Protein and energy provision in critical illness[1–3]

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ABSTRACT

It has recently been recommended that parenterally fed, critically ill patients should receive considerably less energy than the 36 kcal · kg^{-1} · d^{-1} customarily received in earlier years and that mixed amino acid infusions not exceed 1.5 g · kg^{-1} · d^{-1}. The implications of these recommendations should be considered carefully, especially for patients with low body weight. Any sizeable reduction in energy provision will lead to negative energy balance in at least some patients, and negative energy balance is known to increase protein requirements. The optimal rate of amino acid delivery for underfed, critically ill patients is not well defined and could well exceed 1.5 g · kg^{-1} · d^{-1}. In addition, there are good reasons to suspect that the safe protein requirement of severely underweight, critically ill patients is >1.5 g · kg^{-1} · d^{-1}, even when adequate energy is provided.   *Am J Clin Nutr* 2003;78: 906–11.

INTRODUCTION

It is commonly believed that the daily energy expenditure (EE) of critically ill persons exceeds normal resting energy expenditure (REE) by ≈50% and is thus equivalent to a daily energy requirement of 36 kcal/kg (1, 2). This amount of energy is often provided in total parenteral nutrition (TPN), even to patients who are less than critically ill (3, 4). However, the view that this is too much energy in most situations has recently emerged. Adverse outcomes due to overfeeding could explain the failure of TPN to reduce mortality in critical illness, as well as the greater infection risk sometimes reported for TPN than for forced enteral nutrition, which typically advances more slowly and provides less energy than does TPN (5–8).

In fact, the REE of many critically ill patients is normal. This was shown most recently in a study in which the average REE of critically ill patients was found to be ≈23 kcal · kg^{-1} · d^{-1} both before and during TPN (9), thus indicating that critically ill patients who are inactive, moderately stressed, and continuously fed have an average REE close to their total daily EE. Several earlier studies document that the average REE of critically ill patients is 22–25 kcal · kg^{-1} · d^{-1} both before (10–12) and during (13–15) TPN.

The harmful effects of high-energy TPN are attributed to hyperglycemia, which induces immediate adverse metabolic responses (16, 17) and is associated with a greater infection risk and larger ischemic infarctions than is euglycemia (18–21). Prevention of hyperglycemia improves the clinical outcome of patients in surgical intensive care units (22, 23), and the goal of euglycemia is far easier to achieve when energy from carbohydrates is provided at a modest rate (18–20). Against this, however, are reports that the REE of critically ill patients is 36–40 kcal · kg^{-1} · d^{-1} (2, 24–27) or that it ranges between 25 and 36 kcal · kg^{-1} · d^{-1} (28–32). Provision of 22–25 kcal · kg^{-1} · d^{-1} to patients such as these would significantly underfeed them.

A second recent recommendation is that mixed amino acid infusions be reduced below historical recommendations of 1.5–2.0 g · kg^{-1} · d^{-1} (33). This issue has been debated (34), but it is now commonly recommended that daily amino acid infusion rates not exceed 1.5 g/kg (18, 35, 36).

In this article, I review the concepts necessary to assess the energy and amino acid needs of critically ill patients. In addition, I offer suggestions for clinical decision making in this important area of clinical nutrition.

PREDICTING ENERGY EXPENDITURE

Direct measurement of EE is the ideal, but at present most clinicians use predictive equations to estimate the energy requirements of their patients. The most widely used equations are the Harris-Benedict (HB) equations (37, 38). The HB equation for men is

$$REE = 66.5 + 13.75W + 5.003H - 6.775A \quad (1)$$

where *W* is body weight in kg, *H* is height in cm, and *A* is age in y. The HB equation for women is

$$REE = 655.1 + 9.563W + 1.850H - 4.676A \quad (2)$$

According to the HB equation, the REE (values generated by the HB equations are traditionally referred to as "basal energy expenditure") of a 175-cm, 25-y-old "reference man" is 773 +

13.75W kcal/d. Other equations are available from expanded (39) or new (40–42) data sets. A characteristic of all of these equations is that even when W is zero, the REE that they predict (REE_0) is considerably greater than zero. For example, the HB equation predicts that if the reference man just defined is reduced to weightlessness, he will continue to expend 773 kcal/d at rest. A different set of equations is available that predicts REE as a simple multiple of W, such as 22 or 25 kcal/kg (12, 15). The equation of Paauw et al (15) (referred to here as the 25W equation) was developed by forcing the straight-line function relating W and REE to pass through the origin: thus, $REE_0 = 0$. This mathematical tyranny is justified by the convenience of stating REE as a simple multiple of W with no loss in accuracy (15); the introductory section of this article illustrates how frequently this equation is invoked.

