Section 1

General Concepts

1

Nutritional physiology of the critically ill patient

David C. Frankenfield

Introduction

Nutritional physiology refers to the role of food and nutrition in the function of the body. In the critically ill patient there are numerous points at which nutrition affects function, since all fuels, tissues, and mediators ultimately arise from the food consumed by the individual. There are now evidence-based guidelines for the provision of nutrition support in the critically ill patient. Several actions related to feeding improve outcomes such as infection rate, days on mechanical ventilation, days in the critical care unit, and mortality. These actions include the provision of early enteral nutrition, use of tube feedings supplemented with n-3 fatty acids and antioxidants, and reaching minimum targets for energy and protein intake. The minimum target range is an area of debate currently.

This chapter will focus on energy balance, protein and nitrogen balance, and the macronutrient requirements of critically ill patients compared to normal. The potential role of nutrients to modulate inflammatory injury in the critically ill patient will also be examined.

Energy

All functions of the body require energy. Ultimately all energy used by the body is consumed in the diet. Some is used immediately and some is converted to glycogen or body tissue to be used later. In healthy people ingested fuel is used when available and suppresses the use of stored fuel. Stored fuel is mobilized post-prandially as the ingested fuel is consumed. In critically ill patients this priority is altered, with ongoing use of stored fuel, especially protein, even if dietary fuel is available.

Nutrition in Critical Care, ed. Peter Faber and Mario Siervo. Published by Cambridge University Press.

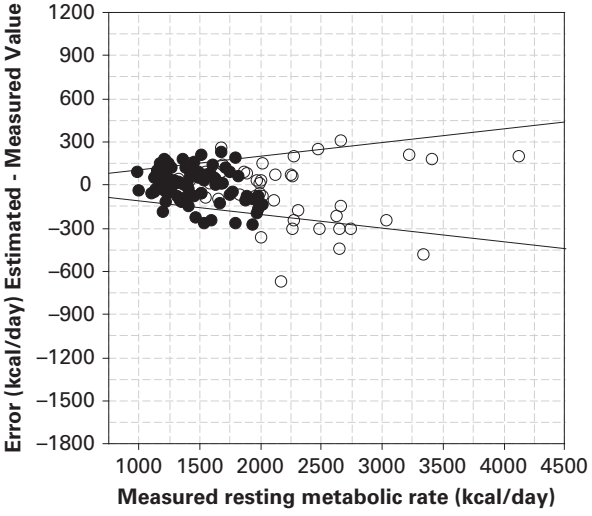

Figure 1.1 Errors in predicting resting metabolic rate using the Mifflin–St. Jeor equation in healthy individuals. Closed circles are patients with body mass index < 30 kg/m^2 and open circles are patients with body mass index ≥ 30 kg/m^2. Within the central band are predictions falling within 10% of measured. Negative values are underestimates and positive values are overestimates. The accuracy rate of the equation in non-obese individuals was 82% compared to 70% in obese people.

In healthy people resting metabolic rate is determined by energy expenditure in the visceral organs. Through relationships among organ mass, fat-free mass, and body weight, resting metabolic rate is predictable from body weight, height, age, and sex. The Mifflin–St. Jeor equation, for example, can predict resting metabolic rate accurately in healthy people about 75% of the time (Figure 1.1). These equations take the following form:

- Resting metabolic rate (men) (kcal/day) = Wt in kg(10) + Ht in cm(6.25) – Age in yrs(5) +5
- Resting metabolic rate (women) (kcal/day) = Wt in kg(10) + Ht in cm(6.25) – Age in yrs(5) – 161.

In critically ill patients, the relationship between body size and resting metabolic rate is still present. However, the utilization rate of fuel is accelerated in the critically ill patient. The hormonal milieu is characterized by a decrease in the ratio of insulin to glucagon, increased catecholamine levels, and insulin resistance. A host of cytokine and eicosanoid mediators also are present, creating an inflammatory response. Under the influence of these mediators the critically ill body increases its rate of gluconeogenesis, proteolysis, acute phase protein production, lipolysis, and oxygen consumption. Energy expenditure is increased on average by about 25%, but there is wide variability, from 25% below expected

Table 1.1 Elevation in resting metabolic rate in critical care patients (as a percentage of predicted healthy resting metabolic rate as estimated by the Mifflin–St. Jeor equation)

		All			Febrile		Afebrile	
Group	N	Mean ± SD	Range	Percent febrile in previous 24 hours	Mean ± SD	Range	Mean ± SD	Range
Trauma	52	1.30 ± 0.18	0.99–2.1	69	1.32 ± 0.19	1.09–2.14	1.24 ± 0.17	0.99–1.77
Surgical	65	1.22 ± 0.17	0.92–1.8	46	1.26 ± 0.16	0.97–1.60	1.19 ± 0.18	0.92–1.83
Medical	85	1.21 ± 0.20	0.75–1.8	38	1.31 ± 0.20	0.93–1.76	1.15 ± 0.17	0.75–1.51
Total	202	1.23 ± 0.19	0.75–2.1	49	1.30 ± 0.18	0.93–2.14	1.18 ± 0.17	0.75–1.83

Data from Frankenfield DC, Schubert A, Alam S, Cooney RN. Validation study of predictive equations for resting metabolic rate in critically ill patients. JPEN J Parenter Ent Nutr 2009;33:27–36.

healthy metabolic rate to more than two times elevation above expected healthy value (Table 1.1).

