

# Appropriate protein provision in critical illness: a systematic and narrative review<sup>1–3</sup>

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## ABSTRACT

**Background:** Widely varying recommendations have been published with regard to the appropriate amount of protein or amino acids to provide in critical illness.

**Objective:** We carried out a systematic review of clinical trials that compared the metabolic or clinical effects of different protein intakes in adult critical illness and comprehensively reviewed all of the available evidence pertinent to the safe upper limit of protein provision in this setting.

**Design:** MEDLINE was searched for clinical trials published in English between 1948 and 2012 that provided original data comparing the effects of different levels of protein intake on clinically relevant outcomes and evidence pertinent to the safe upper limit of protein provision to critically ill adults.

**Results:** The limited amount and poor quality of the evidence preclude conclusions or clinical recommendations but strongly suggest that 2.0–2.5 g protein substrate · kg normal body weight<sup>−1</sup> · d<sup>−1</sup> is safe and could be optimum for most critically ill patients. At the present time, most critically ill adults receive less than half of the most common current recommendation, 1.5 g protein · kg<sup>−1</sup> · d<sup>−1</sup>, for the first week or longer of their stay in an intensive care unit.

**Conclusion:** There is an urgent need for well-designed clinical trials to identify the appropriate level of protein provision in critical illness. *Am J Clin Nutr* 2012;96:591–600.

## INTRODUCTION

The metabolic response to severe tissue injury and sepsis releases a flood of amino acids from their muscle reservoir (1) into the general circulation, enabling new protein synthesis at sites of tissue injury and elsewhere to optimize immune function and regulate the inflammatory response. The cost of this rapid body protein remodeling is anabolic inefficiency: net muscle protein loss greatly exceeds the gain of protein mass elsewhere, and whole-body nitrogen balance becomes strongly negative (2–7).

Plasma amino acid concentrations could provide insight into this process, but they vary widely in critical illness, being affected by the phase and intensity of the injury response; the patient's existing nutritional, metabolic, and hemodynamic status; and the characteristics of the nutritional therapy provided. When measured in previously adequately nourished patients after successful fluid resuscitation and before exogenous nutrient provision, plasma non-essential amino acid concentrations are usually low and essential amino acid concentrations are either normal or low (8–15). But circulating amino acid concentrations show only a static view of what is a highly dynamic process. Amino acid concentrations could be

increased by intense net muscle proteolysis or inadequate liver uptake and metabolism in the setting of liver hypoperfusion or metabolic failure (12, 16–18), or they could be reduced despite a high rate of release from muscle that is still insufficient to match the combined rates of central protein synthesis, gluconeogenesis, and immediate amino acid catabolism, all of which are accelerated in critical illness. By using a simple nonisotopic amino acid infusion technique, a recent study (19) confirmed the suggestions of previous, more complicated techniques (9, 14, 17, 20) that hypoaminoacidemia in severe human sepsis is the result of an ~70% increase in the clearance of essential and nonessential amino acids into the tissues.

The hypoaminoacidemia of critical illness thus appears to represent a state of increased amino acid uptake by the rapidly turning over central proteins [liver, splanchnic organs, bone marrow, and immunologically active tissues (20)], which is constrained by the maximum rate of amino acid release from muscle. This is a portrayal of acute central protein deficiency, and it suggests that sufficient exogenous amino acid provision could improve clinical outcomes, both early by increasing central protein synthesis, optimizing the inflammatory response (7, 21), and mitigating the extensive loss of muscle protein characteristic of the first week of catabolic critical illness (22–24) and in the long term by minimizing the muscle atrophy that commonly occurs in protracted critical illness (22, 23). With only one exception (25), every expert review and clinical practice guideline that has addressed the question of protein requirements in critical illness has concluded that adequate protein provision is necessary to improve body protein economy in all but the most hypercatabolic and hemodynamically compromised patients, and has asserted that the amount of dietary protein required to do this exceeds the normal requirement (26). But specifically how much more protein is required? The recommendation for metabolically normal hospitalized adults is the same as for healthy people: 0.8 g of protein · kg normal body weight<sup>−1</sup> · d<sup>−1</sup> (27). The most common recommendation in critical illness lies between 1.2 and 1.5 g protein · kg normal body weight<sup>−1</sup> · d<sup>−1</sup>, provided as either dietary protein or mixed free amino acids administered either

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<sup>2</sup> No support was received for this study.

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Received December 5, 2011. Accepted for publication May 30, 2012.

