Nutrition in Clinical Practice
Volume 32 Supplement 1
April 2017 142S–151S

DOI: 10.1177/0884533617693610
journals.sagepub.com/home/ncp

Summary Points and Consensus Recommendations From the International Protein Summit

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Abstract

The International Protein Summit in 2016 brought experts in clinical nutrition and protein metabolism together from around the globe to determine the impact of high-dose protein administration on clinical outcomes and address barriers to its delivery in the critically ill patient. It has been suggested that high doses of protein in the range of 1.2–2.5 g/kg/d may be required in the setting of the intensive care unit (ICU) to optimize nutrition therapy and reduce mortality. While incapable of blunting the catabolic response, protein doses in this range may be needed to best stimulate new protein synthesis and preserve muscle mass. Quality of protein (determined by source, content and ratio of amino acids, and digestibility) affects nutrient sensing pathways such as the mammalian target of rapamycin. Achieving protein goals the first week following admission to the ICU should take precedence over meeting energy goals. High-protein hypocaloric (providing 80%–90% of caloric requirements) feeding may evolve as the best strategy during the initial phase of critical illness to avoid overfeeding, improve insulin sensitivity, and maintain body protein homeostasis, especially in the patient at high nutrition risk. This article provides a set of recommendations based on assessment of the current literature to guide healthcare professionals in clinical practice at this time, as well as a list of potential topics to guide investigators for purposes of research in the future. (*Nutr Clin Pract*. 2017;32(suppl 1):142S-151S)

Keywords

protein; lean body mass; enteral nutrition; parenteral nutrition; amino acids

The International Protein Summit was convened September 23–25, 2016, in Charleston, South Carolina. Global experts were invited to participate as speakers and discussants, based on knowledge and international reputation in the areas of clinical nutrition and more specifically protein metabolism. The format of an expert consensus conference or summit offers a rapid fluid process that works to help the practitioner by clarifying clinical issues in the literature and the investigator by providing direction for future research. The main focus and overall objective of the summit was to offer expert consensus opinion pertaining to the provision of protein in the intensive care unit (ICU) and help close the gaps between what is happening in clinical practice and what is recommended through guidelines by nutrition societies (American Society for Parenteral and Enteral Nutrition [ASPEN], Society of Critical Care Medicine [SCCM], European Society for Clinical Nutrition and Metabolism [ESPEN], and Canadian Critical Care Nutrition Guidelines). The summit had 6 objectives: (1) describe clinical outcome benefits and identify patient populations most affected by consumption of a high-protein diet; (2) identify barriers to the delivery of protein; (3) determine the etiology of associated loss of muscle mass and total body protein in the ICU; (4) assess protein requirements for various patient populations (ie pediatrics, sepsis, obesity); (5) identify optimal source, dosing, route, and delivery of feeding regimens high in protein; and (6) provide a potential agenda for future research designed to generate higher levels of evidence supporting protein administration in the critically ill patient.

The highlights of the summit and recommendations reported here represent the opinion of the panel, not those of a national or international nutrition society. The expert panel convened does not represent a formal voting body or guideline committee. While the members of the expert panel were expected to review the literature pertaining to each topic, use of a formal process for grading the quality of evidence in the literature and determining the strength of each recommendation was not feasible for the structure and function of the summit process. Once the manuscript and recommendations were completed, however, participants were sent an anonymous electronic survey and asked to indicate whether they agreed or disagreed with each of the consensus recommendations. Despite these limitations, we felt there was great value in assembling recognized experts in the specific area of protein metabolism where there was a paucity of information available to clinicians. The

information provided in the current article represents a compilation of issues, concerns, and recommendations deemed important by the summit participants. The summit was funded by a grant from the Nestlé Nutrition Institute.

