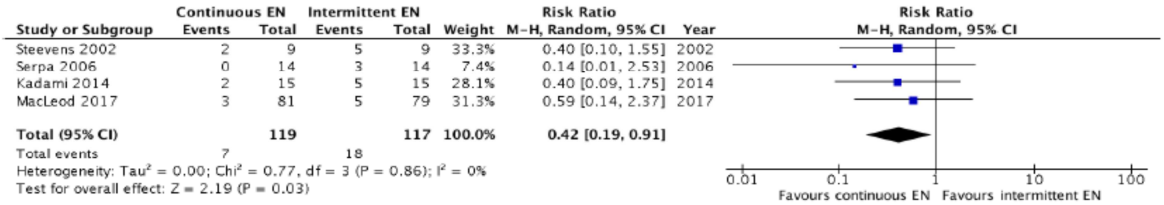
1792 **Figure 4. Meta-analysis of occurrence of diarrhea in patients receiving continuous or**

1793 **intermittent enteral feeding (Meta-analysis III)**.



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1799 **Figure 5. Meta-analysis of feeding intolerance in patients receiving gastric or post pyloric**

1800 **feeding (Meta-analysis IV).**

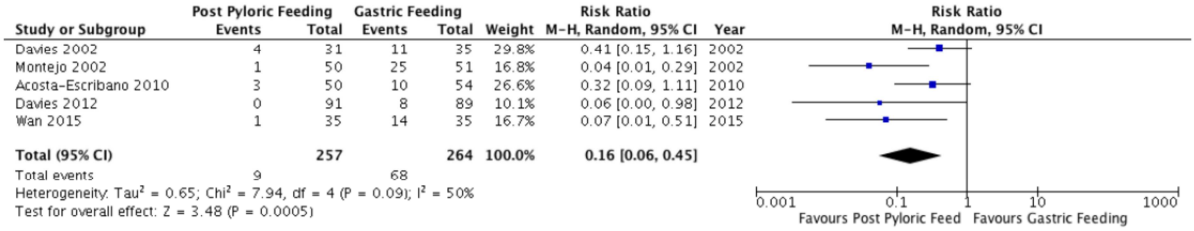

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Figure 6. Meta-analysis of (a) short term mortality and (b) infection complications in patients receiving iso or hypocaloric medical nutrition therapy guided by indirect calorimetry or predictive equations (Meta-analysis VI).

Figure 6.a.

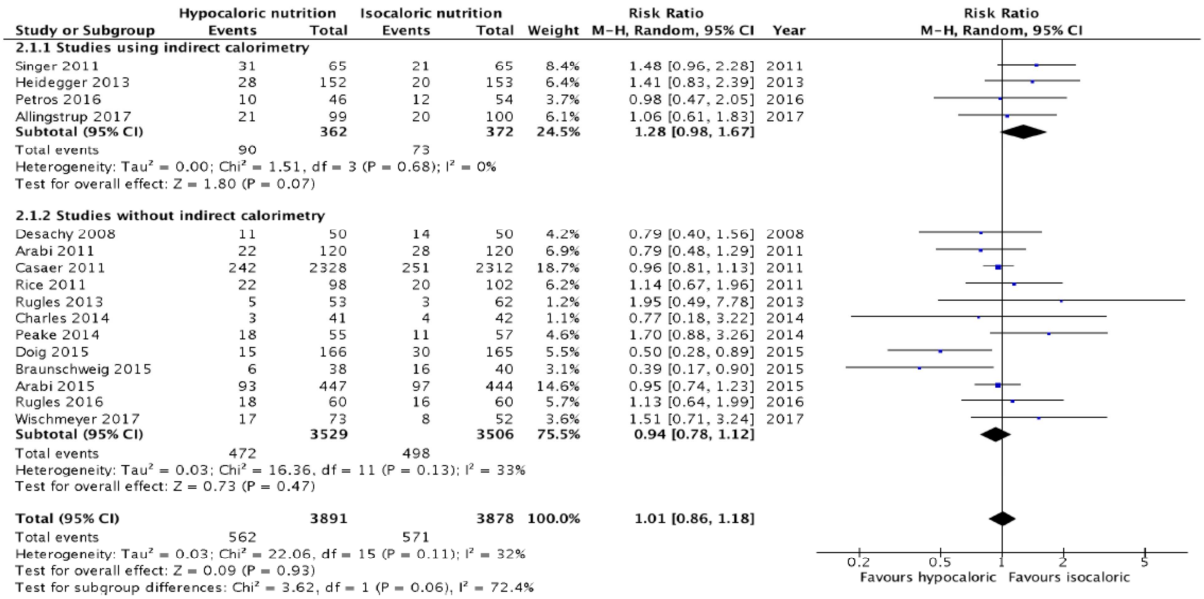
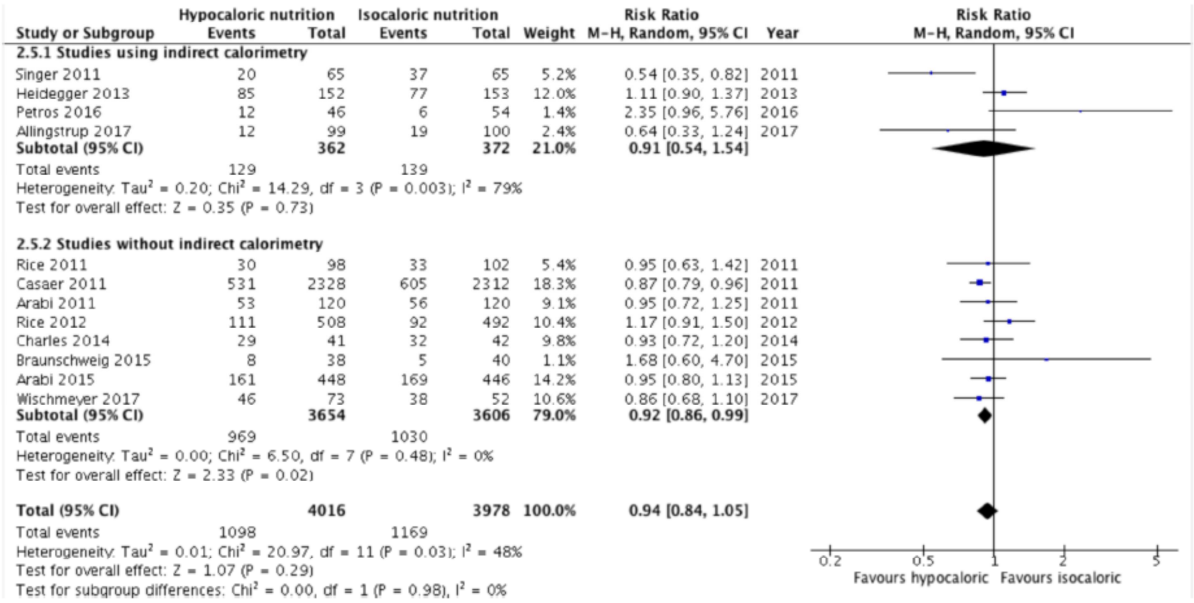


Figure 6.b.



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