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## Pathophysiology-Guided Nutrition Support in Critical Illness



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**Nutrition care guidelines offer differing recommendations about protein and energy provision in critical illness. The lack of agreement is not surprising, when one considers the heterogeneity of critical illness, the complexity and imperfect delivery of nutritional prescriptions, and the inconclusive results of randomized clinical trials of nutrition support in critical illness. The recommendations in the guidelines are meticulous and important, but they do not provide physiologically informed advice about the selection of nutritional regimens for individual patients. This review explains a practical strategy of bedside nutritional-metabolic evaluation that clinicians may use to formulate nutritional regimens appropriate to the situation of individual critically ill patients.**

### INTRODUCTION

**E**vidence based medicine (EBM) operates on the principle that high-quality randomized clinical trials (RCTs) yield the most reliable evidence on which to base clinical decisions. As corollaries of this principle, EBM discounts expert judgment (it is unreliable and prone to bias) and physiological evidence (it is irrelevant as to whether a therapy is, in fact, effective). Yet clinical judgment and physiological reasoning remain crucial elements of sound clinical practice.

Physiological reasoning is necessary to design RCTs intelligently and interpret their results properly. For example, a clinical trial of iron therapy that enrolls patients with any kind of anemia will be useless or worse, no matter

how excellent its technical quality. Individualized patient care requires both clinical judgment and physiological reasoning to evaluate the relevance of patient-specific factors to specific situations, and deal with the uncertainties and gaps that exist in EBM-based guidelines.<sup>1,2</sup> Clinicians ought to be able to understand and explain why they choose to follow a particular guideline recommendation when caring for a specific patient, a process that requires clinical judgment and physiological reasoning.<sup>1</sup>

Physiological reasoning is especially important in critical illness, which creates hindrances to the design, execution and interpretation of RCTs. These hindrances include the many syndromic and sometimes vague definitions of critical illness, enormous heterogeneity within these syndromes, the confounding effects of co-morbidities, practical

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difficulties executing small-enrollment clinical trials, and the absence of sex-disaggregated data.<sup>1</sup> Clinical trials of nutritional therapies face yet greater challenges, for they involve varying combinations of nutrients, are difficult to implement, and relatively infrequently carried out. A problem unique to nutritional therapies is the large discrepancy between targeted and delivered nutrient doses in published clinical trials.<sup>3-5</sup>

The physiological heterogeneity of critical illness has important nutritional implications. For example, the advantages and disadvantages of two frequently studied critical-illness nutrition interventions – low-energy, protein-deficient nutrition (known as “permissive underfeeding”<sup>6</sup>) on the one hand, versus high-energy and potentially energy-toxic, but higher-protein nutrition on the other – would be expected to accrue differently to patients with different critical-illness metabolic phenotypes. Considerations like this seriously challenge the value of blanket conclusions about any one-size-fits-all nutritional regimen in critical illness.<sup>7</sup> It is not surprising that, as with critical illness in general,<sup>8</sup> no critical-illness nutrition regimen has been shown to be superior to another one.<sup>3,9-13</sup>

This is where physiological reasoning comes in. This article provides a practical strategy of physiologically-guided bedside nutritional evaluation that clinicians may use to formulate macronutrient (protein and energy) prescriptions relevant to the situation of individual critically ill patients.

### Pathophysiology-Guided Nutritional Evaluation

► Examine the patient’s muscles. Muscles account for most of the body’s lean tissue mass, which is the main determinant of a person’s resting energy expenditure and minimum protein requirement. Protein requirements are conventionally indicated in relation to body weight (BW) because normal BW is a useful surrogate for lean tissue mass.<sup>14</sup> But BW can be difficult to measure in the intensive care unit, and even when accurately measured it is frequently unreliable, for it overestimates the lean tissue mass of volume-expanded and obese patients.<sup>15</sup> How, then, should one determine a critically ill patient’s “metabolically effective” BW – the BW that reflects their existing lean tissue mass