Overview

- Protein loss, manifested as a reduction in skeletal muscle mass and total body nitrogen content, is observed universally in all critically ill patients. Protein catabolism is part of the metabolic response to critical illness. The magnitude of protein loss is associated with increased morbidity and mortality.[1] The depletion of muscle mass seen clinically has been associated with impaired function and poor clinical outcomes.[1,2] Adequate protein delivery to hospitalized and critically ill patients is very likely essential for optimal nutrition therapy, but high-quality evidence from clinical trials supporting this view is currently lacking.
- Biological value reflects the ideal content and proportion of amino acids contained in a protein that best promotes anabolism. Biological value may be measured by protein efficiency ratio, net protein utilization, protein digestibility corrected amino acid score, and the digestible indispensable amino acid score (DIAAS).
- Under certain circumstances, active catabolism of amino acids during critical illness creates a relative deficiency state for certain amino acids (in the absence of protein malnutrition), which cannot be overcome by provision of dietary protein alone.
- Severe protein energy malnutrition (PEM) is manifested by respiratory failure, lack of wound healing, and immune dysfunction. Strategies to prevent muscle loss focused initially on meeting energy requirements, the assumption being that protein was selectively used (through oxidation) as an energy source. While hypocaloric states do contribute to protein wasting, it has become increasingly clear that the most important nutrient for preserving muscle mass is protein itself. Provision of a small amount of glucose, however, may have a protein-sparing effect protecting against muscle loss and decreasing amino acid oxidation.[2]
- Clinicians need to prioritize their efforts toward delivering goal protein to patients at high nutrition risk. Despite expectations of benefit, provision of increased total calories without increased protein delivery has failed to demonstrate a clear benefit in curtailing protein loss or in improving outcomes. Whereas adequate protein intake has shown benefit, unfortunately in clinical practice, ICU patients receive far less than the recommended amount.

Stimulation and Inhibition of Protein Synthesis in Healthy States

- Protein is digested in the small intestine as a combination of oligopeptides and individual free amino acids. After passing through the enterocytes, only individual free amino acids and a few dipeptides appear in the portal circulation, leading to further oxidation in the hepatocytes. The passage of amino acids through the small bowel epithelium and liver and their subsequent oxidation is termed *first-pass elimination*.[3]
- Due primarily to this first-pass elimination, amino acids administered by the enteral route will generally result in

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Financial disclosure: Financial support for the publication of the supplement in which this article appears was provided by Nestlé HealthCare Nutrition, Inc.

Conflicts of interest: All authors received financial support from Nestlé HealthCare Nutrition, Inc, to speak at the 2016 Nestlé Nutrition Institute International Protein Summit. R.T.H., S.A.M, R.G.M, J.B.O.G., S.J.R., D.K.H., and B.T. have received consulting fees from Nestlé. J.B.O.G. is the chief medical officer for Nestlé HealthCare Nutrition, Inc, in North America. D.K.H. has received honorarium and research grants from Nestlé HealthCare Nutrition, Inc, and Abbott. C.R.M. is the inventor or coinventor of several UCSF-Benioff Children's Hospital Oakland patents/patent-pending applications that include ω-3 fatty acid nutrition supplements and biomarkers of cardiovascular disease related to arginine bioavailability; is an inventor of an Emory University School of Medicine patent application for a nutrition supplement; is a consultant for Pfizer, Nourish Life, and Calithera Biosciences; and has received research support from MAST Therapeutics, the U.S. Food and Drug Administration, and the National Institutes of Health. D.P.-J. participates on scientific advisory panels and has received research funds, travel expenses, and/or honoraria from the American Egg Board, Leprino Foods, the National Dairy Council, and the U.S. Dairy Export Council. S.M.P. reports participation on the scientific advisory board for Axcella Health and Leprino Foods and having received honoraria for speaking and travel expenses and/or research support from the U.S. National Dairy Council, the U.S. National Cattlemen's Beef Association, and the Dairy Farmers of Canada. P J.M.W. has additionally received honoraria for speaking and travel expenses and/or research support from Nutricia, Fresenius Kabi, and Baxter.

