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Consensus and Guideline

Clinical practice guidelines for nutritional assessment and monitoring of adult ICU patients in China

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ABSTRACT

The Chinese Society of Critical Care Medicine (CSCCM) has developed clinical practice guidelines for nutrition assessment and monitoring for patients in adult intensive care units (ICUs) in China. This guideline focuses on nutrition evaluation and metabolic monitoring to achieve optimal and personalized nutrition therapy for critically ill patients. This guideline was developed by experts in critical care medicine and evidence-based medicine methodology and was developed after a thorough review of the system and a summary of relevant trials or studies published from 2000 to July 2023. A total of 18 recommendations were formed and consensus was reached through discussions and reviews by expert groups in critical care medicine, parenteral and enteral nutrition, and surgery. The recommendations are based on currently available evidence and cover several key fields, including screening and assessment, evaluation and assessment of enteral feeding intolerance, metabolic and nutritional measurement and monitoring during nutrition therapy, and organ function evaluation related to nutrition supply. Each question was analyzed according to the Population, Intervention, Comparison, and Outcome (PICO) principle. In addition, interpretations were provided for four questions that did not reach a consensus but may have potential clinical and research value. The plan is to update this nutrition assessment and monitoring guideline using the international guideline update method within 3–5 years.

Introduction

Nutrition monitoring and assessment are important in understanding and addressing the heterogeneous challenges during nutritional therapy in critically ill patients. Clinically assessable biomarkers and parameters that reflect patients' metabolic and disease status from nutrition interventions are essential to satisfying the needs for metabolism during critical illness, in preventing associated physiological disorders, minimizing nutritrauma and, eventually, guaranteeing the achievement of the optimal goals. Nutritional therapy is a basic but complex treatment during critical illness, and monitoring and assessment are necessary and integral throughout the entire treatment process. The "Guidelines for Nutritional Support in Critically Ill Patients (Draft)" released in 2006 was mainly based on expert consensus and limited evidence. But there have been changes and advances since then. The Chinese Society of Critical Care Medicine (CSCCM) organized experts in critical care medicine for the development of this guideline, aiming to provide guidance and standardize the clinical practice of nutritional therapy of critically ill adult patients in China so as to adopt appropriate nutrition strategies and treatment plan and achieve the goal of personalized nutrition therapy under the monitoring guidance.

The guidelines should also be useful for intensive care unit (ICU) physicians and nurses, dietitians, and technicians who are engaged in work relating to the nutritional management of critically ill patients in hospitals and also to nutritional education and research.

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Target Population

The guidelines should be useful for critically ill patients admitted to adult ICU who are to receive or are receiving nutritional therapy.

Guideline Users

The guidelines should also be useful for ICU physicians and nurses, dietitians, and technicians who are engaged in work relating to the nutritional management of critically ill patients in hospitals and also to nutritional education and research.

Relevant Definitions

Nutritional risk (NR)

The actual or potential NRs that lead to adverse clinical outcomes (e.g., increased incidence of infection-related complications, prolonged hospitalization, increased hospitalization costs, etc.) in patients.[1,2]

Nutritional risk screening (NRS)

The process of using a rapid scale to identify patients at NR in a specific population.[3,4]

The NR screening is aimed at reducing the incidence of malnutrition and improving its associated poor outcome. Increased NR implies the potential or presence of malnutrition, as well as the risk of developing complications related to undernutrition or other adverse outcomes that can be prevented with timely and appropriate nutritional interventions. Either acute stress, chronic starvation, or current pathophysiologic processes[5] can lead to a significant increase in NR in critically ill patients.[6] Dynamic screening for NR is, therefore, all the more important. Patients at NR should be assessed and individualized, and those not yet at risk should be screened again after a period of time.

Nutrition assessment

It refers to the comprehensive assessment by clinical professionals according to clinical history, nutritional intake history, nutritional metabolism, and various functions of the body so as to determine the indications for nutritional therapy, formulate nutritional treatment plans, and predict possible adverse events.[4]

Malnutrition

Malnutrition in the broad sense includes undernutrition and overnutrition, which refers to the state of insufficient nutrient intake, impaired nutrient metabolism, or excessive nutrient intake and adversely affects the composition of the human body, physiological function, and clinical prognosis. In clinical occasions, malnutrition is mainly used for undernourished patients, namely those with low body weight malnutrition as determined based on the diagnostic criteria: body mass index (BMI) <18.5 kg/m^2 with poor general condition.[1,7]

The Development Methodology of the Guideline

The development of this guideline followed the rigorous methodologies outlined in the "Principles for the Development/Revision of Clinical Guidelines in China (2022 Edition)," published by the Chinese Medical Association in 2021.[8] The guideline were written with reference to the Reporting Items for Practice Guidelines in Healthcare (RIGHT)[9] checklist.

Guideline registration

A proposal has been written for this guideline, which is also prospectively registered on the Practice guideline REgistration transPAREncy platform (PREPARE) under the registration number PREPARE-2021CN186.

Guideline sponsors

The guideline was initiated by the CSCCM, with methodological support from the Guidelines and Standards Research Center of the Lanzhou University Institute of Health Data Science, the WHO Collaborating Center for Guideline Implementation and Knowledge Translation, and the Lanzhou University GRADE Center.

Guideline working group

A multidisciplinary working group was established for this guideline, including a multidisciplinary team mainly from the critical care medicine, covering experts in the fields of parenteral and parenteral nutrition, general surgery, and evidence-based medicine, which was divided into a steering committee, a writing group, a consensus expert group, and a methodology group according to their responsibilities. The steering committee is composed of 6 experts, whose main duties are to supervise the whole process of guideline development, provide necessary advice and guidance for guideline development, and approve the guideline; the writing group is composed of 17 experts with rich clinical experience, whose main duties are to put forward specific clinical questions, draft and revise recommendations, and draft the full guideline; the consensus expert group was composed of 35 clinicians with rich clinical experience, whose main responsibilities were to vote for consensus on the importance of the clinical questions and the preliminary recommendations; the methodology group was composed of a team of methodology experts from the Guidelines and Standards Research Center of the Lanzhou University Institute of Health Data Science/Lanzhou University GRADE Center, whose main responsibilities were to provide methodology training to the various teams of experts, and to provide guidance on the process of evidence retrieval, evaluation, and grading. All members of this guideline working group have completed a mandatory conflict of interest (COI) disclosure form, declaring relevant financial or non-financial COIs in the last 3 years. None of the working group members had a direct COI in relation to this guideline and, therefore, had unrestricted access to the entire guideline development process.

Collection and selection of clinical questions

After soliciting opinions and suggestions from all parties, members of the writing group fully reviewed and summarized relevant studies published in critical care nutrition, and also referred to previous guidelines and consensus published by domestic and foreign organizations, and initially proposed 26 clinical questions. The methodology group designed a questionnaire on the importance of clinical questions, and allowed the consensus expert group to rate the importance of the clinical questions and provide feedback through an online questionnaire, in which the importance rating was based on a 7-point Likert scale (1–7: increasing importance of the question). In addition, clinicians were also allowed to add other important clinical questions. Finally, according to the results of importance ranking and expert opinions, 24 clinical questions of concern to this guideline were selected after the research feedback from 40 experts.

Retrieval, evaluation, and grading of evidence

Members of the guideline writing group, under the guidance of the methodology group, deconstructed the final included clinical questions according to the Population, Intervention, Comparison, and Outcome (PICO) principle and searched them according to the deconstructed questions. The databases searched included MEDLINE, Cochrane Library, Web of Science, SinoMed, Wanfang, and China National Knowledge Infrastructure (CNKI), as well as the official websites of the American Society for Parenteral and Enteral Nutrition (ASPEN), the European Society for Parenteral and Enteral Nutrition (ESPEN), and the American Society of Critical Care Medicine (SCCM), with supplemental searching of the Google Scholar, etc. The search period was from the inception of the database to July 2023. The search terms mainly included "Critical Care, Critical Illness, Nutritional Support, Enteral Nutrition, Parenteral Nutrition, ICU, etc." If systematic reviews of high methodological quality were found after the systematic search, they were directly included to support the recommendations; if the methodological quality of the existing systematic reviews was low, or if there were no systematic reviews for a particular question after the screening, the primary studies (randomized controlled trials, observational studies, etc.) were included to produce new systematic reviews, thus supporting the formation of recommendations. The GRADE approch was used to grade the level of evidence and the strength of recommendation.

Formation of recommendations

The writing group drafted 24 preliminary recommendations based on the Evidence-to-Decision table after considering the benefits and harms, the patient's values and preferences, and the health economic aspects. The methodology group designed the drafted recommendations into a questionnaire and organized two rounds of the Delphi survey in February 2023 and April 2023 for the consensus expert group. A total of 68 participants were involved in the two rounds of the Delphi survey, and a total of 72 expert opinions were collected. The writing group revised recommendations based on expert opinions, and finally reached a consensus on 18 recommendations (consensus criteria: consensus rate of >75% for each recommendation).

Reporting, external review, and approval of guideline

Based on the consensus recommendations, the writing group completed the first draft of the full guideline and then submited it to external review experts for review. Based on the feedback from the external reviewers, the writing group revised the guideline, and finally, the steering committee discussed and approved the guideline for publication.

Dissemination and implementation

After the release of the guideline, the working group will publicize and promote the guideline mainly through the following ways: (1) publicizing the guideline in professional journals, websites, and other new media; and (2) presenting and interpreting the guideline at the annual academic conferences of critical care nutrition to ensure that clinicians and other stakeholders fully understand and correctly apply the guideline.

Updating of the guideline

The working group plans to update the guideline in 3–5 years after publication, following the international guideline update method.[10]

Guidelines for Responses to Clinical Questions and Evidence

1. Can the Nutritional Risk Screening 2002 (NRS 2002) or the modified Nutrition Risk Score (mNUTRIC) be used for routine NR screening in critically ill patients?

Recommendation: We suggest screening the NR of critically ill patients by either the NRS 2002 or the NUTRIC score (or mNUTRIC) within 48 hours after ICU admission. Patients should be considered to be at high NR if they have NRS 2002 score of ≥5 or mNUTRIC score of ≥5, and a comprehensive nutritional assessment and nutritional therapy should be initiated as soon as possible in order to improve outcome (weak recommendation, low-quality evidence).

Rationale: NRS is the first step in nutritional therapy; the higher the NR, the greater the benefit of nutritional therapy. However, there is still a lack of a uniform, high-quality, evidence-based nutritional screening criterion for critically ill patients. The ESPEN guideline defines critically ill patients admitted to the ICU for more than 48 h as being at NR and at risk for nutritional therapy.[11]; the ASPEN guideline recommends NR screening within 48 h of ICU admission using either the NRS-2002 or the NUTRIC score.[12]

The NRS-2002 scored patients in three components, including nutritional status, disease severity, and age with a total score of 0–7. Patients with an NRS-2002 score >3 were shown to have improved clinical outcomes after receiving enteral nutrition (EN) or oral nutritional preparations. Therefore, patients with an NRS-2002 score >3 are defined as being at NR.[2] According to the results of a prospective study of patients undergoing abdominal surgery,[13] the ASPEN guideline recommends that a high NR exists when critically ill patients have an NRS-2002 score ≥5.