undistorted by excess adipose tissue or extracellular fluid (ECF)? Various empirical methods have been suggested.<sup>16</sup> I suggest the physiologically logical approach of evaluating the patient’s muscles, subcutaneous adipose tissue and ECF volume. After integrating the physical findings, settle on a numeric value for the patient’s adipose tissue-normalized, dry (i.e., ECF-normalized) body mass index (BMI; kg/m<sup>2</sup>). Then measure or estimate the patient’s height (small errors only trivially affect the result) and calculate their “normalized (obesity-corrected) dry (ECF-corrected) BW” (NDBW). For example, after consciously discounting any excessive adipose tissue and edema, one might judge the overall muscular profile of a ~ 1.75m (175cm) adult to be consistent with a BMI of ~23 kg/m.<sup>2</sup> This patient’s NDBW is  $(1.75)^2 \times 23 = \sim 70$  kg. Visual BMI is easy to learn, first by practicing and verifying it on non-obese, non-edematous patients, then extrapolating the skill to patients whose body composition is modified by obesity, edema and even ascites.

Muscle atrophy has many, usually combined, causes. They include the muscle atrophy that occurs in simple starvation disease, chronic systemic inflammation, old age (sarcopenia), disuse muscle atrophy from prolonged inactivity, and as a consequence of glucocorticoid therapy, endocrine pathology (adrenal insufficiency, cortisol excess, pituitary deficiency, testosterone deficiency), and primary neurological or muscle disease.<sup>17</sup> It is important to identify the reasons why a patient has developed muscle atrophy, but the protein dose in their nutritional prescription is determined by severity, not etiology.

Point of care devices capable of indicating the mass of selected muscle groups are rapidly being perfected.<sup>18,19</sup> The sarcopenia index, which relates the renal clearance-adjusted serum creatinine concentration to muscle mass, is a potentially useful addition.<sup>20</sup> As such techniques become validated and incorporated into routine clinical use they may complement, but should not replace, conscientious, bedside physical examination of the patient to immediately identify absent, mild, or severe generalized muscle atrophy.<sup>21-23</sup>

► Evaluate the severity of the patient’s protein-catabolic state and associated rate of muscle atrophy to determine the appropriate amount of protein to

provide them.<sup>24</sup> The rate of body protein loss is determined by measuring nitrogen (N) excretion (or N balance in the fed state).<sup>25</sup> In hospital settings, N balance measurements are accurate and precise enough to determine whether protein catabolism is mild, moderate, or severe, and they are especially practical in intensive care units, where protein or amino acid intake is easily quantified and one-on-one nursing makes accurately timed urine collections feasible. Direct analysis of urinary total N is not possible in most intensive care units, but it may be calculated as the sum of the N in urea, ammonium, and creatinine; formulas are available that extrapolate it from urinary urea N alone. The best-known formula estimates total N loss (g/day) as urinary urea N + 4. A more recent one estimates it as urinary urea N/0.85 + 2.<sup>25</sup>

As a rule of thumb, urinary N excretion (or negative N balance in the fed state) > 10 g/day in a 70 kg adult may be regarded as severe protein catabolism.<sup>26-31</sup> This rate of N loss corresponds to the loss of 62 g protein and 300 g lean tissue/day;<sup>25</sup> few knowledgeable clinicians would dispute the assertion that someone losing > 2 kg muscle mass/week is experiencing severe protein catabolism.

Despite its face validity, technical ease and acceptable precision,<sup>25,32-35</sup> N balance is too often ignored in modern intensive care practice,<sup>5</sup> with preference given to a variety of critical illness

severity scores. These scores were developed and validated to predict the risk of death, not the rate of body protein loss.<sup>9,36</sup> They have never been shown to predict severity of protein catabolism. Their use for this purpose is neither validated nor physiologically rational.

In principle, a protein-catabolic severity score could be developed by measuring N excretion (N balance in the fed state) and relating it to predictive factors such as NDBW, age, sex, disease category, and pertinent biomarkers. Once validated, such a score could predict a patient's rate of body protein loss in the same way the Harris-Benedict equations predict resting energy expenditure.<sup>37</sup> Unfortunately, no predictive equation of this kind currently exists. The current state of affairs leaves no rational alternative to measuring N excretion (N balance in the fed state) to determine protein catabolic severity.