First published online July 18, 2012; doi: 10.3945/ajcn.111.032078.

parenterally or enterally (3, 26, 28–32). By contrast, some experts (33–35), as well as the clinical care guidelines of the Society of Critical Care Medicine (SCCM)<sup>4</sup> and the American Society for Parenteral and Enteral Nutrition (ASPEN), recommend protein or amino acid intakes as high as 2.0 g/kg (36). The SCCM/ASPEN guidelines recommend 2.0 g protein/kg ideal body weight as the minimum amount to provide to severely burned and multitrauma patients and permissively underfed obese patients and a minimum of 2.5 g/kg ideal body weight for critically ill, permissively underfed morbidly obese patients (36). The evidence-based guideline group of the American Burn Association points out, without further comment, that protein provision for severely burned patients varies from 1.5 to 3.0 g · kg<sup>-1</sup> · d<sup>-1</sup> (37). The European Society for Enteral and Parenteral Nutrition (ESPEN) (31) recommends from 1.3 to 1.5 g · kg<sup>-1</sup> · d<sup>-1</sup> for almost all critically ill patients, whereas the European Society of Intensive Care Medicine specifically cautions against protein intakes >1.8 g · kg<sup>-1</sup> · d<sup>-1</sup> (29). One reviewer acknowledged the wide difference of opinion among experts without taking a position as to whether protein provision should be capped at 1.5 g · kg<sup>-1</sup> · d<sup>-1</sup> or provided in excess of 2.0 g · kg<sup>-1</sup> · d<sup>-1</sup> (38). The Canadian clinical practice guidelines refrain from making any recommendation about protein requirements (39).

None of these widely differing recommendations appear to be based on systematic reviews of the evidence (40). Accordingly, we carried out a systematic review of the clinical literature pertinent to the optimum and safe upper limit of protein provision in adult critical illness.

## METHODS

The aims of the literature search were as follows: first, to identify and analyze all prospective clinical trials of any kind that compared clinically relevant consequences of providing different levels of protein or mixed amino acids to critically ill adults; and second, to analyze all of the available evidence pertinent to the safe upper limit of protein provision in critical illness.

MEDLINE was searched for clinical trials published in English between 1948 and 2012 (the last search was on 4 May 2012) that provided original data comparing the effects of different levels of protein provision to critically ill adults, as well as clinical reviews and clinical care guidelines on this topic. We accessed and studied all pertinent articles cited in the primary sources and all articles cited in reviews and clinical care guidelines to justify the protein intakes they recommended. Studies that enrolled uncomplicated surgical patients were not included. There is a metabolic continuum between surgical injury and critical illness (38, 41), but critical illness is a more serious and prolonged protein-catabolic insult than that experienced by most surgical patients. The inclusion of data from non-critically ill surgical patients could bias the data toward an underestimation of the protein requirement in true critical illness. No study was excluded on the grounds of low enrollment, even though such studies often provide only limited information (42).

For the second aim, the same search was expanded to include all articles of any kind that reported or discussed issues related to protein or amino acid excess, maximum administration, or toxicity

that would be pertinent to the usual time course of critical illness. The search included any article that could be identified that described the effects of high-dose protein or amino acid administration on urea and ammonia metabolism in health or critical illness.

The MEDLINE search included the following key words relevant to critical illness: *critical illness*, *critical care*, *burns*, *infections*, *inflammation*, *shock* (including *multiple organ failure*, *surgical shock*, *traumatic shock*, and *systemic inflammatory response syndrome*), *wounds and injuries*, and *trauma*. Articles that reported clinical trials comparing the effects of different levels of protein provision were searched for by using the following key words: *nutritional support*, *dietary proteins*, *proteins*, *amino acids*, *nutritional requirements*, and *nutritional physiologic phenomena*. The intersection of these 2 topic searches yielded a large number of articles that were analyzed as to their eligibility for inclusion in a systematic review of outcomes resulting from different levels of protein or amino acid provision in adult critical illness. The small enrollment, heterogeneity, and variation in diagnosis and study design in the articles that were identified precluded their statistical combination into a meta-analysis. The literature pertinent to the upper limit of protein provision in critical illness was so vague, minimal, and poorly characterized as to require a de novo interpretive analysis.