It is important to recognize that the nonzero REE_0 is physiologically real (43, 44). REE is the sum of the EEs of the body's several metabolically active compartments. Starving and starving-stressed humans do not lose body substance in a constant proportion from their body compartments; rather, skeletal muscle bears the brunt of the loss, whereas central, highly metabolically active lean tissues are relatively spared. Because of this phenomenon, REE/W increases as W decreases. REE/W for the reference man is

$$(773 + 13.75W)/W = 13.73 + 773/W \qquad (3)$$

This is an inverse relation, and the reason that it is inverse is the nonzero REE_0. The phenomenon is illustrated by a study in which the REE of patients with Crohn disease was measured. The more severely underweight patients were found to have higher REE/W (45). These underweight patients should not be considered hypermetabolic because their REE values closely matched those predicted by the HB equation.

There are practical differences between predictive equations with a zero and nonzero REE_0. When both are applied to the same (Gaussian) data set, the 2 equation lines will intersect at the average W. For the reference man,

$$REE_{HB}/REE_{25W} = 0.55 + 31/W \qquad (4)$$

and $REE_{HB} = REE_{25W}$ when $W = 69$ kg. This is close to the average adult weight, so the 25W equation "works" about as well—or as badly—as the HB equation does for most patients. One would not anticipate such agreement for patients with low weight, however. Because its REE_0 is zero, the 25W equation progressively underpredicts the HB equation as W approaches zero. For a reference man starved to 45 kg—and a body mass index (in kg/m^2) of 15—the HB equation predicts an REE/W value of 31 kcal/kg; this is 25% higher than the value predicted by the 25W equation. By the same token, the 25W equation predicts a greater REE for obese patients than do the HB or the Owen equations, which were developed from a data set that specifically included obese persons (40, 41).

In a study of severely underweight, mildly stressed, critically ill elderly patients receiving TPN, Ahmad et al (46) compared measured REE with the values predicted by the HB and 25W equations. Interestingly, the 2 equations agreed closely with each other. On examination, it turns out that, unlike the case with tall, young reference men, the 25W and HB equations for elderly men and women intersect when W is ≈40 kg. This is an interesting demonstration of the fact that the point where the HB and 25W equations converge is influenced considerably by height and age. But the far more important finding of this study was that both predictive equations were wrong. The measured REE values for these elderly, malnourished patients were consistently 25% higher than the predicted values.

VARIABILITY IN ENERGY EXPENDITURE OF CRITICALLY ILL ADULTS

Efforts to identify the determinants of EE in critical illness have generated a complicated and difficult clinical literature. REE and total EE are highly variable both between and within studies. The determinants of EE are many, have unknown dose responses, and overlap with, add to, or subtract from each other in such complicated ways that no equation that adequately predicts the EE of individual patients currently exists (47). Almost all predictive equations are functions of W, so their usefulness depends on its accurate measurement before fluid resuscitation, which can increase W by ≥15 kg (36). Obese or malnourished patients present special problems because obesity lowers the contribution of fat-free mass to W, and malnutrition increases the extracellular fluid volume (48, 49). Trauma and sepsis appear to entrain different metabolic responses (50), although differential effects on REE have not yet been predicted or shown (51). Burn injuries (28, 52) and head trauma (53, 54) are well known to increase REE, but the magnitude of the increase is highly variable. Paralysis, sedation, and β-adrenergic blocking drugs reduce REE (55–60), whereas pressors increase it (27, 56). One would logically predict that the greater the severity of trauma or sepsis, the higher the REE (27, 47), but this has not been consistently observed (30, 31), presumably because of the confounding effects of fever, age, restless physical activity, pharmacotherapy, prior nutritional status, and the duration and evolutionary phase of the critical illness (1, 2, 61). Nutrient provision itself increases EE (33, 62–64), but such increases are probably important only when nutrients are provided in excess of REE (1, 9, 62, 65). However, patients with burn injuries may differ in this regard (28, 52). High intravenous doses of glucose acutely increase whole-body proteolysis (16) as well as heart rate and blood pressure, the latter (and conceivably the former) through free radical–mediated effects (17, 66, 67). It is tempting to speculate that the increased partial pressures of oxygen required by many critically ill patients could exaggerate these effects, but there are no data in the literature that address this. Fever is perhaps the most important easily measured factor responsible for variability in EE (9, 30, 68, 69). Ambient temperature is also important (1, 55, 70), and in patients who are not well insulated or warmed, open wounds probably increase energy production considerably and do so even more in the presence of a pyrogenic stimulus. As a further complication, some researchers who used modern indirect calorimeters to measure REE obtained normal values that were slightly but significantly less than values predicted by the HB equations or values obtained when REE was measured by using a gasometer, mouthpiece, and nose-clip apparatus similar to those used by Harris and Benedict (71, 72).