Body weight is an important parameter in NRS-2002. However, neither the body weight nor index of body weight change

can reflect NR because of a variety of affectable factors, such as edema, multiple plasmapheresis, fluid therapy, underlying patient disease, and nutritional status. When NRS-2002 is used for nutritional screening, it is necessary to determine the appropriate weight index to calculate the BMI, including the actual body weight, ideal body weight (IBW), and adjusted body weight (AdBW). Male IBW (kg)=50 + (2.3 × [height−152])/2.54; female IBW=45.5 + (2.3 × [height–152])/2.54), the unit of height is centimeter. AdBW=IBW+ 0.4 × (actual body weight – IBW).[14] AdBW is recommended for severely obese patients (>30% overweight compared with IBW). Internationally, BMI <20 kg/m^2 is defined as malnutrition, 25.0 kg/m^2 ≤BMI <30 kg/m^2 as overweight, and BMI ≥30.0 kg/m^2 as obesity.

The NUTRIC score grades patients according to the following criteria: age, Acute Physiology and Chronic Health Evaluation (APACHE II) score, Sepsis-related Organ Failure Assessment (SOFA) score, comorbidities, days of hospitalization before admission to the ICU, and interleukin-6 level, with 0–5 points as at low NR, and 6–10 points as at high NR. A NUTRIC score ≥6 is related to increasing death risk and longer duration of mechanical ventilation. In addition, patients with a higher NUTRIC score were more likely to benefit from nutritional interventions than those with a lower score.[15] In recent years, several studies found that a high NUTRIC score was associated with a poor outcome in critically ill patients [16–24] suggesting that the NUTRIC score could be used for NRS in critically ill patients.

The mNUTRIC score is derived from the NUTRIC score but excludes IL-6. mNUTRIC score ≥5 implies high NR and poor outcome.[15] A prospective study[25] compared the results of the mNUTRIC score alone and in combination with the NRS-2002 in predicting in-hospital mortality in critically ill patients. The study showed that the mNUTRIC and NRS-2002 had similar efficacy in predicting hospital mortality (mNUTRIC Area Under Curve [AUC]=0.693, 95% confidence interval [CI]: 0.638 to 0.747 *vs*. NRS-2002 AUC=0.645, 95% CI: 0.587 to 0.703 *vs.* combined AUC=0.666, 95% CI: 0.608 to 0.723).

Evidence summary: A systematic review included four observational studies on NRS-2002 scores (n=918)[17,25–27] and the results suggested that patients with NRS-2002 scores ≥5 had a longer hospital length of stay (mean difference [MD]=2.82, 95% CI: 0.12 to 5.52, P=0.04) and higher mortality (odds ratio [OR]=2.13, 95% CI: 1.60 to 2.83, P <0.001) compared with patients with NRS-2002 scores <5. Another systematic review incorporating 19 observational studies on the mNUTRIC score (n=4288)[19,20,23,25,27–41] found critically ill patients with mNUTRIC scores ≥5 had longer ICU stays (MD=2.37, 95% CI: 1.82 to 2.92, I^2=0, P=0.009) and higher mortality (OR=5.00, 95% CI: 4.28 to 5.83, P <0.001) compared to those with mNUTRIC scores <5.

2. Can the Subjective Global Assessment (SGA) Scale be used for routine nutritional assessment in critically ill patients?

Recommendation: SGA is suggested as a scale tool for nutritional assessment in critically ill patients (weak recommendation, low-quality evidence).

Rationale: The SGA consists of two main components: the patient's medical history (weight change, food intake change, gastrointestinal symptoms, functional capacity, and metabolic needs, etc.) and physical examination (subcutaneous fat loss, muscle loss, edema/fluid accumulation). Three grades are assigned based on the score: grade A, well nourished; grade B, moderately malnourished; and grade C, severely malnourished. The SGA was initially validated in surgical patients and later was generalized and widely used to assess the nutritional status of hospitalized patients.[42] In recent years, several studies in critically ill patients found[43–45] that patients diagnosed as malnourished based on SGA had increased hospital mortality, prolonged ICU stay, and increased risk of nosocomial infections. In addition, studies showed good reproducibility and reliability of SGA in detecting malnutrition in mechanically ventilated patients.[46]

Other commonly used nutrition assessment scales include the Mini-Nutritional Assessment (MNA), the Malnutrition Universal Screening Tool (MUST), and the Malnutrition Screening Tool (MST), but the three scores are mostly used for geriatric and community-based malnutrition assessment,[47,48] and lack application in critical illness.

Evidence summary: A systematic review[49] comparing the efficacy of SGA with MNA and other nutritional assessment tools in predicting adverse outcomes in ICU patients showed that malnutrition assessed by either tool was independently associated with longer ICU stay, increased ICU readmission, increased nosocomial infections, and increased in-hospital mortality; while malnutrition diagnosed by SGA was associated with an increased incidence of nosocomial infections (4.5 *vs*. 0.6 infections/person, P=0.001), ICU readmission (adjusted OR=2.27; 95% CI: 1.08 to 4.80; P <0.05), and the need for care after discharge; malnutrition diagnosed by MNA was not associated with adverse clinical outcomes; malnutrition diagnosed by MUST (which was at mild risk of bias in the study) was associated with a decreased mortality after 1 year of ICU discharge (adjusted OR=0.01; 95% CI: 0.01 to 0.60; P=0.01), but not with other postoperative complications. A total of 10 cohort studies were included in the systematic by the Guideline Working Group[21,50–58], of which 4 studies[53,56–58] (n=464) reported a significantly increased risk of death in malnutrition (SGA grade B and C) compared with good nutrition (grade A) (risk ratio[RR]=2.45, 95% CI: 1.82 to 3.29, P <0.001).

3. Can plasma proteins (albumin [ALB], prealbumin [PAB]) be used as indicators for nutritional screening and assessment in critically ill patients?

Recommendation 3.1: We suggest using ALB or PAB for nutrition risk screening in critically ill patients (weak recommendation, low-quality evidence).

Recommendation 3.2: Do not use ALB or PAB for nutritional assessment in the early stages of acute inflammation in critically ill patients (weak recommendation, very low-quality evidence).

Rationale: Plasma proteins such as ALB, PAB, transferrin, and retinol-binding protein are mainly synthesized by hepatocytes and are important indicators of protein metabolism. The half-life of plasma proteins varies widely, with ALB having a half-life of about 21 days, PAB about 2–3 days, and transferrin and retinol-binding protein about 8 days and 12–14 h, respectively.[59] During the acute inflammatory phase in critically ill patients, autophagy and protein catabolism are activated, along with a downregulation of protein anabolism. In the absence of intervention, plasma levels of ALB, PAB, and transferrin often decrease, while "acute-phase response protein" (e.g., C-reactive protein [CRP]) is significantly increased. Two

recent observational studies have indicated an association between decreased levels of plasma ALB and PAB and increased NR in critically ill patients.[60,61] A secondary analysis of an international multicenter RCT[62,63] demonstrated a significant increase in the 180-day mortality rate in a group of patients with low plasma ALB and PAB on admission compared to those with normal plasma protein concentrations, affirming the value of plasma ALB and PAB levels in predicting NR and poor outcomes. Consequently, plasma proteins can be used as biomarkers for NR screening.

The inflammatory response in the acute phase of critically ill patients leads to increased vascular permeability, redistribution of plasma proteins, and leakage of large amounts of plasma proteins into interstitial space, resulting in the above changes in plasma proteins not being fully consistent with nutritional status assessment or effectiveness of nutritional intervention, and thus cannot be suggested as accurate or independent nutritional status assessment indicators in the early acute phase of critically ill patients.[64] In studies monitoring PAB to assess the effectiveness of the nutritional intervention, early-stage plasma PAB was only associated with inflammation severity and did not reflect the adequacy of energy or protein provision.[65,66] Therefore, in alignment with ASPEN guideline, we suggest not using plasma proteins for nutritional assessment in the early acute stage of critically ill patients due to inadequate evidence.[12,67]

Evidence summary: A retrospective cohort study recruiting critically ill corona virus disease 2019 (COVID-19) patients (n=408) for NR screening found that a reduction in plasma PAB levels (<150 mg/L) was associated with a higher NR (NRS-2002 ≥4) (OR=2.46, 95% CI: 1.62 to 3.72).[60] A prospective cohort study (n=261) found that patients in the group with high NR (mNUTRIC score 5–9) had reduced plasma levels of ALB compared to those in the group with lower NR (mNUTRIC score 0–4) {low NR group (median [interquartile spacing]): 31.30 (29.17, 35.35) g/L *vs*. high NR group: 28.55 (23.56, 33.15) g/L} and also reduced plasma levels of PAB {low NR group (median [interquartile spacing]): 155.20 (116.16, 198.14) mg/L *vs*. high NR group: 119.50 (84.36, 158.58) mg/L}.[61] A secondary analysis of an international, multicenter RCT (n=1389) showed that the group of patients with low plasma ALB levels on admission had a significantly higher 180-day mortality rate (219/676 [32.4%] *vs*. 162/713 [22.7%], fully adjusted hazard ratio [HR]=1.4, 95% CI: 1.11 to 1.77; P=0.005).[62] Similarly, another secondary analysis (n=517) found the group of patients with low plasma PAB levels on admission also exhibited a significantly higher 180-day mortality rate (115/306 [37.6%] *vs*. 47/211 [22.3%], fully adjusted HR=1.59, 95% CI: 1.11 to 2.28; P=0.011).[63]

A retrospective cohort study (n=154) found that in ICU patients receiving EN therapy, change in PAB levels during hospitalization was negatively correlated with CRP (r=−0.554), while no significant correlation was found with energy provisions (≥60% energy target group: [2.74 ± 9.50] mg/dL, <60% energy target group: [2.48 ± 9.36] mg/dL, P=0.86).[65] Another retrospective cohort analysis (n=252) revealed a negative correlation between plasma ALB levels and three inflammatory biomarkers (CRP: ρ=−0.24, white blood cell count: ρ=–0.15, neutrophil-to-lymphocyte ratio: ρ=–0.26). However, changes in plasma ALB and PAB levels showed no significant correlation with energy and protein adequacy (ALB levels and caloric deficit: ρ=0.02, P=0.74; ALB levels and protein deficit: ρ=0.07, P=0.31; PAB levels and caloric deficit: ρ=−0.11, P=0.73; PAB levels and protein deficit: ρ=−0.40, P=0.20).[66]

4. Can skeletal muscle mass (SMM) or lean body mass (LBM) be used for NR screening or nutritional assessment in critically ill patients?

Recommendation: Apply SMM or LBM for NR screening and nutritional assessment in critically ill patients (strong recommendation, moderate quality evidence).

Rationale: LBM (fat-free mass [FFM] excluding bone mineral component) is an important component of the human body, including skeletal muscle and internal organs, as well as connective tissue, representing the body's largest protein reserve. The amount of LBM or skeletal muscle is regulated by protein catabolism and anabolism.[68,69] In critically ill patients, protein metabolism is overbalancing to catabolism due to systemic inflammatory response, neuroendocrine host response, iatrogenic immobility, inadequate nutritional intervention, glucocorticoid administration, senescence physiology, etc.,[70,71] resulting in loss of SMM.[69,72–74] Sarcopenia specifically refers to a syndrome caused by a reduction in SMM, strength, and/or function[75], which is also a common comorbidity in critically ill patients.