## RESULTS

A total of 253,519 articles were found with the following key words or MeSH terms: *critical illness* (MeSH term and keyword; 14,836 articles) or *critical care* (MeSH term and keyword 29,048) or *burns/dh, me, pp, th* (12,855) or *infections/dh, me, th* (27,130) or *inflammation/dh, me, th* (13,889) or *shock* (including multiple organ failure, surgical shock, traumatic shock, and systemic inflammatory response syndrome; 33,889) or *wounds and injuries/dh, me, th* (11,540) or *trauma* (keyword; 151,584). The terms *nutritional support* (including diet therapy, parenteral nutrition, and enteral nutrition; 8329) or *dietary proteins/ad, me, pd, st, to, tu* (20,311) or *proteins/ad, ae, me, pd, ph, st, to, tu* (78,286) or *amino acids/ad, ae, df, me, pd, ph, to, tu* (42,837) or *nutritional requirements* (17,308) or *nutritional physiologic phenomena* (27,093) yielded 181,915 articles. (The search term subheadings *ad, ae, df, dh, me, pd, ph, st, th, to, tu* refer to administration and dosage, adverse effects, deficiency, diet therapy, metabolism, pharmacology, physiopathology, standards, therapy, toxicity, and therapeutic use, respectively.) The intersection of the 253,519 critical illness titles and the 181,915 nutritional titles yielded 3461 articles whose titles or abstracts were individually studied with regard to both aims. Of these articles, 3445 were obviously irrelevant or ineligible. Three articles whose titles or abstracts implied that they involved critically ill patients were excluded because the patients were postoperative rather than critically ill.

## Effects of varied protein intakes on outcomes in critical illness

Only 13 articles met the inclusion criteria for the systematic review of outcomes consequent to the deliberate provision of different levels of protein or amino acids in adult critical illness (10, 43–54); they are described in **Table 1**. Even though it was

<sup>4</sup>Abbreviations used: ASPEN, American Society for Parenteral and Enteral Nutrition; ESPEN, European Society for Enteral and Parenteral Nutrition; ICU, intensive care unit; SCCM, Society of Critical Care Medicine.

**TABLE 1**  
Publications that reported interventions to determine optimum protein or amino acid provision in adult critical illness<sup>1</sup>

First author, year (reference), country	No. of patients studied	Patient characteristics	Intervention	Daily protein and/or mixed amino acid provision g/kg	Daily total energy provision kcal/kg	Outcome measure	Results	Comments
Long et al, 1976 (43), USA	8	Critical illness, chronic sepsis	PN: each patient serially infused with varying amino acid doses for 4-d balance periods	0–3.5	43	N balance	N balance zero at ~1.5 g/kg; increasingly positive with higher doses up to 3.5 g/kg	Open trial, deliberate energy overfeeding
Wolfe et al, 1983 (44), USA	6	Clinically stable ~5 wk after severe burn injury	EN + PN: each patient serially received both protein doses for 3-d periods	1.43 and 2.20	41	Whole-body leucine kinetics and N balance	2.2 g/kg superior to 1.43 g/kg with regard to N balance but not leucine kinetics	Open trial, deliberate energy overfeeding, turnover method not validated, very low statistical power, unclear whether still critically ill
Twyman et al, 1985 (45), USA	21	Critical illness, severe head injury	EN: 10-d RCT comparing 2 protein doses	1.5 and 2.2	~41	N balance	Superior N balance with higher protein dose	Nonblinded, energy overfeeding
Shaw et al, 1987 (46), USA	18	Critical illness, sepsis	PN: comparison of 3 amino acid doses infused for 8 d	1.1, 1.5, and 2.2	~45	Non-steady state lysine and urea turnover	lowest with 1.5-g/kg dose	Nonrandomized, deliberate energy overfeeding, turnover methods not validated, very low statistical power
Griegel et al, 1987 (47), USA	9 (3 patients studied twice)	Critical illness, sepsis	PN: 6-d trial comparing 2 amino acid doses	1.2 and 2.3	133% of measured energy expenditure	N balance	Superior and positive N balance with higher dose	Nonrandomized, deliberate energy overfeeding, very low statistical power
Lapichino et al, 1988 (10), Italy	36	Critical illness, trauma	PN: 6-d comparison trial	1.5 and 2.2	~36	N balance	Superior N balance at higher amino acid dose	Not clearly randomized, complex trial design, energy overfeeding
Larsson et al, 1990 (48), Sweden	39	Critical illness, severe burn injury, or trauma	PN: 8-d RCT comparing 5 different amino acid doses	0–1.88	40–50	N balance	N balance improved until 1.25-g/kg dose but no further improvement at higher doses	Nonblinded, energy overfeeding, large between-group variability, small enrollment, low statistical power
Pitkanen et al, 1991 (49), Finland	50	Critical illness, trauma, and sepsis	PN: RCT with 2-d balance periods comparing 5 PN regimens varying in amino acid and energy dose	0–1.5	7–40	N balance	N balance least negative at highest amino acid and energy dose	Nonblinded, confounding by changing energy dose, short balance periods

(Continued)

TABLE 1 (Continued)