Some patients have normal muscle mass when their critical illness develops, but many others suffer from pre-existing muscle atrophy.<sup>38</sup> Protein-catabolic patients with pre-existing muscle atrophy will lose less muscle protein per day in absolute terms than equivalently protein-catabolic patients with normal muscle mass, but they are in greater danger. They are close to the cliff-edge of lethal muscle atrophy, and their atrophic muscles cannot sustain normal respiratory function

**Table 1. Pathophysiology-Guided Protein and Energy Provision in Critical Illness**

Protein Catabolism or Energy Intolerance	Adipose Tissue	Protein Dose (per kg normalized dry body weight)	Energy Dose (% of energy expenditure)	Urgency
<b>Muscle Mass is Normal</b>				
Mild-moderate	Adequate	Moderate	70-100%	Not urgent
Mild-moderate	Depleted	Moderate	100%	Not urgent
Severe	Adequate	High	50-70%	Semi-urgent
<b>Muscle Atrophy is Present</b>				
Mild-moderate	Adequate	High	70-100%	Not urgent
Mild-moderate	Depleted	High	70-100%	Semi-urgent
Severe	Adequate	High	50-70%	Urgent
Severe	Depleted	High	50-70%	Urgent

See text for details.

or release enough amino acids into the central amino acid pool for acute-phase protein synthesis, immunoregulation and wound healing.<sup>9,24</sup> For these reasons, and because muscle atrophy is so common in modern intensive care units, it is appropriate to define severe catabolic N loss as > 150 mg/kg NDBW/day.

In conclusion, when a critically ill patient is experiencing rapid muscle atrophy, it is physiologically rational to provide protein or amino acids promptly (in a handful of hours or days) in a dose suggested by the severity of their rate of body protein loss; this decision is independent of the patient's syndromic critical illness category. Conversely, when a patient has normal muscle mass and their rate of muscle loss is moderate, the protein dose and urgency of providing it are less.

► Estimate the patient's fuel reserve by examining their subcutaneous adipose tissue. An edema-discounted BMI > 18 kg/m<sup>2</sup> indicates that the patient has enough fat to sustain normal bioenergetics for at least a few weeks of hypoenergetic nutrition support.

► Examine for risk factors and indications of exogenous energy substrate resistance<sup>3</sup> – more generally called anabolic resistance<sup>39</sup> – which exposes patients to the toxic effects of energy overfeeding. Energy substrate resistance commonly manifests as hyperinsulinemia, hyperglycemia, and hypertriglyceridemia.<sup>40</sup> Critical illness both creates energy resistance and amplifies pre-existing anabolic resistance due to non-insulin dependent diabetes mellitus, obesity, old age, renal dysfunction, or glucocorticoid therapy.

Since all methods for estimating energy expenditure are imprecise,<sup>41,42</sup> successful provision of what is intended to be isoenergetic nutrition unavoidably overfeeds some patients. Except in cases of severe fat depletion, the energy dose for a critically ill patient should not routinely be set equal to energy expenditure, but reduced below it: the more severe the energy resistance, the greater the toxicity of exogenous energy provision.<sup>3,43</sup> This suggestion is supported by the repeated failure of RCTs of high-energy, high fluid-volume nutrition support to improve the clinical outcomes of critically ill patients, with suggestions of harm to some of them.<sup>3,5,13,16,44,45</sup>

► Evaluate for coexisting micronutrient

deficiencies.<sup>46</sup> Intracellular deficiencies of potassium, zinc, magnesium, and possibly other micronutrients likely prevent the efficient utilization of amino acids for protein synthesis.

### Selection of Protein and Energy Targets

The preceding discussion makes it clear that appropriate doses of protein and energy, and the urgency of successfully delivering them, are independent of one another.

► Protein. The doses of protein recommended in current guidelines range from 1.3 to 2.5 g/kg/day.<sup>6,16</sup> When deciding which dose to provide a specific patient, consider two factors that are known to increase the minimum protein requirement:

1. hypoenergetic nutrition, which increases the protein requirement of non-critically ill patients and likely does the same in critical illness;<sup>47</sup>
2. severe systemic inflammation, which increases net muscle proteolysis under conditions in which the amino acids released from muscle (as well as dietary amino acids) are inefficiently reincorporated into proteins elsewhere in the body and hence are oxidized and lost.<sup>48</sup>