Studies have shown that SMM decreases by 17–30% in critically ill patients in 10 days of ICU stay,[69,76] and a decrease in lean body/SMM may further contribute to poor outcome, such as increased mortality, prolonged mechanical ventilation days and length of ICU stay, increased morbidity of multiple organ dysfunction, and ICU-acquired weakness.[68,69,77–79] Timely and appropriate nutritional intervention combined with early exercise helps to maintain or increase lean body/SMM in patients.[80,81] A systematic review showed that decreases in lean body/SMM were associated with NR and malnutrition in patients. Therefore, we recommend that lean body/SMM be applied for both NR screening and nutritional assessment in critically ill patients.

Evidence summary: In the context of NR screening, three observational studies (n=458) showed that measurement of phase angle (PhA) with Bioelectric Impedance Analysis (BIA) can be used to predict high NR (mNUTRIC ≥5) with an area under the receiver operating characteristic curve (AUROC) (95% CI) of 0.79 (0.59 to 0.83); when the cut–off value for PhA was 5.5°, the sensitivity and specificity for prediction were 62.3% and 65%, respectively.[77] The cross-sectional area (CSA) of the masseter measured with computed tomography (CT) to predict high NR (prognostic nutritional index [PNI]<36.083) yielded an AUROC (95% CI) of 0.60 (0.41 to 0.80); the AUROC (95% CI) for the CSA of muscle at third lumbar vertebrae level measured with CT to predict high NR was 0.65 (0.54 to 0.77).[82] The AUROC for maximum compressed quadriceps femoris muscle thickness (mcQFMT) with ultrasound to predict high NR (mNUTRIC ≥5) was 0.68, with a sensitivity of 61% and a specificity of 71% at the mcQFMT cut–off value of 1.69 cm; when using mcQFMT to predict higher NR (mNUTRIC ≥6), the AUROC increased to 0.75, with a cut–off value of 1.36 cm providing a sensitivity of 79% and specificity of 70%. Thus, mcQFMT measured with ultrasound was an independent risk factor to predict NR and was significantly associated with high NR (mNUTRIC ≥5: OR=0.26, 95% CI: 0.08 to 0.80; mNUTRIC ≥6: OR=0.14, 95% CI: 0.03 to 0.60).[83]

In terms of nutritional assessment, four observational studies (n=190) found that LBM measured with BIA was effective in predicting severe malnutrition (BMI ≤ 16) (AUROC=0.954, 95% CI: 0.84 to 0.995), with a sensitivity of 80% and a specificity of 91% at a cut-off value of 0.24.[84] After categorizing malnourished patients by SGA, there was a significant difference in the number of patients with reduced muscle mass (PhA<5° as measured with BIA) within each group (P=0.042).[85] Two studies found that the thickness of the intramuscular muscles (TAPM) measured with ultrasound could predict malnutrition (SGA classes B and C) with an AUROC (95% CI) of 0.82 (0.73 to 0.91) and 0.61 (0.46 to 0.76) respectively, and TAPM <15 mm was associated with malnutrition (RR=1.63, 95% CI: 1.06 to 2.5).[53,86]

5. What methods is reliable as assessment of SMM or LBM in critically ill patients?

Recommendation: Use ultrasound and BIA for real-time monitoring of SMM or LBM in critically ill patients (weak recommendation, low-quality evidence).

Rationale: Magnetic resonance imaging (MRI) or CT measurement of skeletal muscle CSA at the third lumbar vertebrate is a reliable method to assess SMM in critically ill patients.[87] However, CT and MRI cannot be used as routine methods for real-time monitoring of SMM in critically ill patients due to factors such as radiation exposure and risks associated with transportation.

Ultrasound is a non-invasive and point-of-care diagnostic tool widely used in critically ill patients. Ultrasonic assessments of SMM in critically ill patients predominantly focus on measurements of quadriceps muscle layer thickness (QMLT) or rectus femoris muscle area (RFMA), typically performed at the midpoint or lower third of the line connecting the anterosuperior iliac spine and superior border of the patella.[88–96] It is important to acknowledge that factors such as age, gender, baseline body weight,[92] and tissue fluid retention in critically ill patients may affect the accuracy of measurement.[97] Therefore, when using ultrasound for individualized and dynamic assessment of SMM in critically ill patients, standardized measurement methodology and quality-controlled protocol are crucial to improve the accuracy and consistency of these measurements.[98]

The BIA is a non-invasive measurement of body composition at the bedside,[99] which is categorized into single-frequency and multi-frequency BIA devices, as well as bioelectrical impedance spectroscopy. The BIA measures tissue resistance, reactance, and impedance and then calculates body composition using empirical regression equations.[100] Parameters in BIA, such as FFM, LBM, and SMM, can be used to reflect skeletal muscle/LBM in the body.[101] However, reference ranges and regression equations for BIA are derived from data in healthy individuals (i.e., people with normal body weight and hydration status) and may not be applicable to patients with fluid overload, ascites, pleural effusion, or obesity.[100,102] Therefore, limitations of the measurements with BIA should be noted when applying BIA in critically ill patients. The PhA is a derived parameter in BIA and may reflect cellular function and LBM. The PhA is relatively less affected by body hydration status, and a higher PhA is consistent with large quantities of intact cell membranes and LBM.[101]

Evidence summary: No systematic reviews related to the area of ultrasound assessment of skeletal muscle/LBM were found. After a systematic search, six prospective observational studies (n=366) found[89,91,92,94,95,103] good inter- and intra-group reproducibility of ultrasound measurements, with a median (range) intra-group correlation coefficient (ICC) of 0.946 (0.7, 0.992) between operators, and an intra-operator ICC of 0.98 (0.74, 0.998). In comparing the agreement with CT measurements of SMM, six observational studies (n=458) found significant correlations between ultrasound-measured QMLT[89,90,92,93] and RFMA,[90,96] and CT-measured CSA of skeletal muscle at the third lumbar vertebrae (correlation coefficients: r of 0.45 and 0.7 for QMLT; ρ of 0.48 for RMFA).[90] Ultrasound and CT measured SMM at the same site exhibited minimal bias (Bland–Altman analysis showed that the 95% limits of agreement for bias in assessing the same site with both methods were (−0.34, +0.36) cm[97] and (−0.356, 0.55) cm[91]). When using reduction in skeletal muscle area measured at the third lumbar vertebral level with CT as gold standard for determining reduced muscle mass, the AUROC (95% CI) for ultrasound-measured QMLT in predicting reduced muscle mass was 0.79 (0.65 to 0.92)[89];the AUROC (95% CI) for QMLT in predicting a low skeletal muscle index was 0.84 (0.74 to 0.94), and the AUROC (95% CI) for RFMA was 0.77 (0.65 to 0.88).[90]

In terms of BIA assessment of skeletal muscle/LBM, a systematic search yielded five prospective observational studies (n=388),[85,104–107] and no relevant systematic reviews were found. One prospective observational study found that the ICC (95% CI) for SMM and the PhA measured by BIA was 0.873 (0.697 to 0.950) and 0.910 (0.775 to 0.965), respectively[85]; in comparing the agreement of SMM measured by BIA and CT, four prospective observational studies (n=366)[104–107] found that SMM was significantly correlated with CT-measured skeletal muscle CSA at the third lumbar vertebral level {r (median [range]) of 0.651 (0.584–0.834)}[104–106]; PhA showed correlation with CT-measured skeletal muscle area and muscle density at the third lumbar vertebral level (with r values of 0.542, 0.589 for muscle area and 0.701, 0.776 for muscle density).[104,106] When using reduction in skeletal muscle area measured at the third lumbar vertebral level with CT as the gold standard for determining reduced muscle mass, the AUROC for PhA in predicting reduced muscle mass was 0.67; an integrated logistic regression model incorporating age, gender, BMI, and PhA for predicting reduced muscle mass showed an AUROC of 0.78.[107]

6. Can we base on EN amount or currant gastrointestinal symptoms when defining enteral feeding intolerance?

Recommendation: We suggest diagnostically defining feeding intolerance during enteral feeding by identifying the presence of two or more gastrointestinal symptoms clinically. Notice that high gastric residuals are emphasized as a fundamental and essential symptom. As a secondary option, feeding intolerance can be identified as a feeding amount less than 20 kcal/(kg·day) persisting for 72 consecutive hours (weak recommendation, low-quality evidence).

Rationale: Feeding intolerance in EN serves as a crucial indicator for evaluating the efficacy of enteral feeding, as endorsed by international nutritional guidelines[11,12] and expert consensus.[108–110] However, it is important to note that there is currently no universally accepted clinical objective standard for defining feeding intolerance. In 2012, the Acute Gastrointestinal Injury (AGI) consensus introduced a clinical criterion to address this gap, suggesting that a feeding amount persistently below

20 kcal/(kg·day) for 72 consecutive hours be used as the threshold for diagnosing feeding intolerance.[108] While this criterion, based on feeding amount, provides a measurable parameter, its limitation lies in the absence of consideration for clinical symptoms. Relying solely on feeding amount may pose challenges in the early diagnosis and management of feeding intolerance.

In the realm of EN, feeding intolerance often manifests with diverse gastrointestinal symptoms, with high gastric residual volume (HGRV) emerging as the most prevalent at 36.11%. Other common presentations encompass vomiting (18.68%), loss of bowel sounds (15.54%), abdominal distension (12.19%), and diarrhea (5.24%).[111] A systematic review conducted by Blaser et al.[109] underscored the historical reliance on HGRV, either alone or in combination with vomiting, diarrhea, and abdominal distension, as a common symptom/method employed in studies assessing feeding intolerance. However, defining the threshold for HGRV has exhibited significant variation, ranging widely from 75 mL to 500 mL. Notably, a recent systematic review challenged the traditional view by suggesting that HGRV might not effectively reflect gastric emptying and, consequently, lacks a statistically significant correlation with the incidence of feeding intolerance.[110] It is crucial to note that this conclusion did not definitively negate the potential impact of measurement errors and threshold standards in gastric residual volume (GRV) assessment. In recent years, technological advancements in ultrasound have introduced new and more accurate means for assessing GRV. Studies indicate that three-dimensional ultrasound technology effectively evaluates the gastric emptying ability of patients with conditions like gastroparesis, with GRV measurements closely aligning with those obtained through magnetic resonance measurements.[112,113]

When considering definitions of feeding intolerance in EN, criteria based on a feeding amount persistently below 20 kcal/(kg·day) provide clear threshold standards. However, it's crucial to acknowledge their potential limitations in managing critically ill patients. The challenge arises from the fact that a fixed caloric threshold might not adequately account address the dynamic and complex nutritional requirements of these individuals. Critically ill patients often undergo fluctuations in their metabolic demands, and a strict adherence to the <20 kcal/(kg·day) criterion may not account for these variations accurately. For instance, meeting the recommended 20 kcal/(kg·day) of EN feeding can prove challenging, especially in the early stages of severe acute illness. Additionally, focusing solely on caloric intake might overshadow other vital factors influencing nutritional status in this population, such as the proportion of surgical patients impacting the overall mortality risk of ICU patients with feeding intolerance. Hence, when using feeding amount to diagnose feeding intolerance, it becomes crucial to adjust diagnostic timing and feeding thresholds based on the acceptable degree of nutritional inadequacy specific to the disease type and stage. Typically, diagnosing feeding intolerance based on feeding amount typically involves a 72-h diagnostic time window. However, recent meta-analysis findings suggest diagnosing feeding intolerance based on two or more gastrointestinal symptoms, with HGRV considered a primary symptom (referred to as feeding intolerance definition based on gastrointestinal symptoms). It's important to acknowledge the limitations of the 72-h diagnostic time window, alongside outcome risk assessment and incidence, while employing this diagnostic approach.[111] Given the higher prevalence of feeding intolerance diagnosed based on feeding amount in hospital settings and its association with overall mortality risk, a careful consideration between the two diagnostic methods or a combination thereof is recommended. This decision should weigh the practical and clinical nuances of each approach to better address the complexities in managing feeding intolerance among critically ill patients.