First author, year (reference), country	No. of patients studied	Patient characteristics	Intervention	Daily protein and/or mixed amino acid provision	Daily total energy provision	Outcome measure	Results	Comments
Müller et al, 1995 (50), Germany	20	Critical illness, nonsurgical multiple organ failure	PN: open study with sequential 12-h infusions varying in energy and amino acid content	0.5–2.0	14–56	N balance corrected for urea pool size change	Optimum N balance at highest amino acid (and energy) dose	Complex study regimen, confounding by variable energy provision, extremely short balance periods
Ishibashi et al, 1998 (55), New Zealand <sup>2</sup>	23	Critical illness, sepsis, and trauma	PN and EN: retrospective observational study of relation between protein dose and subsequent fat-free mass	0.9, 1.2, and 1.5 g/kg initial body weight corrected for excess hydration	~35	Fat-free mass after 10 d nutrition support	1.2 and 1.5 g/kg superior to 0.9 g/kg but not significantly different from one another	Retrospective observational study without random sampling, small enrollment, and low statistical power; energy overfeeding; hydration-corrected body weight highly variable; unclear translation of body- composition data to clinically practical indicators
Scheinkestel et al, 2003 (51), Australia	11	Critical illness, acute renal failure	PN: open study with incrementally increased amino acid dose during continuous renal replacement therapy	1.0 with increase of 0.25 every 24 h to a maximum of 2.5	Equal to measured energy expenditure	N balance, plasma amino acid profile	Best N balance and most normal amino acid profile required 2.5 g/kg	Sequential and not randomized, time effects not excluded, 17% of infused amino acids lost in dialysate
Scheinkestel et al, 2003 (52), Australia	50	Critical illness, acute renal failure	PN and EN: RCT that compared 3 protein doses during continuous renal replacement therapy	40 patients had dose increased from 1.5 to 2.0–2.5 at 48-h intervals; 10 patients constantly received 2.5	Equal to measured or predicted energy expenditure	N balance, survival in ICU and hospital	N balance and clinical outcomes superior in 2.5-g/kg group	Nonblinded, complicated trial design
Singer et al, 2007 (53), Israel	14	Critical illness, nonoliguric moderate acute renal failure	PN: 4-d clinical trial comparing 2 amino acid doses	75 and 150 g	~2300	N balance, furosemide requirement, water balance	All outcomes superior in 150-g group	Body weight not indicated (higher dose approximately equivalent to 2.1 g/kg), nonblinded, not explicitly randomized
Verbruggen et al, 2011 (54), Germany	9 adolescents aged 13–18 y	Critical illness, sepsis	PN: RCT comparing effects of sequential 1-d infusions of 2 amino acid doses	1.5 and 2.8	33–38	Whole-body leucine turnover and oxidation	Whole-body protein balance more positive with higher amino acid dose	Small enrollment, extremely short balance periods

<sup>1</sup> EN, enteral nutrition; ICU, intensive care unit; N, nitrogen; PN, parenteral nutrition; RCT, randomized controlled trial.<sup>2</sup> Although ineligible, this study is listed because it is one of the most frequently cited studies to justify current recommendations for protein provision in critical illness.

patently ineligible, one retrospective observational study is included in Table 1 (55), because it is one of the most frequently cited articles in the literature on protein provision in critical illness. The clinical trials were either sequential (43, 44, 50, 51) or concurrent (10, 45, 46, 48, 49, 52–54) or both (47). They tested a variety of different protein or amino acid doses, up to a maximum of  $2.5 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ , for various periods of time. Only 4 studies (45, 48, 49, 52) were randomized; none were blinded. The outcome measures were as follows: nitrogen balance in 12 studies, aspects of whole-body protein turnover in 3 studies (44, 46, 54), change in body composition in 1 study (55), plasma amino acid profile in 1 study (51), and clinical outcomes in 2 studies (52, 53).

Every study showed at least one, and usually several, of the following weaknesses in design, execution, or interpretation: unclear definition of critical illness; low enrollment and such wide intergroup heterogeneity as to make it impossible to identify any particular level of protein provision as maximally beneficial; failure to appreciate that a nutrient intake that is adequate *on average* is, by definition, insufficient for half of a population whose outcome data are symmetrically distributed; failure, except in the ineligible study (55), to explain how the protein or amino acid dose was calculated from body weight—a crucial consideration, given that body weight is a notoriously unreliable surrogate for normal dry body weight or lean tissue mass in critical illness (24, 56); deliberate or inadvertent energy overfeeding, a strategy historically used to maximize body nitrogen retention but avoided in modern critical care because of its toxicity; and inappropriate calculation of mixed amino acid dosages as equivalent to formed protein, whereas free amino acid mixtures actually provide 17% less protein substrate than does formed protein (57). Other issues are identified in Table 1.

Despite their suboptimal quality, every study, including the ineligible one (55), indicated improving nitrogen balance, protein turnover, or better clinical outcomes as protein or amino acid provision increased. The highest protein level studied was  $2.5 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ . Two clinical trials indicated better clinical outcomes at the highest protein dose provided.