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lower circulating levels in the systemic circulation than a similar amount delivered by the parenteral route.[3,4]

- While nitrogen balance is the traditional way of measuring protein utilization, its use may not be reliable in short-term situations and requires a very dedicated group to obtain consistent accurate results.[5] However, this technique is the only bedside measurement tool available to practitioners.
- The use of nonradioactive tracer technologies to assess protein utilization may yield better estimates than nitrogen balance. Assuming that the intake of an amino acid is known, whole-body protein synthesis, whole-body protein degradation, and whole-body protein balance can be estimated based on the rate of plasma amino acid appearance and disappearance.[6]
- Measures of protein turnover by tracer techniques are promising, but these snapshot measures must be interpreted with caution.[6]

Protein Kinetics and Metabolic Effects Related to Disease States and Sepsis

- Heterogeneity in the critically ill patient population and the wide spectrum of disease processes seen in an ICU setting make assessing protein kinetics difficult.[7]
- Additional factors such as age, sex, obesity, preexisting nutrition state, route of nutrition therapy, and status of the intestinal microbiome may all play a role in determining body protein kinetics.[7]
- The complexity of protein kinetics is amplified in septic critically ill patients compared with non-ICU or nonseptic patients. The inflammatory and dysregulated immune responses seen in sepsis and major trauma lead to organ dysfunction and catabolic signaling. While hepatic protein synthetic rates may be normal or only minimally elevated in sepsis, total systemic degradation rates are dramatically increased.[8]
- Anabolic resistance is the failure of normal anabolic stimuli to induce net protein synthesis. Such a response occurs, although by different mechanisms, in the elderly and in stressed ICU patients.[9,10] Primary drivers of anabolic resistance are thought to include splanchnic sequestration of amino acids, decreased availability of amino acids to muscle and possibly other organs, and a blunted anabolic response to the provision of amino acids.[9,10]
- The use of specific individual amino acids (ie, citrulline, glutamine, arginine, leucine) to maximally stimulate the rate of protein synthesis has not been shown to consistently improve ICU outcomes. This finding may be attributable to a number of factors, such as the disparity between the normal rate of protein synthesis and the markedly increased rate of degradation observed in sepsis.

Acquired Amino Acid Deficiencies

- Arginine deficiency states can occur in critically ill patients, worsening outcomes by impairing adaptive immune responses and endothelial function, among other problems. The arginine deficiency occurs generally as a result of increased destruction by the enzyme arginase.[11,12]
- Prototypes of arginine-deficient states include trauma/surgery patients where the source of arginase is from myeloid-derived suppressor cells and hemolytic disorders like sickle cell disease (SCD) where the arginase is derived from the red blood cell, released into the circulation through hemolysis.[11–13]
- Arginine and glutamine supplementation in SCD appears to be safe, is well tolerated, and may provide clinical benefit.[14,15]
- Oral or parenteral supplementation of L-arginine hydrochloride at doses of 100 mg/kg/d or 7–10 g given 2 or 3 times daily has been used safely in SCD with clinical improvements reported for acute vaso-occlusive pain, leg ulcers, priapism, and pulmonary hypertension. No recommendations can be made at this time until further research is completed, but controlled clinical trials are ongoing.[16]
- The results of phase II–III clinical trials support the use of oral glutamine supplementation for SCD.[15,17] Benefits of glutamine therapy given in steady-state conditions (not in crisis) include decreased incidence of pain and reduced need for hospitalization. Doses as high as 10 mg per os 3 times daily have been used without serious adverse events.[15,17] Glutamine can function as an arginine prodrug, increasing global arginine bioavailability. Glutamine has been granted orphan drug status for the treatment of SCD.

Variation in Protein Origin and Utilization in the Healthy State

- Dietary protein obtained by oral consumption or delivered through nutrition support therapy is a fundamental prerequisite for muscle protein synthesis and maintenance of function.[18]
- There is likely an upper limit to the quantity of protein necessary to maximally stimulate muscle protein synthesis in healthy individuals.[18] Although no "optimal amount" has been identified for all subjects, a total of 20–35 g of high-quality protein per meal spread evenly throughout the day is likely needed to maximize protein synthesis.[18] The intermittent delivery of protein appears to yield better uptake than a single bolus of protein given once daily.
- Branched-chain amino acids (BCAAs), especially leucine, act as a trigger for increasing muscle protein synthesis. Leucine is an insulin secretagogue and potent

activator of the mammalian target of rapamycin (mTOR) nutrient signaling pathway.[19] Leucine supplementation may not further enhance muscle protein synthesis in patients already consuming a protein/leucine-sufficient diet (ie, >1.0 g/kg/d).[20]