Evidence summary: This systematic review, encompassing 26 observational cohort studies with a total sample size of 25,189 critically ill patients, provides comprehensive insights into the incidence and outcomes of feeding intolerance. The studies included 10 prospective studies[114–123] and 16 retrospective studies.[124–139] The overall incidence rate of feeding intolerance in critically ill patients was found to be 0.40 (95% CI: 0.34 to 0.46), indicating a substantial association with adverse patient-centered outcomes. Particularly noteworthy is the OR for all-cause ICU mortality risk, which was 1.99 (95% CI: 1.69 to 2.35). The analysis further revealed a correlation between the proportion of surgical patients and an elevated ICU mortality risk associated with feeding intolerance. The breakdown of this trend by surgical patient proportion showed varying ORs, with a noticeable increase as the percentage of surgical patients rose. Setting the threshold for feeding inadequacy at different levels revealed interesting patterns. At a 50% threshold, the ICU mortality risk for feeding intolerance reached its peak (OR=5.24, 95% CI: 2.55 to 10.74), while at an 80% threshold, the ICU mortality risk OR decreased to 1.87 (95% CI: 1.08 to 3.24). When examining specific symptoms, the ICU mortality risk OR for HGRV was 2.31 (95% CI: 1.63 to 3.27). However, the correlation between other individual gastrointestinal symptoms and ICU mortality risk was not statistically significant. Increasing the minimum number of gastrointestinal symptoms required to diagnose feeding intolerance was associated with a rise in ICU mortality risk. For instance, having one or more gastrointestinal symptoms resulted in an OR of 2.29 (95% CI: 1.98 to 2.65), while having three or more symptoms increased the risk to 4.49 (95% CI: 1.87 to 10.83). This was accompanied by a decrease in the incidence of feeding intolerance. Thee overall incidence rate of feeding intolerance based on feeding amount was 0.46 (95% CI: 0.27 to 0.65). Notably, there was a statistically significant difference in all-cause hospital mortality risk for feeding intolerance based on feeding amount (OR=1.90, 95% CI: 1.03 to 3.50), surpassing the all-cause hospital mortality risk for feeding intolerance based on gastrointestinal symptoms (OR=1.48, 95% CI: 0.88 to 2.50). In summary, these comprehensive findings highlight the significant implications of feeding intolerance for mortality outcomes in critically ill patients and underscore the importance of considering various factors, including the threshold for feeding inadequacy and specific symptoms, in clinical management and decision-making.

7. Can gastrointestinal ultrasound predict feeding intolerance to EN in critically ill patients?

Recommendation: We suggest that gastrointestinal ultrasound measurement be used to predict feeding intolerance in critically ill patients during EN (weak recommendation, low-quality evidence).

Rationale: Feeding intolerance in critically ill patients is a prevalent issue, with an incidence ranging from 30.5%–67.5%, and is associated with adverse patient outcomes.[140] Common

indicators for assessing feeding intolerance include HGRV, along with symptoms like vomiting, absence of bowel sounds, abdominal distention, and diarrhea. However, the diagnostic threshold for GRV varies significantly, spanning from 75 mL to 500 mL. The measurement of GRV using aspiration methods poses challenges in standardization, with objective accuracy affected by factors such as the position and size of the gastric tube and the patient's posture. Consequently, international nutrition guidelines no longer routinely recommend the use of GRV in clinical practice.[109,110] Meta-analysis findings reveal that, except for HGRV, there is no substantial correlation between individual types of gastrointestinal symptoms and the overall risk of all-cause mortality in the ICU. This underscores the complexity and limitations associated with relying solely on specific symptoms, particularly GRV when accuracy is warranted for predicting patient outcomes in critically ill settings.

Gastrointestinal ultrasound offers a comprehensive assessment, including the measurement of gastric antrum area, gastric antrum motility index, intestinal structure, and dynamic changes. It provides an objective reflection of GRV through the measurement of gastric antrum CSA. Preliminary research suggests that ultrasound measurement of gastric sinus CSA holds significant promise for evaluating and predicting feeding intolerance in critically ill patients. Studies have indicated that ultrasound measurement of CSA is more reliable in reflecting GRV compared to aspiration methods (98% *vs*. 85%, *P*=0.016).[141–143] Ultrasound measurements of CSA in various positions, such as semi-recumbent, supine, and right lateral positions, show strong correlations with GRV measured by CT and aspiration methods. In patients with feeding intolerance, gastric antrum CSA is notably higher compared to the feeding-tolerant group. Thresholds of CSA ≥3.917 cm^2, 3.395 cm^2, and 4.402 cm^2 demonstrate sensitivities of 92.0%, 69.6%, and 92.3%, and specificities of 69.2%, 92.3%, and 71.4%, respectively.[144] The AUROC for predicting feeding intolerance based on gastric antrum CSA is 0.699. The optimal cut–off value for predicting feeding intolerance is 7.092 cm^2, with a sensitivity of 0.727 and a specificity of 0.755.[145] Following the initiation of EN, ultrasound-derived parameters related to gastric antral echo intensity also exhibit high predictive value for feeding intolerance. The 50th percentile, 85th percentile, and mean grayscale distribution (ED50, ED85, and EDmean) in feeding intolerance patients are higher than those in the tolerant group (ED50: 67.8 *vs*. 56.1, *P*=0.02; ED85: 85.6 *vs*. 71.2, *P*=0.01; and EDmean: 70.3 *vs*. 57.6, *P*=0.01).[139] Moreover, ultrasound detection of intestinal wall thickness, circular folds, and peristalsis proves to be a valuable approach for predicting feeding intolerance in critically ill patients.[146]

Hence, while the existing research on gastrointestinal ultrasound and its predictive value for feeding intolerance is preliminary, it has demonstrated promise. Despite the current limitations in the quality of research evidence, the significance lies in the absence of more robust predictive methods. Gastrointestinal ultrasound stands out due to its capacity to offer a direct and visual representation of gastrointestinal structure, function, and pathological conditions. As a result, it holds considerable potential as a crucial auxiliary tool for predicting feeding intolerance.

Evidence summary: This systematic review incorporated four cohort studies (three prospective studies[139,145,146] and one retrospective study,[144] *n*=351). In a multicenter prospective observational study[145] with 150 participants, the AUROC for predicting feeding intolerance in critically ill patients using gastric sinus CSA was 0.699 (95% CI: 0.514 to 0.883), pinpointing the optimal cut-off value was 7.092 cm^2 with a sensitivity of 0.727 and a specificity of 0.755. The retrospective analysis[143] (*n*=42) revealed higher gastric antral CSA in critically ill feeding intolerance patients: (8.53 ± 4.07) cm^2 in the semi-recumbent position, (5.15 ± 2.75) cm^2 in the supine position, and (10.32 ± 4.06) cm^2 in the right lateral position. In comparison, feeding-tolerant patients had lower values of (4.60 ± 2.76) cm^2, (2.61 ± 1.32) cm^2, and (4.95 ± 3.20) cm^2, respectively. This difference was statistically significant (*P* <0.005). AUROC analysis indicated predictive potential in the semi-recumbent (AUROC=0.815), supine (AUROC=0.833), and right lateral (AUROC=0.849) positions. Moreover, gastric antral wall ultrasound echo intensity, evaluated through histogram analysis[139] (*n*=43), showed significantly higher values in feeding intolerance patients at EN initiation for ED50 (67.8 *vs*. 56.1, *P*=0.02), ED85 (85.6 *vs*. 71.2, *P*=0.01), and EDmean (70.3 *vs*. 57.6, *P*=0.01). The cut–off value for predicting feeding intolerance using ED50, ED85, and EDmean were 63, 77.5, and 65.9, respectively, each yielding good specificity, sensitivity, and AUROC values. Additionally, a prospective observational study[146] (*n*=116) demonstrated intestinal ultrasound's potential in predicting feeding intolerance, showcasing AUROC values: 0.60 for intestinal diameter, 0.76 for intestinal circular folds, 0.71 for intestinal wall thickness, 0.77 for intestinal wall layers, and 0.78 for intestinal peristalsis.

8. Can monitoring intra-abdominal pressure (IAP) predict feeding intolerance to EN in critically ill patients?

Recommendation: Do not monitor IAP to predict feeding intolerance to EN in critically ill patients routinely (weak recommendation, very low-quality evidence).

Rationale: The incidence of intra-abdominal hypertension (IAH) in critically ill patients is reported to be between 32.1% and 81%. Numerous studies indicate that an elevation in IAP serves as an independent risk factor for predicting the prognosis of critically ill patients.[147–149] Elevated IAP is closely linked with gastrointestinal dysfunction[150–152], impacting the effective implementation of EN in critically ill patients. The 2018 ESPEN guidelines advocate for a cautious approach in cases of elevated IAP during EN. Specifically, it recommends slowing down the rate of EN and contemplating the suspension of EN if elevated IAP is detected in patients with intra-abdominal hypertension.[11] In China, the early clinical practice consensus for EN in critically ill patients suggests reducing the rate of EN if IAP exceeds 16 mmHg and advocating for the suspension of EN if IAP surpasses 20 mmHg.[153] These recommendations are fundamentally rooted in the idea that monitoring IAP can serve as a predictive measure for feeding intolerance, underscoring the crucial role of IAP monitoring throughout the EN process.

However, the impact of intra-abdominal pressure (IAP) on feeding tolerance is indeed subject to considerable variation. Studies indicate that patients with higher APACHE II scores may experience feeding intoleranceat at lower IAP levels.[114] This suggests that the relationship between IAP and EN tolerance varies with different levels of disease severity, posing challenges in establishing a unified standard for monitoring and intervention. Moreover, research by Bordejé et al.[154] suggests a stronger correlation between feeding intolerance and the daily

maximum IAP as opposed to the daily average IAP. This indicates a lack of consensus regarding the choice of monitoring indicators, adding complexity to the assessment and management of feeding intolerance in critically ill patients. For patients without IAH, there is limited research on whether routine monitoring of IAP during early EN can reliably predict the occurrence of feeding intolerance. Additionally, existing studies on this matter provide contradictory results.[155,156]

Therefore, despite the theoretical potential for elevated IAP to influence gastrointestinal function and the occurrence of feeding intolerance, there are currently no standardized monitoring criteria for IAP or reference thresholds for different populations. Moreover, existing studies have not confirmed the benefits of routine IAP monitoring to guide EN. Considering the invasiveness and cost-effectiveness of monitoring IAP, we do not recommend routine IAP monitoring to predict the occurrence of feeding intolerance in critically ill patients.

Evidence summary: An earlier study demonstrated that combining IAP and APACHE II scores is predictive of EN tolerance in critically ill patients. Higher APACHE II scores correlate with feeding intolerance at lower IAP levels, while lower APACHE II scores associate with feeding intolerance at higher IAP levels.[114] Additionally, Bordejé et al.'s research[154] indicated that feeding intolerance patients have a significantly higher daily maximum IAP ([19.4 ± 4.8]mmHg *vs*. [16.8 ± 4.6]mmHg, P <0.001), yet there is no noteworthy difference in daily average IAP between groups with and without feeding intolerance ([14.8 ± 3.7]mmHg *vs*. [14.8 ± 4.1]mmHg, P=0.801).