### Upper limit of protein provision

An expert working group studied the upper limits of human protein consumption, noting that strength-training athletes sometimes consume as much as  $4 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$  without adverse consequences, and that as much as  $8 \text{ g protein} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$  has been given for short periods without reported ill effects (58, 59). Late paleolithic humans consumed  $\sim 250 \text{ g protein/d}$  (60, 61). According to a recent observational study, adults with severe burns in the United States and Australia are routinely provided with  $2\text{--}3 \text{ g protein} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$  in the form of high-energy enteral nutrition (62).

A study in 24 acutely (but not critically) ill surgical patients compared the effects of 3 different parenteral nutrition solutions on nitrogen balance and liver protein content as measured in liver biopsies obtained before and after  $\sim 11 \text{ d}$  of treatment (63). Two solutions provided  $1.1 \text{ g amino acids}$  and  $\sim 55 \text{ kcal} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$  with different amounts of lipid, and one solution provided  $3.1 \text{ g amino acids}$  and  $35 \text{ kcal} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ . Nitrogen balance was equally positive with all regimens, with no indication of toxicity at the  $3.1\text{-g/kg}$  dose. Average liver protein content (which was

subnormal at baseline) was normalized only in the patients who received the  $3.1\text{-g/kg}$  dose. Tulikoura (64) subsequently compared the effects of 3-d isocaloric ( $39 \text{ kcal/kg}$ ) infusions of either  $1.2$  or  $3.1 \text{ g amino acids} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$  on nitrogen balance and circulating visceral protein concentrations in 14 adequately nourished postoperative, non-critically ill patients. In this study, nitrogen balance was much more positive and circulating albumin and transferrin concentrations were better maintained in the patients who received  $3.5 \text{ g amino acids} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ .

The SCCM/ASPEN recommends that all hypocalorically fed, critically ill, obese patients receive between 2 and 2.5 protein  $\cdot \text{kg ideal body weight}^{-1} \cdot \text{d}^{-1}$  (36). This recommendation appears to be based on a small number of low-enrollment clinical trials that have been formally reviewed so often that the number of published reviews (36, 56, 65–80) now exceeds the number of original research reports. It is sufficient for the purposes of this review to summarize those aspects pertinent to the upper limit of protein provision. Most, but not all (81–83), hypocaloric, high-protein clinical trials enrolled patients who were critically ill, and most, but not all, enrolled obese patients. Only 3 reviews (75, 78, 80) distinguished between “hypocaloric nutrition” (selective energy restriction with a compensatory increase in protein provision) and “permissive underfeeding” (global underprovision of all nutrients) despite the profoundly different physiologic and nutritional implications of these different nutritional regimens. Every review concluded that short-term hypocaloric nutrition is scientifically plausible, because it is supported by metabolic indicators and limited but promising clinical outcome data, but awaits definitive testing.

Only one clinical trial appears ever to have been carried out to determine the protein requirement of hypocalorically fed, hospitalized patients. Greenberg and Jeejeebhoy (81) randomly assigned non-critically ill, nonobese patients (described as having adequate fat stores) to receive, as their sole nutrition, either  $0.83$  or  $1.83 \text{ g amino acids} \cdot \text{kg ideal body weight}^{-1} \cdot \text{d}^{-1}$ . Nitrogen balance of the patients who received  $0.83 \text{ g amino acids/kg ideal body weight}$  was consistently negative, whereas that of those who received  $1.83 \text{ g}$  was positive (81).

Most reviews of hypocaloric nutrition, and the SCCM/ASPEN guidelines (36), either explicitly or implicitly assert that the more favorable metabolic and clinical outcomes attributable to hypocaloric feeding may rely on their generous protein provision. This reasoning underlies the current SCCM/ASPEN recommendation that hypocalorically fed, obese patients receive a minimum of  $2.0 \text{ g protein} \cdot \text{kg ideal body weight}^{-1} \cdot \text{d}^{-1}$ .

A clinical trial that compared different protein intakes in the treatment of protein-energy malnutrition (84) was cited as indicating that high protein intakes are dangerous (25). Collins et al (84) provided either  $2.4$  or  $4.6 \text{ g protein} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$  to severely malnourished adults (average weight:  $34 \text{ kg}$ ) in a famine zone. The higher protein dose was associated with worse outcomes in the subset of patients suffering from edematous malnutrition. However, clinical outcomes were similar with either treatment in the nonedematous patients who accounted for the majority of the patients, and correction for biased treatment allocation could well eliminate the adverse effect attributed to the higher protein dose in the edematous patients (85). For the majority of these severely malnourished adults, the so-called low-protein dose of  $2.4 \text{ g protein} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$  was well tolerated by all patients, and their clinical outcome was favorable (84).