- Optimal dietary protein should contain a complete profile of amino acids, including all essential amino acids. Supplementation with an incomplete protein source could lead to less than optimal skeletal muscle mass and function.[21] Delivery of a single amino acid in large quantities can also have a negative effect on protein synthesis.
- DIAAS is a new and improved scoring system that is used to quantify the quality of dietary protein and is the best tool for determining whether a protein source is of high quality. The DIAAS recognizes that amino acids are individual nutrients and that protein quality is contingent on both amino acid content and ileal digestibility.[22] The DIAAS has recently been recommended for widespread adoption by the Food and Agriculture Organization of the United Nations.[23]
- In the health state, provision of high-quality protein, as scored by the DIAAS (eg, an animal-based source of protein is superior to a plant-based source), appears to optimize protein synthesis.[22,23]

Factors Affecting the Delivery and Utilization of Protein in the ICU

- Worldwide, ICU patients fail to receive protein in the range of 1.2–2.0 g/kg/d as recommended for most hospitalized patients by the SCCM-ASPEN 2016 Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient.[24]
- Studies evaluating critically ill patients have demonstrated that exercise and physical therapy rehabilitation strategies improve physical function and decrease the duration of mechanical ventilation.[25,26] These benefits were observed in patients whose nutrition intake either was not recorded or was documented to be insufficient. Combining protein delivery with exercise/rehabilitation strategies may be an opportunity to further improve outcomes.
- Delays incurred when initiating enteral nutrition (EN) in the ICU ultimately lead to overall caloric deficits but, more important, underdelivery of protein. Both enteral and parenteral options for protein-enhanced formulations should be explored to reach goal protein delivery as early in the ICU stay as possible.
- Several strategies are available for increasing protein/amino acid delivery in ICU patients. They include use of high-protein EN formulas, the addition of protein supplements for the patient already receiving EN, supplementing EN with parenteral amino acids, and implementing EN feeding protocols that enhance protein delivery (eg, volume-based feeding, the Enhanced Protein-Energy Provision via the Enteral Route Feeding Protocol [PEP uP]).[27–29]
- Monitors to help the clinician determine whether an individual patient in the ICU has received sufficient protein administration are needed. One approach is to develop serum biomarkers that are sensitive to adequacy of protein provision. Two such potential biomarkers have been identified. The nutrient-sensing pathways, mTOR and general control nondepressible-2, which regulate distinct gene and protein responses, reflect amino acid availability and thus might prove useful to practitioners in the future as a clinical monitor of adequacy of nutrition therapy.[30] These biomarkers are currently used only on an experimental basis and would need further validation before being used routinely for clinical decision making.
- Another approach to gauge adequacy of protein provision is to follow changes in muscle mass. A crude but simple method of assessing muscle mass is by physical examination at the bedside. Ultrasonography (U/S), performed over the mid-upper leg quadriceps muscle, is a practical way to measure muscle mass (area or thickness) and muscle quality (fat stippling). Interobserver variation is still an issue, and as techniques improve, the clinical usefulness of this technology should increase. Assessment of muscle mass can also be made by evaluating a number of factors such as the area of muscle, the ratio of fat to muscle, and the fat content of the muscle at the third lumbar vertebrae (L3) from a computed tomography (CT) scan. For example, a reduced area of muscle mass at L3 (<170 cm^2 for males, <110 cm^2 for females) documented during the first few days following admission to the ICU is associated with worse outcomes compared with those who have normal L3 muscle mass.[31] However, we lack evidence to support the notion that these patients with low muscularity will benefit the most from aggressive protein supplementation.
- A number of other potential techniques may assist in the evaluation of body composition and the changes in muscle mass that occur in critical illness, such as serum creatinine, serum cystatin C, urinary creatinine excretion, multifrequency bioimpedance, and CT imaging.[32–34]

Protein Requirements in the ICU

- There is a lack of randomized controlled trials (RCTs) that evaluate critically ill patients randomized to different doses of protein provision, adjusted for ideal energy intake, and then followed for long-term clinical outcomes.[35,36]
- Protein and calorie doses are typically recommended based on actual body weight.[24,37] These recommendations

may be problematic in critically ill patients in the ICU who undergo large-volume resuscitation causing fluid shifts into the extracellular space.