For these reasons, provide 1.3 to 1.5 g protein/kg NDBW/day (approximately twice the normal adult minimum protein requirement of 0.8 g/kg/day) during hypoenergetic nutrition of any patient – a nutritional regimen known as hypocaloric high-protein nutrition.<sup>3,35,43</sup> Provide higher doses, up to 2.5 g/kg NDBW/day, to patients with increasingly severe protein catabolism.<sup>35</sup> When prescribing parenteral nutrition bear in mind that, unlike with intact protein, free amino acids are hydrated; the additional molecule of water attached to each amino acid reduces the mass of protein substrate delivered to the patient. Thus, 100 g of a mixture of free amino acids delivers ~ 83 g protein substrate.<sup>25</sup>

► Energy. Critical-care nutrition care guidelines have traditionally recommended isoenergetic nutrition, but this view is changing. Physiological reasoning and the current RCT evidence do not justify the routine provision of isoenergetic nutrition to patients with an adequate store of body fat. The European Society for Clinical Nutrition<sup>16</sup>



now defines energy provision as low as 70% of estimated energy expenditure as “normocaloric.” The American Society for Parenteral and Enteral Nutrition and Society of Critical Care Medicine<sup>6</sup> recommend hypocaloric high-protein nutrition for morbidly obese patients, although they do so without explaining why this recommendation should not extend to all patients who have ample or adequate body fat.<sup>3</sup>

Table 1 summarizes the physiological factors that should be evaluated when formulating a critically ill patient’s protein and energy prescription: they are muscle mass, protein-catabolic severity, adipose tissue reserve, and energy resistance. For simplicity, protein-catabolic severity and energy resistance are included under one heading, because both conditions increase the dietary protein requirement.

### Convergence of EBM and Physiological Reasoning in Individualized Patient Care

Physiological reasoning enriches and complements EBM by providing clinicians with principles and conceptual tools they can use to reason for themselves about individual patients, and when confronted by gaps and disagreements within and between different clinical care guidelines. The principles summarized in this article are well known and uncontroversial.<sup>26,42,49</sup> It would be a straightforward and desirable exercise to include them in the design of large RCTs. Unfortunately,

this has not yet happened. The reasons why physiological reasoning has been neglected in RCT design may be rooted in the history and evolution of critical-care nutrition research.<sup>3,9</sup> For many years, clinical trial experts shone their investigative searchlight narrowly on energy provision, to the near-exclusion of protein. This “streetlight effect”<sup>50</sup> can, to a large extent, be attributed to the ready availability and convenience of using pre-manufactured nutrition products with a fixed, low protein-to-energy ratio that is appropriate in normal nutrition, but unsuited to the pathophysiology of protein-catabolic illness.<sup>3,9,51-53</sup> Even today, protein-deficient permissive underfeeding and hypocaloric high-protein nutrition continue to be confused or conflated in some of the critical care literature.

Indeed, until recently it was not feasible – and it still may not be in some intensive care units – to deliver either adequate amounts of protein, or appropriately generous amounts of it without energy-overfeeding some patients. This no longer has to be the case. High amino-acid parenteral nutrition products and devices are now available that allow independent selection of amino acid and dextrose doses.<sup>54</sup> Similarly, enteral nutrition products and techniques are now available that allow independent selection of protein and energy doses and hence the provision of appropriately generous amounts of protein without energy overfeeding.<sup>5,54-56</sup>

The defining feature of individualized patient care is its focus on the individual. Many of the procedures explained in this article depend on information and insight obtained by astute physical examination of the patient. An added benefit of this process is that in carrying it out, clinicians are reminded that their patients are neither algorithms nor scores, but specific, unique individuals.

### CONCLUSION

Critical-care nutrition guidelines are important. Their chief responsibility is to assess, compile and evaluate high-quality clinical evidence, especially the evidence derived from RCTs; but RCTs alone do not tell the whole story. Physiological reasoning, by itself, is an unreliable guide to clinical decisions, but this fact does not justify the absurd bias that physiological reasoning can

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be ignored when designing RCTs and interpreting their results. Many critical-care nutrition RCTs have been poorly informed by physiological insight, and they have relied on nutrition products ill-suited to the pathophysiology of critical illness. The metabolic heterogeneity of critical illness mitigates against any one-size-fits-all approach to nutritional recommendations. The principles explained in this article fit within the envelope of existing guidelines, while providing a conceptual framework that clinicians can use to make personal, physiologically rational decisions about the nutritional support of individual patients. ■

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