The most obvious way that protein can be toxic is by generating ammonia in excess of the urea cycle's capacity. Rudman et al (86) determined the maximum rate of liver urea synthesis in 10 healthy adults and 34 patients with stable cirrhosis, no ascites, and normal renal function. After consuming a basal diet containing  $0.7 \text{ g protein} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ , volunteers were provided with single- or divided-protein meals containing from 0.57 to 2.86 g protein/kg. This study indicated that a healthy adult can convert 3.8 g protein/kg into urea per day. The maximum urea synthetic rate in persons with stable cirrhosis was approximately one-half that rate, with very wide variability. The metabolic indicators of protein intolerance were hyperaminoacidemia and hyperammonemia.

Hyperammonemia and encephalopathy are well-known complications of protein or amino acid provision to patients with severe liver dysfunction (87) and a rare but well-documented complication of dietary protein or parenteral amino acid provision to previously asymptomatic adults with heterozygous ornithine transcarbamoylase deficiency (88) or other urea cycle disorders (87, 89). Severe hyperammonemia has been reported in patients with previously normal liver function who underwent an orthotopic lung transplantation (90); the etiology is multifactorial, and parenteral amino acid provision is one risk factor (91).

In 1977 Hackl et al (92) reported that after a week of parenteral amino acid administration, which provided  $0.8\text{--}1.6 \text{ g amino acids} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$  to 47 patients, most of whom were critically ill, blood ammonia concentrations increased in every patient to an average maximum value of  $\sim 110 \text{ } \mu\text{mol/L}$ , with a modest downward trend thereafter. There was no correlation with serum urea concentrations nor with serum alkaline phosphatase or glutamic oxaloacetic transaminase concentrations. The clinical implication of these observations is unclear, especially because early commercial amino acid solutions were contaminated with ammonia (93, 94).

Patients with overwhelming critical illness and hepatic hypoperfusion develop hyperaminoacidemia (9, 16, 17), even in the absence of amino acid infusions (18). Sprung et al (18) compared plasma amino acid and ammonia concentrations in severely infected but hemodynamically stable patients and septic hypotensive patients with an altered sensorium. Amino acid concentrations were markedly higher in the hypotensive group (especially the aromatic amino acids, which are catabolized only in the liver). Average plasma ammonia concentrations were above normal in the normotensive patients ( $127 \text{ } \mu\text{mol/L}$ ) but were substantially higher in the hypotensive patients ( $425 \text{ } \mu\text{mol/L}$ ). Almost nothing is known about the prevalence and severity of asymptomatic hyperammonemia or orotic aciduria (95) in critically ill patients with normal or mildly abnormal hepatic function, nor on the effects of dietary protein or mixed amino acid infusions in these patients.

Amino acid infusions limited to the essential amino acids can induce hyperammonemia in children and, more rarely, in adults (96, 97), presumably because they lack arginine (93, 98). By comparison, the molar fraction of arginine in modern complete parenteral amino acid mixtures is  $\sim 60\%$  greater than in dietary proteins (57). Mild hyperammonemia has been reported to be relatively common in infants infused with complete amino acid mixtures (94) and is more likely when high doses are administered shortly after birth. Thus, 6 of 30 very-low-birth-weight infants infused with  $4 \text{ g amino acids} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$  shortly after

birth experienced mild elevations in blood ammonia ( $97\text{--}127 \text{ } \mu\text{mol/L}$ ) (99).

Some reviewers regard an abnormally increased serum urea concentration (azotemia) as evidence of amino acid toxicity (34, 35, 100); one expert specifically regards a serum urea concentration  $>80 \text{ mg/dL}$  ( $30 \text{ mmol/L}$ ) as undesirable (101). Mechanisms by which simple azotemia could be harmful or increase risk have not been articulated, however. The rate of amino acid oxidation (and corresponding urea synthesis rate) is increased in critical illness (102), and although urea synthesis is strongly influenced by the rate of protein provision, circulating urea concentrations are far more greatly influenced by renal blood flow and renal parenchymal functional mass than by the protein provision rate (103). Thus, Twyman et al (45) observed that the administration of  $2.2 \text{ g protein} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$  led to greater nitrogen excretion (and more positive nitrogen balance) than did  $1.5 \text{ g protein} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ , but there were similar serum urea concentrations. Singer et al (53) compared the metabolic effects of providing either 75 or 150 g parenteral amino acids/d to critically ill patients with nonoliguric renal failure who were not receiving renal replacement therapy. Baseline serum urea concentrations ( $\sim 50 \text{ mg/dL}$ ) increased by 30% (to 59 mg/dL) when 75 g amino acids/d was provided and by 22% (to 64 mg/dL) when 150 g was provided. Clinical outcomes were superior in the patients who received 150 g/d.