- A number of physiologic studies and observational trials suggest that providing protein doses >1.2 g/kg/d may improve mortality in critical illness.[38–40] Certain patient populations (such as those who are obese or have sustained trauma) may require higher protein doses in a range of up to 2.0–2.5 g/kg/d.[24] In most patients, enteral protein intake should be increased if feasible to >1.2 g/kg/d by the fourth day following admission to the ICU.
- Observational ICU data have demonstrated that after controlling for caloric intake, a significant reduction in mortality is seen when >80% of protein requirements are delivered (compared with <80%). In contrast, no mortality benefit is seen with increasing caloric administration after controlling for the amount of protein delivered.[41]

Caloric Requirements in the ICU

- Energy overfeeding (>90% of measure energy expenditure) during critical illness may decrease capillary blood flow and amino acid transfer to the muscle and should be avoided.[42] Early energy supply from any enteral or parenteral source should be conservative, at 80%–90% of measured energy expenditure.
- One distinct metabolic response that occurs in critically ill patients involves a reduced rate of oxidation of glucose. Inflammatory cytokines released in response to critical illness potentially affect the mitochondrial conversion of pyruvate to acetyl CoA, leading to lower glucose oxidation and less efficient conversion to useable energy.[43]
- This alteration in glucose oxidation and energy conversion does not improve with insulin delivery, as it has no effect on pyruvate dehydrogenase.[43]
- High-protein (1.7 g/kg/d) hypocaloric (15 kcal/kg/d) feeding strategies have recently been shown in a prospective RCT to reduce the average daily insulin requirement and decrease the percentage of patients requiring any insulin.[44]
- High-protein hypocaloric feeding may help glucose control (less risk of hypoglycemia/hyperglycemia), reduce the need for supplemental insulin, and improve nitrogen balance in ICU patients.[44,45]

Protein Requirements in the Obese ICU Population

- Obesity is present in >25% of patients admitted to the ICU and is associated with numerous metabolic consequences (eg, diabetes mellitus, hypertriglyceridemia, nonalcoholic fatty liver disease).[46–48] Energy overfeeding (≥25 kcal/kg/d) can worsen not only these obesity-associated comorbidities but also hypercapnia and subsequent respiratory compromise and thus should be avoided.[49,50]
- Simple weight-based equations may be used to guide provision of protein and energy in the critically ill obese patient. An initial protein intake of 2 g/kg ideal body weight (IBW)/d should be given to those with a body mass index (BMI) 30–39.9 kg/m^2, while those patients with a BMI ≥40 kg/m^2 should receive 2.5 g/kg IBW/d. Obese patients with BMI in the range 30–50 kg/m^2 should be given a caloric intake of 11–14 kcal/kg actual body weight/d, while those with BMI >50 kg/m^2 should be dosed 22–25 kcal/kg IBW/d.[47]
- Older obese patients (aged >60 years) are at greater risk for azotemia and anabolic resistance than those of younger age.[51] A recent study, though, demonstrated that there was no clinically relevant difference in serum urea nitrogen concentrations and no significant difference in nitrogen balance between younger (aged <60 years) and older patients given hypocaloric nutrition with 2 g/kg IBW/d of protein.[52] Therefore, the recommendations for a high-protein hypocaloric feeding strategy in obese adults should remain the same regardless of age.