TABLE 1
Hypocaloric nutritional support and nitrogen balance[1]

				Fuel provision/kg IBW		
Reference	Therapy	n[2]	Percentage of IBW	Energy	Protein	Nitrogen balance
			%	*kcal/d*	*g/d*	*g/d*
Greenberg and Jeejeebhoy (86)	TPN	6	NA	6.5	1.8	1.5
		6	NA	4	0.8	−3.6[3]
Dickerson et al (88)	EN	13	208	22.5	2	−0.6
Burge et al (93)	TPN	7	167	22	2	2.8
		9	152	10	2	1.3
Choban et al (90)	TPN	14	160	36	2	4
		16	165	22	2	4
Frankenfield et al (75)	TPN	10	113	32	1.9	−7.5
		10	113	16	1.9	−7.9
McCowen et al (8)[3]	TPN	19	107	21	1.4	−0.6
		21	115	15	1.1	−8.0[4]
Dickerson et al (96)	EN	12	168	30	1.8	−1.2
		12	188	22	1.4	−2.5

[1] Except for Dickerson et al (88), all studies were randomized clinical trials. TPN, total parenteral nutrition; EN, enteral nutrition; IBW, ideal body weight; NA, information not available.
[2] Number of patients in each treatment group.
[3] Nitrogen balance measured in only one-half of the patients.
[4] Significantly different from comparison group.

PROTEIN REQUIREMENT OF CRITICALLY ILL ADULTS

The principal goal of nutritional therapy in critical illness is to protect lean tissue mass and function. Lean tissue loss is unavoidable when trauma or sepsis cause significant injury, and the rate and ultimate magnitude of the loss are greatest when the injury is severe and persistent (32, 36, 73). The therapeutic goal in this setting is to minimize ongoing lean tissue loss through appropriate provision of energy and amino acids (32, 35, 74, 75). Amino acids reduce body nitrogen loss, but protein sparing is not improved by infusion rates $> \approx 1.5$ g $\cdot$ kg^{-1} $\cdot$ d^{-1} (24, 76–78). These reports form the basis for recent recommendations that amino acid infusions not exceed 1.5 g $\cdot$ kg^{-1} $\cdot$ d^{-1}, but it should be noted that these recommendations are based on average responses of heterogeneous groups of patients and may not apply to all patients. More importantly, the investigations were carried out in patients whose average weight was normal and who were provided with generous amounts of energy, which tends to maximize nitrogen retention. Negative energy balance increases protein requirements (PRs), and, as explained in the final section of this article, the PR of even adequately fed, underweight patients is probably >1.5 g $\cdot$ kg^{-1} $\cdot$ d^{-1}.

EFFECT OF ENERGY BALANCE ON PROTEIN REQUIREMENTS

It is well established that energy deficiency worsens nitrogen balance (33, 79–82). The results of the famous Minnesota starvation study (48) illustrate this phenomenon. The Minnesota volunteers (energy intake: ≈ 22 kcal $\cdot$ kg^{-1} $\cdot$ d^{-1}) had substantial lean tissue loss despite adequate protein consumption (0.75 g $\cdot$ kg^{-1} $\cdot$ d^{-1}). Indeed, energy intakes were set high in the early years of TPN largely because it was believed that no amount of dietary protein could protect the lean tissue store in

the face of a negative energy balance (80). We now know that when nitrogen balance studies are carried out long enough for metabolic adaptation to take effect—a process that requires 3–4 d (83, 84)—high protein intakes do spare the lean tissues in many energy-deficient states (85–90). Nor is the protein-sparing effect of high protein intakes during energy restriction necessarily limited to obese persons. In an interesting study, normal-weight men who were made energy deficient for 10 wk while consuming 94 g protein/d had only minimal weight loss that could be attributed to lean tissue loss (91).

Given the inadequacy of current REE predictive equations, it is reasonable to predict that routinely providing 22–25 kcal $\cdot$ kg^{-1} $\cdot$ d^{-1} in TPN will render many patients energy deficient, and unless EE is directly measured, it could be difficult to identify who those patients are. A mild energy deficit is actually likely to benefit obese, critically ill patients (88, 92–96). However, quantitative information about the effects of hypocaloric nutritional support on the nitrogen balance of critically ill patients is lacking. The information that is available indicates that important protein sparing is indeed possible, but it does not permit the conclusion that 1.5 g amino acids $\cdot$ kg ideal body wt^{-1} $\cdot$ d^{-1} provides maximal protein sparing (**Table 1**).