On balance, the available evidence indicates that protein provision in doses between 2.5 and 3.0 g/kg normal body weight per day are safe for use in clinical trials and careful clinical practice, except in patients with refractory hypotension, overwhelming sepsis, or serious liver disease. The determination as to when a particular patient has refractory hypotension, overwhelming sepsis, and serious liver disease is based on clinical judgment; no specific information is available to guide the choice of any protein or amino acid dose in these situations.

## DISCUSSION

The prevalent opinion in modern critical care nutrition is that  $1.2\text{--}1.5 \text{ g protein} \cdot \text{kg normal body weight}^{-1} \cdot \text{d}^{-1}$  is sufficient—and hence not usually to be exceeded (26). This widespread opinion appears to be based on the biased selection of a small and unrepresentative subset of low-quality studies published between 14 and 36 y ago that enrolled critically ill, energy-overfed patients. These studies are praiseworthy for their innovative and ambitious design and execution and for the physiologic insight they provided. It is noteworthy that every study suggested that insufficient protein provision leads to serious and preventable body protein wasting. Notwithstanding claims made by some of their authors, no study was sufficiently powered to rule in or out any specific protein or amino acid intake as maximally beneficial. Several other problems are apparent.

First, no author appreciated that a level of nutrient intake that is adequate *on average* is, by definition, insufficient for half of a population whose data are symmetrically distributed. The correct procedure is to calculate an allowance for individual variability to arrive at a "safe" recommended intake. Second, protein intakes were based on body weight, but in every study except for one (55), the investigators failed to explain how they determined body weight. In critical illness even accurately measured body weight is an extremely unreliable surrogate for

the biologically relevant variable, lean tissue mass (24, 56). Third, the majority of patients were deliberately energy overfed as a tactic to maximize body nitrogen retention. The protein requirement of patients in energy equilibrium or negative energy balance could be considerably higher. Fourth, the majority of studies (17, 44, 46, 55) calculated amino acid dosages as though they are equivalent to formed protein, but they are not: free amino acid mixtures provide 17% less protein substrate than does formed protein (57). Other studies used the conventional factor 0.16 to convert amino acid nitrogen to its protein equivalent; this factor does not apply to free amino acid mixtures (57).

The main conclusion of this systematic review is that nitrogen balance improves with increasing protein provision up to the highest studied dose of  $2.5 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ . Some studies suggest that higher levels of protein provision increase the rate of whole-body protein synthesis (104, 105). How valid are these conclusions? The nitrogen balance measurement provides important physiologic insight and practical clinical guidance, but it is technically difficult and susceptible to random and systematic errors (106, 107). Nitrogen balance measurements, especially in the ambulatory setting, could be prone to overestimate nitrogen balance at high protein intakes (108), although this is by no means a universal observation (47, 48, 63, 109).

In fact, as has been frequently pointed out, it is strongly biologically plausible that sufficiently generous protein provision in the crucial early days of critical illness could improve clinical outcomes, even in the absence of any measured improvement in nitrogen balance or whole-body protein synthesis (5, 7, 31, 63). During the early phase of critical illness, the body's priority is central protein synthesis at the expense of protein loss from the skeletal muscle compartment, which normally accounts for ~80% of the total lean tissue mass (1). Exogenous protein could increase protein synthesis in the small, but crucial, central compartment, with benefit to the patient, without necessarily requiring a commensurate reduction in muscle protein catabolism. Nitrogen balance is simply too crude a measurement to capture this and other related metabolic phenomena. For example, the protein turnover literature summarized earlier broadly suggests that in critical illness glucose infusions mitigate body nitrogen loss largely by stimulating insulin release and by inhibiting muscle proteolysis. By contrast, sufficient protein provision (up to the requirement level) mitigates nitrogen loss by promoting central and peripheral protein synthesis. The latter scenario is clearly preferable when the body's priority is to mobilize peripheral amino acids in support of central protein synthesis. Thus, sufficient amino acid provision increases central and peripheral protein synthesis, improving nitrogen balance in the process, whereas dextrose with insufficient protein improves nitrogen balance by inhibiting muscle proteolysis and thereby inhibiting the transfer of amino acids from muscle to crucial sites of central protein synthesis, with potential harm to the patient (110).