In a systematic evaluation encompassing two observational studies[155,156] involving 260 patients, the focus was on determining whether routine IAP monitoring during early EN could predict feeding intolerance in patients without IAH. The results indicated that monitoring IAP during the EN process did not significantly decrease the incidence of feeding intolerance compared to those patients who were not monitored (RR=1.0, 95% CI: 0.82 to 1.22, I^2=91%, P=1.00). Moreover, there was no significant difference in IAP levels observed between the EN-tolerant group and the intolerant group during EN feeding period (MD=−0.32, 95% CI: −1.24 to 0.61, I^2=6%, P=0.5). Additionally, no significant distinction was found in ICU mortality rates (OR=0.73, 95% CI: 0.43 to 1.25, I^2=89%, P=0.26) between the monitored and non-monitored groups.

9. Is energy metabolism evaluation required during nutritional therapy for critically ill patients?

Recommendation: We suggest that indirect calorimetry be used to measure actual energy expenditure (EE) for the determination of energy supply during nutritional therapy in critically ill patients (weak recommendation, low-quality evidence).

Rationale: Energy deficiency or insufficient intake can cause varying degrees of protein depletion, affecting organ structure and function and consequently deteriorating patient prognosis. Therefore, accurately measuring the patient's actual EE to guide caloric delivery can prevent both overfeeding and underfeeding. Several predictive equations are commonly practiced to predict resting energy expenditure (REE). However, one recent meta-analysis[157] has demonstrated the inaccurate prediction in these equations for their over- or under-estimate REE[158,159] and does not reflect the patients' dynamic needs of metabolic substrates. Estimating REE by indirect calorimetry is an ideal method for determining energy requirements and can be used to guide energy delivery in critically ill patients. A recent meta-analysis[160] showed that indirect calorimetry -guided energy delivery strategy improved short-term mortality in mechanically ventilated ICU patients without increasing the length of hospitalization, duration of mechanical ventilation, and complications compared with predictive equations.

If the patient's condition permits, REE should be measured early and assessed based on metabolic and condition characteristics. The early target amount should be between 70% and 100% of measured REE to avoid under- or overfeeding. There is currently no consensus regarding the optimal time or frequency of evidence-based indirect calorimetry measurements. During the resuscitation period within 24–48 h of ICU admission, higher oxygen concentrations and frequent mechanical ventilation adjustment may confound the results of oxygen and carbon dioxide measurements. Therefore, it is not recommended to perform indirect calorimetry during this period.[161] Some clinical experts recommend that for patients who are beginning to stabilize (hemodynamic and mechanical ventilation parameters are stable, with an inspired oxygen concentration of <0.6 and a positive end expiratory pressure [PEEP] of <12 mmHg), patients may begin indirect calorimetry monitoring. Indirect calorimetry -REE should be performed every 2–3 days or 2–3 times/week and repeated when clinical conditions change.[162] Notably, 30-min indirect calorimetry measurements predict measured 24-h EE showed a high accuracy acceptably well for clinical purposes.[163] The respiratory quotient (RQ) can also be measured by indirect calorimetry technique, with the appropriate range of 0.85–1. RQ <0.85 and RQ >1.0 are less sensitive in predicting underfeeding and overfeeding in mechanically ventilated patients (55.8% and 38.5%, respectively) and should not be used to guide energy delivery. RQ >1.0 may be related to the increased respiratory rate and the need for command ventilation and adjustment of nutritional therapy regimens.[164]

When the indirect calorimetry technique is not available, calculating EE based on carbon dioxide (EE-VCO_2) measurements has been proposed as an alternative to the indirect calorimetry technique. Some ventilators can provide continuous VCO_2, which results in an EE measurement based on VCO_2. The 2018 ESPEN guidelines recommend that VCO_2 obtained from the pulmonary arterial catheter or derived from the ventilator will better estimate EE than predictive equations.[11]

Evidence summary: A systematic evaluation published in 2021[160] included eight RCTs[165–171] (n=991) and showed that, compared with the predictive equations, indirect calorimetry -REE guided energy delivery strategy significantly reduced short-term (defined as the longest period of observation in the ICU or during hospitalization or follow-up within 90 days of admission) mortality (RR=0.77, 95% CI: 0.60 to 0.98, I^2=3%; P=0.03) without increasing the duration of mechanical ventilation (MD=0.61 days, 95% CI: −1.08 to 2.29, I^2=72%; P=0.48) or ICU stay (MD=0.32 days, 95% CI: −2.51 to 3.16, I^2=73%; P=0.68) or hospitalization (MD=0.30 days, 95% CI: −3.23 to 3.83, I^2=0%; P=0.87). In pneumonia (RR=1.01, 95% CI: 0.58 to 1.75; I^2=60%; P=0.98), bacteremia (RR=1.74, 95% CI: 0.90 to 3.40; I^2=0%; P=0.78), urinary tract infections (RR=1.00, 95% CI: 0.49 to 9.65, I^2=48%; P=0.17), and abdominal infection (RR=1.03, 95% CI: 0.25 to 3.90, I^2=0%; P=1.00) were not statistically significantly different in the incidence of adverse events.

10. Is it necessary to monitor plasma PAB levels during nutritional therapy in critically ill patients?

Recommendation: We suggest that plasma PAB levels be monitored during nutritional therapy in critically ill patients to evaluate the metabolic status and the response to nutritional therapy (weak recommendation, very low-quality evidence).

Rationale: PAB, or transthyretin, is an acute-phase protein synthesized by the liver and used as a nutrition-related marker. Several meta-analyses have suggested that decreasing plasma PAB levels are associated with disease progression and increased mortality.[172,173] Compared to ALB and transferrin, PAB has a short half-life (about 2.5 days) and is not affected by the hydration status of the body. In addition, PAB is simple to measure, making it ideal for monitoring rapid changes in metabolic status during nutritional therapy.[174,175] A meta-analysis published in 2020 suggests that ALB and PAB levels increased significantly after nutritional treatments without altering the risk of all-cause mortality, respiratory infections, urinary tract infections, and nutrition-related complications.[176] It is important to note that in the ICU population, low plasma PAB alone may be influenced by the inflammatory response and does not accurately reflect nutritional status.[177] Although nutritional therapy has been initiated, PAB levels may still decrease due to the hypercatabolism state.[178] On the other hand, even if a patient does not receive adequate nutrition or continues to lose weight, PAB levels may recover as the inflammatory response decreases.[179] In contrast, dynamic changes in PAB help evaluate responsiveness to nutritional therapy. In the acute phase, weekly measurements of PAB in combination with CRP levels appear to be a more comprehensive "window" into metabolic status. When inflammatory indicators are stabilized, PAB levels may reflect whether the nutrient intake is adequate.

Evidence summary: A systematic evaluation based on COVID-19 critically ill patients[172] included 19 observational studies (n=4616) and showed that serum PAB levels were significantly lower in COVID-19 critically ill and non-survivor patients compared with mildly ill or survivor patients (standardized mean difference [SMD]=−0.92, 95% CI: −1.10 to −0.74, I^2=77.9%; P <0.001). This finding was confirmed in further subgroup analyses. Another meta-analysis incorporating four RCTs[176] (n=429) suggested that PAB levels were higher after parenteral nutrition (PN) combined with EN use compared to EN alone (MD=−0.02, 95% CI: 0.00 to 0.04, I^2=79.7%; P=0.036). However, it did not change the risk of all-cause mortality, respiratory infections, urinary tract infections, and nutrition-related complications.

11. Is urea/creatinine ratio (UCR) monitoring required during nutritional therapy in critically ill patients?

Recommendation: We suggest that UCR be monitored during nutritional therapy in critically ill patients (weak recommendation, low-quality evidence).

Rationale: In recent years, elevated UCR has been found to be able to reflect persistent critical illness and critical illness-related catabolism.[180,181] Elevated UCR may, on the one hand, indicate that the patient's muscle proteolysis leads to an increased activity of the body's urea cycle, which, in turn, leads to an elevated amino acid catabolism. On the other hand, an elevated UCR may also indicate a decrease in serum creatinine levels, which is a catabolic product of skeletal muscle phosphocreatine. Thus, the UCR reflects the release of nitrogen from the body and decreased muscle mass. The increased morbidity associated with elevated UCR may also reflect the pathologic effects of hyperammonemia. For example, elevated serum ammonia levels are known to decrease muscle function and the mass of muscle structures while increasing muscle autophagy. Ammonia adversely affects mitochondrial function, leading to the depletion of tricarboxylic acid cycle intermediates and decreasing adenosine triphosphate (ATP) availability.[182,183] Several findings suggest elevated UCR may reflect muscle loss associated with severe diseases.[180,184,185]

Muscle protein loss in critically ill patients has been demonstrated to be associated with various adverse outcomes.[186–188] Several studies have shown that elevated UCR levels are significantly associated with impaired organ function, infectious complications, prolonged ICU or total hospitalization,[189] and even increased mortality.[180,184,185] Therefore, UCR, as a simple, cost-effective, and accurate marker of catabolism, is extremely convenient to be used for dynamic monitoring of muscle protein during the treatment of ICU patients with high catabolism.

Notably, although UCR serves as a most promising marker of catabolism, its levels are directly or indirectly influenced by the patient's renal impairment, disease state, and therapeutic interventions (e.g., high-dose glutamine supplementation, etc.).[190] Thus, in these cases, dynamic monitoring of the UCR is more clinically relevant. In addition, UCR should be further evaluated in a broader critically ill population and at the individual level.

Evidence summary: Through a systematic search, we identified six studies (n=36,882) related to the topic without any systematic meta-analyses available. One study reported that among 1173 trauma patients who survived to at least day 10, there was a significant difference in the temporal trend in UCR. Although UCR initially increased in all patients, patients with ICU stay ≥10 days had a larger rise in UCR (from 62 to 141, P <0.01) than patients discharged from ICU before day 10 (UCR increased from 61 to 97) (133% *vs*. 59%; P <0.01). The reproducibility of UCR changes was further confirmed in this study's analysis of the Medical Information Mart for Intensive Care (MIMIC)-III database trauma cohort (n=2876).[180] Similarly, in another retrospective study[181] (n=22,868), patients with persistent critical illness showed a significantly greater increase in UCR from day 4 to day 10 after ICU admission than patients without persistent critical illness (both P-values <0.05) as well as a higher in-hospital mortality rate (25%, 163/643, *vs*. 16%, 3665/22,225; P <0.001). These results support the earlier findings of Iwashyna et al.[191], suggesting that a specific length of hospitalization (≥10 days or <10 days) be identified as a transition point at which patients have a worse outcome and admission disease severity is no longer predicted.

The increase in UCR occurred in parallel with a progressive decrease in muscle mass. Volbeda et al.[192] examined the time course of UCR in 248 ICU patients and found that UCR rose rapidly without any decline over 30 days of ICU admission, emphasizing the concern for a continuous catabolic state in ICU patients. Haines et al.[180] found a rapid decline in muscle mass and a significant negative correlation between UCR and the rate of muscle loss in 53 critically ill patients with data from serial CT scanning tests by assessing the L3 and L4 psoas major CSA (R^2=0.39, P <0.001 and R^2=0.44, P <0.001). In a study of 321 patients operated for pancreatic cancer,[189] elevated UCR

accurately reflected skeletal muscle atrophy in postoperative surgical patients. Meanwhile, multifactorial logistic regression showed that UCR was an independent predictor of postoperative complications in patients (OR=1.89, 95% CI: 1.52 to 2.14, *P*=0.015). Patients with a UCR above the median had more complications (17.4% *vs*. 35%; *P*=0.007) and longer days of hospitalization postoperatively ([9.6 ± 4.3] days *vs*. [14.6 ± 5.5] days; *P*=0.017).