Protein Requirements in Renal and Liver Failure

- Acute kidney injury (AKI) is common during critical illness and can be present in >57% of patients admitted to an ICU.[53] Protein requirements in AKI can be calculated by the rate of urea nitrogen appearance.[54] The provision of protein to ICU patients with AKI not yet on renal replacement therapy (RRT) should be determined in the same manner as other critically ill patients (ie, 1.2–2.0 g/kg/d).[24]
- Management strategies such as continuous renal replacement therapy (CRRT) or intermittent hemodialysis are associated with a large amount of amino acid/protein loss.[55] ICU patients undergoing RRT may require between 1.5 and 2.5 g/kg/d of protein to achieve positive nitrogen balance.[56,57]
- The data supporting the use of parenteral supplementation with essential amino acids (EAAs) are lacking. Such use does not change mortality, fails to improve nitrogen balance, and thus cannot be recommended.[58]
- An increase in protein catabolism occurs with acute liver failure and decompensated cirrhosis. PEM is associated with compensated cirrhosis.[59] Protein should not be restricted in patients with acute liver failure and cirrhosis. Protein provision in those patients should be determined in a similar fashion to any other critically ill

patient in the ICU.[24] Dry weights should be used for estimating the amount of protein to be delivered to patients with cirrhosis.

- BCAA formulas have been used in critically ill patients with liver disease. Data supporting supplementation of BCAA in patients with decompensated cirrhosis and hepatic encephalopathy in the ICU are lacking, and thus their use is not recommended in the critical care or hospital settings.[24]

Protein Requirements in the Elderly ICU Patient

- Protein provision in elderly ICU patients (aged >60 years) is challenging due to a number of factors, such as baseline loss of muscle mass compared with younger patients, a reduced ability to recover muscle function following a period of disuse, and a lower anabolic response to circulating amino acids involved in skeletal muscle protein synthesis (MPS).[60–62]
- Higher levels of protein are needed in elderly trauma patients to achieve the same level of nitrogen balance as their younger counterparts.[63] Older critically ill ICU patients can overcome these challenging factors and have been shown to achieve nitrogen balance, but only when the amount of protein delivered approached the range of 2.0–2.5 g/kg/d.[64]
- Protein sources are not equal in their ability to stimulate skeletal MPS and/or limit muscle protein breakdown.[65] Protein quality depends both on digestibility and content of EAAs. High-quality protein can play a role in preservation of lean body mass in older ICU patients.[66,67] There is strong evidence that a primary stimulant of skeletal MPS is the BCAA leucine, but testing this hypothesis in larger RCTs of patients receiving nutrition support is needed.[67,68]
- Physical therapy (PT) in the elderly ICU patient may increase MPS and improve mobility.[69] Even low amounts of resistance training may enhance anabolism and MPS, while preventing further loss of muscle mass.[70] There are numerous barriers to providing PT and early mobilization in the ICU.[69] ICU protocols and safety guidelines can be implemented to overcome these barriers.[71]

Nutrition Therapy in Persistent Inflammation Catabolism Syndrome

- Because of advances in ICU care of the critically ill patient, the percentage of patients who die of multiple-organ dysfunction (MOD) early in the ICU course has decreased.[72] Those who survive MOD will often develop immunosuppression and a persistent inflammation catabolism syndrome (PICS).[72]
- Specific nutrition support recommendations for patients who have PICS are drawn from other chronic inflammatory conditions with similar pathophysiology such as cancer, sarcopenia, and burns.[73–75] Protein should be provided over a range of 1.2–2.0 g/kg/d to patients with PICS.
- Arginine-enriched EN formulas have been shown to improve clinical outcomes in major elective-surgery patients at risk for MOD.[76] Arginine supplementation in patients with PICS may assist with wound healing (through ornithine production) and restore lymphocyte proliferation.
- BCAAs (especially leucine) have been shown to stimulate MPS in chronic conditions similar to PICS (eg, advanced age, sarcopenia, and cancer). Although not specifically studied in MOD or PICS, use of BCAAs would be expected to be beneficial, but RCTs are needed to confirm this hypothesis.[77,78]
- Anabolic agents have demonstrated some benefit using strict protocols in chronic inflammatory conditions (mainly burns) similar to PICS. Use of these agents (which include insulin, oxandralone, and propranolol) could be considered in patients with PICS.[79,80]