A more important problem, with both nitrogen balance and protein turnover, is that they are surrogate outcomes that can, at most, provide provisional, hypothesis-generating conclusions. Biological and surrogate indicators such as nitrogen balance and protein turnover are essential for gaining insight into physiologic processes, identifying the causes of metabolic and clinical heterogeneity, establishing biologically plausible therapeutic hypotheses, and designing clinical outcome trials intelligently. But

it is incorrect to substitute them for clinical outcomes in clinical practice guidelines, as is currently the practice (111–113). To date, the only high-quality clinical-outcome clinical trials that evaluated the effects of different protein intakes in critical illness have been in children (114–116); they indicate better outcomes with higher levels of protein provision.

The virtually complete absence of high-quality data on protein requirements in critical illness in adults is especially troubling in light of the fact that in modern times, the typical critically ill patient is fed exclusively by the enteral route and consequently is substantially undernourished for the first week or longer of treatment in an intensive care unit (ICU) (117–120). The ESPEN guidelines address this problem by recommending that parenteral nutrition be commenced within 2 d of admission to an ICU when enteral nutrition is failing to achieve its target. By contrast, the SCCM/ASPEN (36) and Canadian (39) guidelines recommend tolerating a “permissively underfed” state for up to 10 days before resorting to parenteral nutrition, except in the presence of pre-existing malnutrition (117).

The phenomenon of underfeeding by enteral nutrition is commonly described as a “calorie” shortfall (121, 122); it is more biologically coherent to describe it as a *protein shortfall* (21). The magnitude of the problem was recently shown by a large clinical trial, which compared the clinical consequences of following the ESPEN or the SCCM/ASPEN recommendations (123). When the SCCM/ASPEN recommendation was implemented, daily median protein provision never exceeded ~0.1 g/kg normal body weight for the entire 15-d observation period. The patients in this treatment arm received less than one-tenth of the commonest recommended amount of protein, at precisely the time when generous protein provision could be most beneficial. When the ESPEN recommendation was implemented (enteral nutrition supplemented by increasing intravenous glucose for 2 d, followed by standard parenteral nutrition), median parenteral amino acid provision had barely risen to ~0.7 g · kg<sup>-1</sup> · d<sup>-1</sup> by the seventh day in the ICU. Because 0.7 g free amino acids provides ~0.6 g protein substrate (57), these data indicate the following: first, that despite the use of parenteral nutrition, amino acid provision was grossly inadequate throughout the first 7 d in the ICU; and second, that median all-source protein provision never exceeded ~0.7 g/kg on any day during the entire 15-d observation period. The patients in this arm received less than half the current average protein recommendation, and most patients possibly received only a third or less of their individual requirement. Protein provision that is as grossly deficient as this could be well below the minimum necessary to detect any clinical benefit. Another large recent clinical trial of intensive insulin therapy in critical illness failed to provide any analyzable information about protein intake (124). On the basis of the low amount of energy provided, it appears that the patients enrolled in the trial were even more seriously protein malnourished than those in the ESPEN-SCCM/ASPEN trial (123).

The time is long overdue to launch thoughtfully designed and appropriately targeted prospective clinical trials to test the hypothesis that early and sufficient amino acid supplementation of inadequate enteral nutrition can improve the clinical outcome of many critically ill patients. Certain pitfalls will have to be avoided when designing these studies. Patients who are not critically ill should not be enrolled, because they might require no

more than  $0.8 \text{ g protein} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ . Patients with borderline liver function should be excluded until more information on tolerance is available. Patients who have refractory hypotension or overwhelming sepsis should be excluded, because very large amounts of protein are unlikely to reverse their clinical course and could be toxic. Criteria for excluding such patients need to be developed. Critically ill patients with increased urinary urea excretion (125) and hypoaminoacidemia would seem to be the most suitable for enrollment in initial, dose-finding phase 2 clinical trials. Because protein intake calculations are based on body weight—an unreliable surrogate for lean tissue mass in critical illness (126–129)—it will be essential to use an explicit, practical rule for estimating a patient's body weight corrected for volume expansion and excess adipose tissue.

In conclusion, the limited amount and poor quality of the available evidence preclude conclusions or clinical recommendations but strongly suggest that  $2.0\text{--}2.5 \text{ g protein substrate} \cdot \text{kg normal body weight}^{-1} \cdot \text{d}^{-1}$  is safe and could be optimum for most critically ill adults. At the present time, most critically ill adults receive less than half the commonest current recommendation,  $1.5 \text{ g protein} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ , for the first week or longer of their ICU stay. There is an urgent need for well-designed clinical trials to identify the appropriate level of protein provision in critical illness.

The authors' responsibilities were as follows—LJH and BRB: separately reviewed the literature and prepared individual manuscripts, which LJH merged. Both authors then agreed on the systematic search criteria, which LJH executed, and the results of which both authors used to prepare the final manuscript. There were no conflicts of interest.

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