12. Is it necessary to monitor blood phosphorus during nutritional therapy in critically ill patients at risk for refeeding syndrome (RES)?

Recommendation: We suggest monitor blood phosphorus levels for the patients at risk of RFS before and during nutritional therapy (weak recommendation, very low-quality evidence).

Rationale: Phosphorus is the major intracellular anion and is essential for many biological processes. In particular, it is involved in the conversion of adenosine diphosphate to adenosine triphosphate, glycolysis, intracellular buffering, and the formation of cellular membranes.[193] Clinically, low phosphorus is associated with cardiac hypoplasia, arrhythmias, and respiratory insufficiency.[194] Both low and high phosphorus are associated with increased mortality in a U-shaped curve.[195] Tight glycemic control with insulin can cause or exacerbate hypophosphatemia in patients and is one of the indicators evaluated in RFS.

This is due to the movement of phosphorus ions from extracellular to intracellular. Continuous renal replacement therapy (CRRT) often results in low phosphorus.[182] The presence of refeeding hypophosphatemia (blood phosphorus <0.65 mmol/L or a decrease in blood phosphorus greater than 0.16 mmol/L) in ICU patients should be a concern.[196] A meta-analysis suggested that the incidence of RFS-related hypophosphatemia in the ICU was as high as 27%.[197] Two meta-analyses suggested that low phosphorus in critically ill patients might be associated with poor outcome.[198,199] There are two peaks of low phosphorus in ICU patients. The first peak is usually at about 12 h after ICU admission and is associated with insufficient intake, while the second peak is at 3–5 days after the start of nutritional therapy. Therefore, attention must be paid to the screening of patients at high risk of RFS before nutritional therapy, such as patients with a longer period of insufficient nutritional intake or recent starvation, increased losses, gastrointestinal malabsorptive disorders (e.g., inflammatory bowel disease), chronic alcoholism, low body weight, unintended body weight loss of >15% in 3 months, and hypokalemia, hypophosphatemia, and hypomagnesemia immediately prior to nutritional therapy.[200] Refeeding patients with hypophosphatemia requires monitoring of electrolyte levels two to three times a day and supplementation as needed,[196] with caloric restriction for the first 48 h of nutritional therapy, followed by a gradual increase.[201]

Evidence summary: A meta-analysis[198] published in 2020 (12 observational studies, *n*=7626) reported that hypophosphatemia in the ICU was associated with prolonged hospitalization (SMD=2.19 days, 95% CI: 1.74 to 2.64, I^2=0%, *P* <0.001) and prolonged stay in the ICU (MD=2.22 days, 95% CI: 1.00 to 3.44; I^2=98%, *P* <0.001), and not associated with increased all-cause mortality (RR=1.13, 95% CI: 0.98 to 1.31, I^2=59.6%, *P*=0.09). Another meta-analysis published in 2022[202] (10 observational studies, *n*=60,358) also showed that hyperphosphatemia was an independent risk factor (OR=2.85; 95% CI: 2.35 to 3.38, I^2=86.5%, *P* <0.0001) in the ICU patients. Meanwhile, ICU patients with hyperphosphatemia required more renal replacement therapy (RRT) (OR=4.96, 98% CI: 2.43 to 10.12, I^2=94.9%; *P* <0.0001). For the incidence of RFS, a meta-analysis in 2021[197] (35 observational studies, *n*=6251) showed that in adult patients, the RFS incidence ranged from 0% to 62%, and the feeding hypophosphatemia (RH) incidence ranged from 7% to 62%. In the subgroup analyses, the RH results were highly heterogeneous, with the ICU patients and those initially fed >20 kcal/(kg·day) appearing to have a higher incidence of RFS (44%; 95% CI: 36 to 52) and RH (27%; 95% CI: 21 to 34).

13. Is it necessary to monitor blood glucose during nutritional therapy in critically ill patients?

Recommendation: We suggest monitor blood glucose level dynamically in critically ill patients receiving nutrition therapy (weak recommendation, very low-quality evidence).

Rationale: Glycemic abnormalities, including hypoglycemia, hyperglycemia, and hyperglycemic variability, are common in the ICU, regardless of whether the patient has diabetes. It is associated with an increased mortality and poor outcome in ICU patients.[203,204] Blood glucose should be measured at least every 4 h after ICU admission or during the first 2 days of nutritional therapy. Insulin should be administered when blood glucose exceeds 180 mg/dL. Ideal blood glucose targets remain unestablished. Observational studies have shown increased mortality with severe hyperglycemia (>180 mg/dL), hyperglycemic variability (coefficient of variation >20%), and mild hypoglycemia (<70 mg/dL).[205–207] It is recommended to start insulin therapy when blood glucose exceeds 150 mg/dL or 180 mg/dL.[208] Glycemic control is essential and should target a level of 6–8 mmol/L, which has been shown to be associated with improved outcome.[209–212] More frequent measurements may be needed in patients with unstable blood glucose, while frequency can be decreased when a stabilization phase is reached.

The glycemic control process consists of several steps[213]: (1) Blood draw: central venous or arterial is preferred. Avoid fingertip pricks in critically ill patients. (2) Glucose measurement device: a blood gas analyzer or central laboratory analyzer is essential. (3) Insulin: for patients on long-term nutritional support (EN or PN), continuous insulin infusion from a vein using a micro-infusion pump may be used. Severe hyperglycemia, mild hypoglycemia, and hyperglycemic variability should be avoided since many cohort studies have consistently reported the relationship between these glycemic abnormalities and increased mortality and mobility. The use of the lower limit of the blood glucose target range >90 mg/dL (5 mmol/L) and dynamic titration of insulin infusion, adjusted as appropriate, are reasonable strategies.

Evidence summary: One recent meta-analysis[214] (57 RCTs,[203–210] *n*=21,840) showed that ICU patients who received tight glycemic control had a significantly lower all-cause mortality rate (OR=0.89, 95% CI: 0.80 to 1.00, I^2=32%; *P*=0.04), a lower rate of infection (OR=0.65, 95% CI: 0.51 to 0.82, I^2=47%; *P*=0.0002), lower incidence of acquired sepsis (OR=0.80, 95% CI: 0.65 to 0.99, I^2=0%; *P*=0.04), and shorter ICU stay (MD=−0.70, 95% CI: −1.21 to −0.19, I^2=70%; *P*=0.007). However, patients in the glycemic control (80–110 mg/dL, 4.4–6.1 mmol/L) group had a significantly higher risk of

severe hypoglycemia (OR=5.63, 95% CI: 4.02 to 7.87, I^2=67%, P <0.00001).

14. Does continuous glucose monitoring (CGM) contribute to glycemic management during nutritional therapy in critically ill patients?

Recommendation: We recommend that CGM be carried out during nutritional therapy in critically ill patients (strong recommendation, moderate quality evidence).

Rationale: Based on the available evidence, accurate regulation of blood glucose is critical for most critically ill patients. Several point-of-care blood glucose measurements, such as fingertip, venous, and arterial blood, are currently available and are commonly used to guide insulin therapy. However, the disadvantages of these techniques are that they can only detect immediate glucose value, the increased time and cost associated with frequent blood collection, and hypoglycemic events between measurements that do not reflect long-term circadian glucose levels.[215–217] CGM provides point-of-care glucose values continuously and automatically, which is a safeguard against hypoglycemic events and reduces glycemic variability and smooth control. Among the current CGM technologies, subcutaneous CGM has the most mature clinical application.[215]

Subcutaneous CGM can measure glucose in interstitial fluid via a minimally invasive subcutaneous sensor.[218] Numerous studies have shown that subcutaneous CGM devices have relatively good accuracy in measuring interstitial glucose levels independent of electrolyte and acid–base imbalances, disease severity, and BMI in critically ill patients.[219] In addition, CGM is less invasive, has a lower risk of infection, and less blood loss, making it popular among ICU healthcare professionals for its ease of use.[217,219] A meta-analysis[220] suggests that CGM significantly reduces the incidence of hypoglycemia and decreases short-term mortality when compared with intermittent glucose monitoring methods. The mean glucose fluctuation was significantly lower in the CGM group, and the coefficient of variation of glucose also tended to decrease. In addition, the infection rate was lower with CGM compared with intermittent glucose monitoring.

Evidence summary: A recently published meta-analysis[221] (19 RCTs, n=1852) showed that CGM significantly reduced the incidence of hypoglycemia compared with intermittent glucose monitoring methods (OR=0.35, 95% CI: 0.25 to 0.49, I^2=0%; P <0.0001), and significantly reduced short-term mortality (OR=0.35, 95% CI: 0.34 to 0.86, I^2=56%; P=0.01). Mean glycemic fluctuations were significantly lower in the CGM group (MD=−1.41 mmol/L, 95% CI: −2.24 to −0.58; I^2=95%; P=0.0009); and the coefficient of variation for glycemia tended to be lower during CGM treatment (MD=−1.41%, 95% CI: −3.50 to 0.46; I^2=88%; P=0.08). Infection rate was significantly lower in the CGM group (RR=0.21, 95% CI: 0.10 to 0.44, I^2=9%; P <0.0001). Only two RCTs described costs between the two strategies, with one showing a lower mean cost per day for patients in the CGM group and the other reporting no difference between groups.

15. Is it necessary to monitor the relevant indicators of enteral perfusion during early EN in critically ill patients?

Recommendation: We suggest dynamic monitoring of the enteral perfusion relevant indicators, such as blood pressure, dosage of vasoactive drugs, arterial lactate, and skin spotting scores, in critically ill patients using vasopressors during early EN (weak recommendation, very low-quality evidence).

Rationale: Intestinal blood flow accounts for 20%–25% of cardiac output. The vascular characteristics of the small intestinal villi, including countercurrent blood flow and arteriovenous short circuit, make the intestinal epithelium a higher requirement for circulating blood volume and perfusion pressure. During EN, local artery and portal venous blood flow increases. Once insufficient perfusion exists during shock, it may aggravate the mismatch between mucosal epithelial oxygen supply and demand, aggravate intestinal ischemia, and even cause non-occlusive mesenteric ischemia (NOMI).[222] A study showed that the incidence of enteral feeding intolerance was increased in critically ill patients with norepinephrine (NE) >0.2 μg/(kg·min).[223] It has been shown that peripheral perfusion indices, such as skin spotting score and arterial lactate, were correlated with feeding intolerance in patients with shock.[131] Therefore, the initiation of EN in critically ill patients who are at high risk of intestinal ischemia or not weaning from vasopressors, especially in the early stages of critical illness when feedings are increased, dynamic monitoring of the dosage of vasoactive drugs and evaluation of circulatory and tissue perfusion were needed.