Protein Requirements in the Pediatric ICU Patient

- EN is the preferred method for delivery of protein during critical illness in infants and children.[81]
- A number of studies have demonstrated that in children between the ages of 3 months and 13 years, provision of EN achieved positive nitrogen balance with receipt of protein in doses of ≥2 g/kg/d,[82–86] yet this same dose of protein given via parenteral nutrition (PN) did not achieve positive nitrogen balance.[87,88]
- A systematic review found a correlation between higher energy and protein intakes and achievement of positive protein balance in critically ill children.[89]
- A recent multicenter cohort trial in critically ill children demonstrated that intake of >60% of prescribed protein was associated with lower 60-day mortality.[90]

Consensus Recommendations

Anonymous electronic survey responses were returned by 18 of 20 participants of the protein summit (90%). Results are presented as a percent consensus on whether participants answered agreed and disagreed and are included in brackets following each recommendation.

1. We recommend assessment of nutrition risk in every ICU patient, focusing on signs of protein/muscle wasting, Nutrition Risk Score 2002 or the Nutrition Risk in Critically Ill score, age >60 years, low BMI (<18.5 kg/m^2), and muscle mass (through CT, bioelectrical

impedance analysis, U/S, and physical exam) [100%; 18 agree, 0 disagree, 0 did not answer].
2. We recommend that a minimum of 1.2 g/kg/d of protein (with doses up to 2.0–2.5 g/kg/d) be used in critically ill patients admitted to the ICU [94.4%; 17 agree, 1 disagree, 0 did not answer].
3. We recommend initial provision of 80%–90% of caloric energy requirements in ICU patients, as long as it is partnered with recommended protein doses in the range of 1.2–2.5 g/kg/d. Routine nutrition assessment should be repeated to ensure that metabolic demands are being met. Energy provision may be increased to meet energy requirements as patients recover from the acute phase of critical illness [88.9%; 16 agree, 2 disagree, 0 did not answer].
4. We recommend that certain patient populations may need delivery of protein at the higher end of the recommended range, such as patients aged >60 years or those with burns, obesity, trauma, or need for CRRT. Enhanced protein delivery in the ICU may overcome the anabolic resistance seen in these patients [88.9%; 16 agree, 2 disagree, 0 did not answer].
5. We recommend that strategies be used to promote protein delivery through the use of enteral feeding protocols and the availability of appropriate high-protein, low-calorie enteral products in the ICU [100%; 18 agree, 0 disagree, 0 did not answer].
6. We recommend that formulas supplemented with L-arginine should be given to high-risk surgical patients [76.5%; 13 agree, 4 disagree, 1 did not answer].
7. We recommend a minimum intake of protein in critically ill infants and children of 1.5 g/kg/d to achieve positive nitrogen balance. Overall calorie delivery should be ≥57 kcal/kg/d [86.7%; 13 agree, 2 disagree, 3 did not answer].
8. We recognize that nitrogen balance has its limitations in short-stay ICU patients, but it is one of the few tools available for evaluating whole-body protein economy over time in individual patients not in renal failure [83.3%; 15 agree, 3 disagree, 0 did not answer].
9. Although results from physiologic studies and observational trials might suggest that supplemental intravenous amino acids (not PN) be added to insufficient protein delivery by EN alone, lack of data from interventional RCTs precludes recommendation at this time [100%; 18 agree, 0 disagree, 0 did not answer].
10. Although we recognize that some data suggest a benefit of anabolic agents such as leucine, hydroxy methylbutyrate (HMB), insulin, or growth hormone to stimulate protein synthesis in patient populations outside the ICU setting, we cannot make a recommendation regarding the use of these agents due to the lack of data and potential safety concerns in critically ill patients [94.1%; 16 agree, 1 disagree, 1 did not answer].
11. Although we recognize there is evidence in patient populations outside the ICU setting for whom intermittent (vs continuous) delivery of protein may improve protein synthesis, we cannot recommend intermittent feeding to stimulate protein synthesis due to the lack of evidence in the critically ill [94.4%; 17 agree, 1 disagree, 0 did not answer].
12. We recommend that if an enteral protein product or module is required to supplement standard EN feedings to achieve daily protein goals, a source of high-quality protein (soy, whey, casein) should be used. Low-quality sources such as collagen should be avoided [100%; 18 agree, 0 disagree, 0 did not answer].
13. We recommend that if physical activity (PA) is performed in the ICU to enhance protein synthesis, delivery of protein supplements should closely approximate the time of the PA sessions [94.4%; 17 agree, 1 disagree, 0 did not answer].