STARVATION AND THE PROTEIN REQUIREMENT PER KILOGRAM OF BODY WEIGHT

The adult PR is proportional to body weight. Stated mathematically,

$$PR = PR_0 + kW \qquad (5)$$

where, according to current recommendations, PR is the safe PR in g, k is 0.8, and PR_0 is a constant that is presumed to be zero (97, 98). The reasons for assuming that $PR_0 = 0$ are not available. Actually, there are good reasons for predicting that it is considerably greater than zero.

The PR of the whole organism is the sum of the requirements of its different lean tissue compartments. The greater the mass of protein that is actively turning over in a given compartment, the greater the rate that amino acids have to be supplied to make up for obligatory amino acid efflux and catabolism. Although it is undoubtedly correct to assume that PR is proportional to *W*, it would seem even more accurate to consider PR as a function both of the amount of metabolically active proteins in the body and their turnover rates. Human tracer studies indicate that the protein turnover rate affects the efficiency of exogenous protein retention and endogenous amino acid recycling. Protein turnover is reduced in simple starvation, presumably reflecting the entrainment of adaptive mechanisms to conserve body protein stores. The adaptation to starvation is reversed by catabolic stress, which increases protein turnover, thereby widening the mismatch between protein synthesis and breakdown, increasing amino acid catabolism, and making nitrogen balance negative (74, 83, 84, 99, 100).

As with EE, the body is heterogeneous with respect to the protein turnover rates in its different compartments. As weight decreases, the more-rapidly-turning-over central protein compartment assumes a greater proportion of the total lean tissue mass. In the same way that sparing of these tissues during starvation causes REE/*W* to increase, so must it also increase the protein turnover rate/*W* (101), and this, in turn, may be presumed to increase PR/*W*. The conclusion that PR/*W* increases as *W* decreases is equivalent to stating that $PR_0 > 0$.

In the absence of clinical data, it is prudent to assume that PR/*W* is greater in underweight persons than in normal-weight persons. How much greater is PR/*W* in underweight persons? Because the 25W and PR equations are both forced through zero, one might, as a first approximation, assume that the PR/*W* of an underweight person increases by approximately the same proportion that the HB prediction, with its appropriately nonzero REE_0, exceeds the 25W prediction in a starved, young reference man. Another way to attempt the approximation is to assume that the PR/*W* of a severely underweight, elderly person is greater than that of an otherwise similar, normal-weight person by the same fraction that measured REE values exceeded REE values predicted by the 25W equation in Ahmad et al's (46) study of stressed, severely underweight elderly patients. By coincidence, both approximations yield the same figure: 25%.

CONCLUSIONS

There is no equation currently available that adequately predicts the EE of critically ill patients, so it is inevitable that any general introduction of lower-energy TPN regimens will cause a negative energy balance in some patients. No amount of protein will prevent important lean tissue loss in the most severely catabolic patients, but many, or even most, underfed, less critically ill patients might benefit from ≥ 2 g amino acids $\cdot$ kg normal body $wt^{-1} \cdot d^{-1}$ to mitigate the loss of proteins caused by their intentional or unintentional energy deficiency. Currently available data do not justify limiting amino acid infusion rates to 1.5 g $\cdot kg^{-1} \cdot d^{-1}$ in this situation.

Ahmad et al (46) showed that existing predictive equations underestimate the REE of severely underweight, mildly stressed, critically ill elderly patients. When direct REE measurement is impractical, it would be prudent to assume that the

daily REE of such patients (eg, persons whose body mass index is ≤ 17) is ≥ 31 kcal/kg dry body weight, in keeping with the results of Ahmal et al (46). By coincidence, the HB equation predicts that the REE of a 25-y-old, 1.75-m reference man with a body mass index of 16 is ≈ 30 kcal/kg. Therefore, pending further clinical information, it is reasonable to assume that the daily maintenance energy requirement of all severely underweight patients is ≥ 31 kcal/kg.

Despite the universal assumption that the human PR is a simple multiple of weight, Equation *5* (where *k* is the conventional proportionality constant, but where PR_0 is a nonzero constant analogous to REE_0 in the REE equation) is more biologically plausible. The clinical implication is that PR/*W* of severely underweight, stressed patients is probably greater than that of comparably stressed, normal-weight patients. Pending the accumulation of clinical data, it is prudent to assume that the PR/*W* of severely underweight patients is greater than that of normal-weight patients by approximately the same proportion that the 25W equation (with its similarly incorrect assumption that $REE_0 = 0$) underestimates REE, ie, by 25%. A severely underweight patient in neutral or positive energy balance who, under current guidelines, would receive 1.5 g amino acids $\cdot kg^{-1} \cdot d^{-1}$ may actually require $\approx 25\%$ more than this, or 1.9 g $\cdot kg^{-1} \cdot d^{-1}$.

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