Evidence summary: After a systematic literature search, we identified six relevant studies (n=53,281) but with no systematic evaluation. A prospective study including 66 patients with shock showed[223] that predicting feeding intolerance with a NE threshold of 0.2 μg/(kg·min) had a specificity of 47.1%, a sensitivity of 88.1%, and an AUC of 65.3% (95% CI: 48.2 to 82.5, P=0.067). A retrospective study including 259 patients with shock similarly showed[224] that the dosage of NE was higher in the feeding intolerant group than in the tolerant group (0.23 μg/(kg·min)*vs*. 0.157 μg/(kg·min)). Another single-center retrospective observational study in patients with septic shock (n=120) showed[132] that the likelihood of EN tolerance was higher in the subgroup of NE dose lower than 0.14 μg/(kg·min) (ratio OR=2.35, 95% CI: 1.16 to 6.41, P=0.021). A recent large-sample retrospective observational study[225] (n=52,563) showed that in shock patients with NE <0.3 μg/(kg·min), the 28-day mortality in the early EN group was significantly lower than that in the delayed EN group, while in patients with NE >0.3 μg/(kg·min), there was no significant difference in the 28-day mortality between the early EN group and the delayed EN group (OR=1.4%, 95% CI: −7.4 to 4.7). Considered collectively, the above studies suggest that early EN is relatively safe in patients with NE <0.2–0.3 μg/(kg·min).

In addition, indicators reflecting tissue perfusion in patients with shock could be helpful for predicting early feeding intolerance. A prospective study[226] including 141 patients with shock showed that the 12-h skin spotting score was an independent risk predictor of EN failure (RR=1.28, 95% CI: 1.09 to 1.50, P=0.003). Another retrospective study,[131] including 132 patients with shock, showed that elevated blood lactate was also an independent risk factor for feeding intolerance (OR=2.7, 95% CI: 1.6 to 4.4, P <0.001).

16. Is it necessary to monitor bilirubin and cholestasis during nutritional therapy in critically ill patients?

Recommendation: We suggest dynamically monitoring of blood bilirubin and cholestasis in critically ill patients in long

term total parenteral nutrition (TPN) and/or with hepatic dysfunction. To assess TPN-related intrahepatic cholestasis, blood bilirubin is recommended (weak recommendation, very low-quality evidence). To assess extrahepatic cholestasis, abdominal ultrasound is recommended (weak recommendation, very low-quality evidence).

Rationale: Clinical and experimental studies in the early years proved that the main pathologic changes of TPN-associated stasis, which was manifested as blockage of capillary bile ducts in the confluent area of the hepatic lobules, was associated with excessive glucose intake, lack of food stimulation in the gastrointestinal tract, alteration of the hepatic-intestinal circulation, and reduction of the secretion of gastrointestinal hormones, such as cholecystokinin, gastrin, and YY peptide. These lead to weakening of the contraction of the gallbladder, thickening of the wall of the gallbladder, and intrahepatic biliary stasis. Three major studies of TPN-associated biliary sludge after 2000,[227–229] including a large-sample multicenter RCT study, a prospective multicenter cohort study, and a prospective self-control study, have shown that biliary sludge during nutritional therapy is primarily associated with PN. In contrast, initiation and increase of EN, reduction of glucose supply, and optimization of fatty acid types can lead to improvement of biliary sludge. Therefore, in critically ill patients requiring prolonged TPN and patients with liver dysfunction, hyperbilirubinemia, and intestinal failure, bilirubin, liver enzyme levels, and hepatobiliary ultrasound should be monitored during nutritional therapy.

Evidence summary: After a systematic literature search, three observational studies (n=5427) were found with no systematic review or meta-analysis. A prospective multicenter cohort study of critically ill patients[227] (n=725) compared the incidence of intrahepatic cholestasis and hepatic insufficiency in patients with PN *vs*. EN. In this study, intrahepatic cholestasis was defined as alkaline phosphatase (ALP) >280 IU/L, gamma-glutamyltransferase (gamma-GGT) >50 IU/L, or bilirubin >1.2 mg/dL. The study showed that there was a higher risk of intrahepatic cholestasis in the TPN group (OR=1.7, 95% CI: 1.04 to 2.9). In addition, the incidence of hepatic insufficiency was higher in the TPN group (30% in TPN *vs*. 18% in EN, P <0.001), and the incidence of hepatic insufficiency was correlated with the duration of TPN (13 days *vs*. 8 days, P <0.001) and with the high caloric supply of TPN (25.54 kcal/(kg·day) [interquartile range: 24.49–30 kcal/(kg·day)] *vs*. 25 kcal/(kg·day) [interquartile range: 23.33–29.41 kcal/(kg·day)], P <0.05). In another large-sample RCT study (n=4640), comparing early PN (within 48 h) with delayed PN (after 8 days) in critically ill patients, the early PN group had a higher incidence of cholestasis as detected by gallbladder ultrasound (45% *vs*. 37%, P=0.04), and showed higher serum r-GGT (50 IU/L *vs*. 38 IU/L, P=0.0007) and ALT (28 IU/L *vs*. 24 IU/L, P=0.005) with ALP (178 IU/L *vs*. 159 IU/L, P=0.02).[228] Another multiple-center prospective observational study recruited 62 postoperative abdominal surgery patients with abnormal liver function indexes. The study showed that the total bilirubin decreased significantly after 4 days of EN treatment ([9.28 ± 5.39] mg/dL *vs*. [15.14 ± 8.9] mg/dL, P <0.0001),[229] but in this before–after study, other factors could also cause the bilirubin decrease, such as disease recovery after abdominal surgery, and other treatments may benefit liver function.

17. Is it necessary to monitor triglycerides during nutritional therapy in critically ill patients?

Recommendation: We suggest monitoring plasma triglycerides level during nutritional therapy for critically ill patients, especially those with acute pancreatitis and severe burns (weak recommendation, very low-quality evidence).

Rationale: Oversupply or too quick infusion of fat emulsions can lead to fat overload, impaired triglyceride clearance, and even liver injury. In critically ill patients receiving PN or prolonged propofol sedation is applied, fat overload and lipid metabolism should be monitored. Different types of fat emulsions (e.g., long-chain fat emulsions, physically mixed medium and long-chain fat emulsions, or structured medium and long-chain fat emulsions) have different rates of fat contouring.[230–232] In addition, more studies have demonstrated that in critically ill patients, such as those with acute pancreatitis and severe burns, high blood triglyceride was correlated with disease severity and led to increased complications and mortality.[233,234] Patients at high risk for abnormal lipid metabolism, such as hyperlipidemic pancreatitis, acute and chronic liver injury, sepsis, and severe hypoproteinemia, have impaired lipid metabolism. In this circumstance, plasma triglyceride should be monitored during nutritional therapy and should not exceed 3 mmol/L (265 mg/dL) during the fat emulsion infusion.[232] The dosage and rate of fat emulsion infusion should be adjusted based on the serum triglyceride level.

Evidence summary: After a systematic literature search, we identified eight studies, including three small-sample RCTs, one unblinded crossover design study, one observational study, and three meta-analyses. A crossover study that included 10 patients with acute kidney injury (AKI) showed that high energy intake caused elevated triglyceride levels (+1.36, P=0.007).[230] Several small-sample RCTs compared the effect of nutritional therapy with different fat emulsions on blood triglyceride levels. A prospective randomized, double-blind study recruited 32 patients with sepsis. It found that the blood triglyceride concentration decreased after TPN therapy with a mixture of fat emulsions of olive oil, soybean oil, and fish oil in comparison with the pre-treatment period ([169.9 ± 36.5] mg/dL *vs*. [132.12 ± 15.5] mg/dL) (baseline *vs*. post-treatment); whereas, blood triglyceride levels did not change significantly before or after treatment ([232.5 ± 40.4] mg/dL *vs*. [240.7 ± 55.7] mg/dL) in TPN with soybean oil.[231] Another study recruited 38 postoperative surgical patients. It compared the soybean oil plus medium long-chain fatty emulsion with soybean oil plus medium long-chain fatty emulsion plus fish oil. It showed that blood triglyceride levels were significantly lower in the fish oil group on postoperative day 4 ([120 ± 45] mg/dL *vs*. [88.3 ± 37.3] mg/dL).[232]

Several researches have studied the relationship between prognosis and blood triglyceride levels in severe pancreatitis. Hypertriglyceridemia was found to be associated with a poor outcome. A meta-analysis that included 7285 patients with acute pancreatitis found that patients with hypertriglyceridemia were more likely to develop organ failure (renal failure OR=3.18, 95% CI: 1.92 to 5.27, P <0.00001; respiratory failure OR=2.88, 95% CI: 1.61 to 5.13, P <0.0001; shock OR=3.78, 95% CI: 1.69 to 8.44, P <0.0001) and a higher risk of death (OR=1.90, 95% CI: 1.05 to 3.45, P <0.01).[233] Another study

including 22 severe burns patients also showed that the mortality was higher in patients with pre-existing hyperlipidemia.[234]

18. Should electrolyte and acid–base balance be monitored routinely in adult critically ill patients with AKI/chronic kidney disease (CKD) and those undergoing RRT when receiving nutritional therapy?

Recommendation: We suggest that electrolyte and acid–base balance should be monitored when adult critically ill patients with AKI/CKD and those undergoing RRT receive nutritional therapy (Best Practice Statement).

Rationale: In patients with AKI and advanced CKD, the capacity of the kidneys to clear excess water, sodium, potassium, phosphorus, or hydrogen ions[235] is significantly reduced, leading to the risk of water and sodium retention, hyperkalemia, hyperphosphatemia, or acidosis. The electrolyte and acid–base metabolic changes associated with AKI/CKD can be exacerbated by excessive or inadequate intake of sodium, potassium, or phosphate in critically ill patients receiving nutritional therapy. Meanwhile, RRT has a very high electrolyte clearance capacity, and so it is easy to induce hypophosphatemia, hypokalemia, and hypomagnesemia.[236,237] Therefore, electrolyte and acid–base balance are prone to disorder in critically ill patients with combined acute/chronic kidney injury and those undergoing RRT during nutritional therapy, which will lead to poor clinical prognosis. Hyperkalemia due to the use of renin-angiotensin-aldosterone system (RAAS) inhibitors, β-blockers, non-steroidal anti-inflammatory, etc., or potassium released from the intracellular space as a result of metabolic acidosis, trauma, or catabolism,[238] is as common as hypokalemia due to diarrhea, metabolic alkalosis, diuretic therapy, etc.[236,239] in patients with AKI/CKD. Both hyperkalemia and hypokalemia due to inappropriate potassium intake in patients on RRT are potential reasons for sudden death in patients with AKI/CKD. Blood potassium levels should, therefore, be monitored. Combined renal osteodystrophy in patients with AKI/CKD may result in disturbances in calcium and phosphorus metabolism,[240,241] and elevated phosphate levels may lead to secondary hyperparathyroidism and arterial and cardiac valvular calcification, increasing cardiovascular mortality.[242] Prolonged RRT may lead to hypophosphatemia, and the addition of EN may trigger RFSs, including hypophosphatemia.[196] Hypophosphatemia may aggravate respiratory failure, prolong the weaning process, and induce cardiac arrhythmias in critically ill patients.[182,194,243] Therefore, regular monitoring of phosphorus levels can help to limit the phosphorus load[244] and avoid hypophosphatemia. The ability of the kidneys to neutralize immobilized acids in patients with AKI/CKD reduces, and protein intake during nutritional therapy may lead to a high intake of immobilized acids, which increases the body's acid load.[245] In the meantime, metabolic acidosis decreases glomerular filtration rate in patients with CKD stages 2–4 (P-trend=0.02)[246,247] and increases the risk of end-stage kidney disease (ESKD) (P=0.05),[248] which may also lead to complications such as bone demineralization, insulin resistance, and hyperkalemia. Therefore, it is necessary to monitor electrolyte levels and acid–base balance when administering nutritional therapy to critically ill patients with AKI/CKD and those receiving RRT.