Appropriate Questions to Guide Future Research Trials

During the International Protein Summit, a special session was held to forge a research development pathway that might generate new and better evidence to support the use of protein provision in the critically ill patient. Each speaker was asked to develop and put forth questions involving the topic of his or her presentation as it pertained to future research involving protein metabolism and optimizing the role of protein in nutrition therapy. A summary of these questions is provided below.

Mechanistic Questions

1. What is the recovery process of muscle following critical illness (as measured by serial muscle biopsies/functional assessment, etc)?
2. What are the roles of myeloid-derived suppressor cells in recovery from PICS?
3. What is the effect of administration of exogenous protein/amino acids on muscle protein synthesis/balance vs total body protein synthesis/balance rates in critically ill patients?
4. Do changes in protein synthesis (either from muscle or whole body) correlate with other more clinically available physiological measures (eg, nitrogen balance studies) in this population?
5. How can the anabolic response from exogenous protein/amino acids be optimized?
6. Is there an upper limit to the amount of protein that should be administered (after which there is more harm done than benefit)?

7. Does the use of a high-protein enteral formula, compared with standard enteral formula, affect glucose control and the need for insulin use?
8. Can we use protein/amino acid administration to manipulate stress response pathways, such as mTOR, to influence outcome independent of any effect on protein balance/muscle outcomes (via pathways that influence immunity, inflammation, and organ function)?

Clinical Research Questions (Observational Cohort Trials)

1. Do changes in protein synthesis (either from muscle or whole body) correlate with long-term functional and/or clinical outcomes?
2. Does the presence of baseline low skeletal muscle mass identify a subgroup of patients who will benefit the most (reduced mortality) from protein intervention?
3. Beyond administration route (eg, enteral vs parenteral), should severity of illness influence protein intervention goals/recommendations?
4. What measurement techniques (muscle biopsy, muscle function testing, imaging, blood, urine tests, etc) might be used to assess the effectiveness of candidate nutrition therapies?
5. More specifically, is U/S of quadriceps a reliable estimate of low muscularity?
6. Does U/S of quadriceps (either baseline or changes over time) predict long-term functional outcomes?
7. Is U/S of quadriceps sensitive to change in nutrition intervention studies? Can it be used both as an outcome and a monitoring tool in the ICU setting?
8. Is the estimated lean body mass, as opposed to weight-based equations, a better predictor of total daily caloric and protein needs?

Clinical Research Questions (Interventional Trials)

1. Compared with usual care (0.7–0.8 g/kg/d via the enteral route), what is the effect of increased protein administration on short-term (ICU length of stay, ventilator days, etc) and long-term clinical outcomes (mortality, measures of physical recovery, etc) for "at-risk" critically ill patients?
2. What is the effect of a combination of amino acid supplementation plus early in-bed cycle ergometry vs standard bedrest and underfeeding on physical recovery of ICU patients?
3. What is the effect of enteral administration of whole-protein diets compared with parenteral amino acids on functional and/or clinical outcomes?
4. What is the effect of an arginine-containing formula compared with standard high-protein EN on infection and mortality in critically ill patients?
5. Does a bundled or multifaceted approach (combining all the anabolic therapies together) compared with single-component therapy (nutrition, activity, pharmacologic agents tested separately) maximize outcomes in ICU patients?

Important Health Services Research Questions

1. What is the most cost-efficient and reliable way to achieve higher protein/amino acid delivery in ICU patients (ensure the prescription is achieved)?
2. How do we better communicate the value of protein, to influence attitudes and behaviors to other health care professionals?

Statement of Authorship

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