Evidence summary: After a systematic search, no direct research evidence was retrieved.

Clinical Questions with No Consensus and Need for Future Research Attention

In addition to the above clear recommendations, there are many more questions to discuss about nutritional assessment and monitoring in critically ill patients. Evidence due to limited sample size, low quality, lack of practicality in China, and different opinions of the experts thus cannot reach a uniform consensus, but these topics deserve further attention and more robust evidence. Here are the issues that have been discussed the most or are expected to be the direction of future research.

Question 1: Should intestinal barrier function indicators be monitored during early EN in critically ill patients?

AGI is often associated with intestinal mucosal barrier disruption, toxin and bacterial translocation, secondary infections, and multiorgan dysfunction.[249,250] In 2012, the European Society of Intensive Care Medicine (ESICM) Working Group on Abdominal Problems proposed the definition of AGI and classified it into four levels according to severity,[108] suggesting that the diagnosis of AGI should be established based on gastrointestinal symptoms, IAP, GRV, and systemic conditions. However, the AGI classification system is highly subjective and focuses on feeding intolerance, whereas the gastrointestinal dysfunction score (GIDS), developed based on its principles, is more definitive and less subjective. GIDS can either work on its own or as a complement to the SOFA for gastrointestinal dysfunction judgment, which is shown to be a good predictor of mortality.[251] The GIDS is more specific and less subjective than the AGI. Both GIDS and AGI are diagnosed based on IAP, as with gastrointestinal symptoms and GRV, which often appears delayed and lacks sensitivity. In fact, once a patient is recognized as having high-grade AGI based on clinical symptoms and signs, it means a disrupted EN and even a risk of aspiration and intestinal ischemia. Clinicians expect early and effective markers to indicate intestinal barrier impairment, to help monitor EN tolerance, and thereby to guide nutritional decision-making and optimize patients' nutritional outcomes. Currently, there are many clinical indicators that may suggest intestinal mucosal barrier function impairment, such as citrulline, intestinal fatty acid-binding protein (I-FABP), diamine oxidase, D-lactate, and angiopoietin-2.

Citrulline is synthesized in enterocytes and released to the portal circulation, and thereafter converted to arginine in the kidneys.[252,253] Citrulline <10 mmol/L indicates enterocyte mass damage, suggesting that the intestinal mucosal barrier is structurally impaired.[254–256] Only when intestinal epithelial cells have ischemic necrosis does I-FABP enter the bloodstream or urine. Serum I-FABP >100 pg/mL suggests acute mesenteric ischemia, and >355 pg/mL suggests a poor outcome. However, I-FABP needs to be interpreted cautiously because it has a very short half-life (11 min) and is susceptible to renal function.[254,257] D-lactate is a product of bacterial fermentation in the lumen and cannot be synthesized by the body. When the intestinal barrier is compromised, D-lactate enters the bloodstream through the compromised mucosa; therefore, plasma levels are elevated, but the time of elevation (>10 mmol/L) is delayed compared to the time of intestinal compromise/ischemia.[258] Enteric endotoxin is mainly derived from luminal bacteria,[257] and when serum endotoxin is elevated (>20 U/L), it may indicate intestinal mucosal barrier disruption and increased permeability, toxin, and bacterial

translocation.[255] Nevertheless, it has a low diagnostic efficacy and is susceptible to systemic infection.[256] All in all, the cut-off values for the aforementioned indicators of intestinal mucosal barrier function are generally controversial and can only be performed in some available hospitals.

The concentrations of intestinal mucosal barrier markers will change after initiating EN in critically ill patients, suggesting that intestinal mucosal barrier markers may be used to assess early EN tolerance in the critically ill. The iSOFA study[118] observed the plasma citrulline and plasma I-FABP in 224 adult ICU patients and found that plasma citrulline concentration was significantly increased in patients who initiated EN (P=0.049); the citrulline concentration continued to increase in patients who reached 80% of the feeding target on day 4 of EN, while the non-attainment group showed a mild decrease. On the other hand, I-FABP was also significantly elevated in the early EN group (P=0.004) and reached the highest mean value in patients who reached the feeding target on day 3 (646 [IQR 313, 1116] pg/mL *vs*. 278 [IQR 190, 701] pg/mL, P=0.022). The NUTRIREA-2 study[259] showed that plasma citrulline levels were significantly higher in the early EN group compared with the early PN group (18.7 [13.4; 29.2] mmol/L *vs*. 15.3 [9.8; 21.2] mmol/L, P=0.01) in mechanically ventilated patients as well with shock; on days 3 and 8 after initiating nutrition therapy, plasma I-FABP was significantly higher in the early EN group than in the early PN group (day 3: 159 pg/mL *vs.* 50 pg/mL, P=0.005; day 8: 225 pg/mL *vs.* 50 pg/mL, P=0.03). Low-quality evidence suggests that elevated D-lactate and endotoxin are associated with higher AGI risk.[256,260] In summary, intestinal barrier indicators (e.g., citrulline, I-FABP, D-lactate, etc.) are expected to assess EN tolerance in critically ill patients in the future, yet there is a lack of robust clinical evidence.

Question 2: Should nitrogen balance (NB) be monitored during nutritional therapy in critically ill patients?

NB is a widely used and reliable indicator for assessing the state of systemic protein metabolism (i.e., protein loss or gain).[261] A positive NB suggests an increase in systemic protein, while a negative NB suggests a depletion of systemic protein. Negative NB in critically ill patients is often caused by infection, trauma, inflammation, medications, and other factors, leading to a poor outcome[262–266]; positive NB achieved by protein supplementation through nutritional therapy promotes protein synthesis in the body, shortens the length of hospitalization, and improves morbidity and mortality.[186,266–268] A systematic review[269] included eight RCTs (n=1409) to investigate the correlation between NB and clinical prognosis in critically ill patients. Five RCTs compared NB in the survivors and non-survivors and found no significant difference in initial NB between the two groups (MD=1.20 g/day, 95% CI: −0.70 to 3.11; I^2=77%, P=0.22), whereas final NB was significantly higher in the survivors than in the non-survivors (two studies, n=263; MD=3.69 g/day, 95% CI: 1.92 to 5.46; I^2=55%, P <0.0001), suggesting that it is the final NB status rather than the initial NB that determines the clinical prognosis of critically ill patients, and that a positive NB contributes to better clinical prognosis. NB is positively correlated with protein intake and is more easily achieved at protein intakes >2 g/(kg·day).[266] ESPEN guideline recommends a protein target of at least 1.3 g/(kg·day) for critically ill patients[11]; ASPEN guideline recommends a protein intake of 1.2–2 g/(kg·day) in critically ill patients; and 1.5–2.5 g/(kg·day) of protein intake is required in elderly patients to achieve positive NB.[270] On the other hand, it has been suggested that aggressive nutritional supply in the early acute phase may inhibit autophagy, which may lead to severe myopathy.[271,272] Therefore, early protein supply needs to be gradually achieved under the guidance of objective monitoring (such as NB).

It should be noted that NB only reflects the overall net protein balance and does not indicate the rate of protein synthesis or catabolism. Besides, NB monitoring has some limitations, as mentioned below:

(1) The concentration is affected by inflammatory and metabolic status, renal function, CRRT, urine output, collection facilities, etc., e.g., 24-h urine nitrogen collection is difficult; oliguria (urine output ≤500 mL/day) and anuric patients are hard to apply; patients underwent CRRT need to measure the nitrogen content of ultrafiltrate[273]; nitrogen loss at special sites (e.g., wound drains) may affect the accurate assessment of NB.[274] (2) Extra-urine nitrogen is evaluable and varies with critical illness. (3) Continuous testing is more objective. It requires dynamic evaluation and comprehensive interpretation for clinicians.

Question 3: Should 24-h nitrogen excretion be monitored during nutritional therapy in critically ill patients with renal impairment?

It is important to note that increased protein intake may increase renal burden and cause azotemia, increasing the risk of death.[262,263] For critically ill patients with renal impairment who have a decreased renal function reserve, inappropriate protein intake may lead to increased renal injury risk. On the other hand, these patients may require RRT who have hypermetabolism and higher nitrogen loss due to filters usually cannot reach the target protein goal and thus get a worse outcome. The means to determine the protein requirements of patients with AKI/CKD is an urgent clinical topic.

Nitrogen loss can be calculated, and NB is assessed clinically by measuring 24-h urine urea nitrogen.[275] Several studies[261,266,267,276–281] have used 24-h urea nitrogen measurement to assess NB in critically ill patients to evaluate the efficacy of nutritional therapy, but none of them have made a comparison of clinical outcomes between monitoring 24-h urea nitrogen group and no monitoring group. As a result, no recommendation for whether 24-h nitrogen excretion should be monitored in critically ill patients with renal insufficiency can be made in this guideline.

Measurement of 24-h urine urea nitrogen level usually requires certain laboratory conditions, which are difficult to achieve in many hospitals in China and thus difficult to promote in Chinese ICUs. On the other hand, there is no standardized method for assessing total nitrogen loss through urine urea nitrogen, which makes it difficult to achieve accurate assessment[261,282]; in addition, 24-h urine urea nitrogen measurement is time-consuming and characterized by unreliable accuracy. A study[283] used 6-h urine nitrogen measurement instead of 12-h urine nitrogen measurement and 24-h urine nitrogen measurement and found no significant difference between the three groups though the study excluded patients with liver failure and renal failure. Nonetheless, urine nitrogen levels (reflecting NB) may still be a promising reference for setting protein goals in critically ill patients.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jointm.2023.12.002.

Appendix: measurement of nitrogen excretions

Methods of monitoring nitrogen excretion in patients free from RRT

Because most of the nitrogen is excreted in urine, we can estimate nitrogen excretion by urinary nitrogen. Nitrogen intake and nitrogen loss were calculated as follows.

NB=nitrogen intake – nitrogen loss

Nitrogen intake (g/day)=protein intake/amino acid intake (enteral/parenteral)/6.25

Nitrogen loss (g/day)=urine urea nitrogen + change in body urea nitrogen pool + unmeasured nitrogen loss

Urinary urea nitrogen (g)=urinary urea (mg/dL) × 0.01 (converting mg/dL to g/L) × urine output (L) × 0.466 gN/g urea

Change in body urea nitrogen pool (g)=(plasma urea on day a [mg/dL] – plasma urea on day a–1 [mg/dL]) × 0.01 (converting mg/dL to g/L) × volume of urea distributed (≈0.6 × body weight) × 0.466 gN/g urea

Unmeasurable nitrogen loss (e.g., fecal nitrogen, skin nitrogen excretion, etc.)=non-urea urinary nitrogen loss + non-urinary nitrogen loss ≈4 g

Methods of monitoring nitrogen excretion in patients underwent RRT

Nitrogen loss (g/day)=urinary urea nitrogen + nitrogen contained in RRT filtration effluent/dialysis effluent + change in body nitrogen pool + unmeasured nitrogen loss

The nitrogen content of RRT filtration effluent/dialysis effluent was determined by the following method: three samples of dialysate were taken at 8-h intervals, and urine samples were taken at the same time as the dialysate samples for patients with urine output of more than 500 mL/day. Each dialysate (urine) sample was then analyzed for total nitrogen using the Kjeldahl method.

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