The increase is not related to illness severity as measured by APACHE (Acute Physiology and Chronic Health Evaluation) score, or by type of illness/injury. However, body temperature does discriminate the degree of hypermetabolism. The respiratory effort, measured as minute ventilation, also increases as more fuel consumption results in more carbon dioxide production that must be removed by the lungs. These physiological changes can be exploited to predict the increase in energy expenditure. The Penn State equations use the Mifflin–St. Jeor equation to capture the association between resting metabolic rate and body size, and then use body temperature and minute ventilation to account for the metabolic effects of inflammatory response:

- Resting metabolic rate (kcal/day) = Mifflin(0.96) + Tmax(167) + Ve(31) – 6212
- Resting metabolic rate (kcal/day) = Mifflin(0.74) + Tmax(85) + Ve(64) – 3085

where Mifflin is Mifflin–St. Jeor equation, Tmax is maximum body temperature in the previous 24 hours (centigrade), and Ve is minute ventilation (L/min).

Using this equation, resting metabolic rate can be predicted accurately about 75% of the time (Figure 1.2).

Over time, indirect calorimetry measurements must be repeated every 3 to 4 days to be more accurate than daily recalculation of metabolic rate using the Penn State equation (Figure 1.3). Other common prediction methods such as the Harris–Benedict equation or the rule of thumb from the American College of Chest Physicians (25 kcal/kg body weight) are accurate at best 50% of the time, and in the case of the ACCP (American College of Chest Physicians) standard there is proportional bias (increasing underestimation as measured metabolic rate increases).

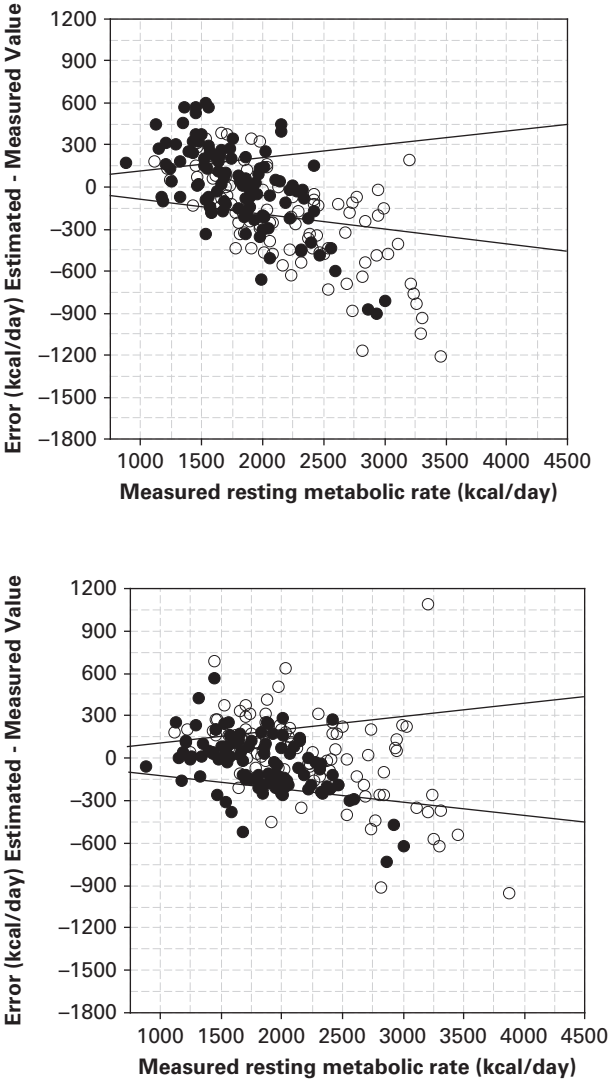

Figure 1.2 Errors in predicting resting metabolic rate using the ACCP standard of 25 kcal/kg body weight (top) and the Penn State equation (bottom). Closed circles are patients with body mass index < 30 kg/m^2 and open circles are patients with body mass index ≥ 30 kg/m^2. Within the central band are predictions falling within 10% of measured. Negative values are underestimates and positive values are overestimates. For the ACCP standard, estimates were accurate 52% of the time vs 67% for the Penn State equation. With a modification to the equation for patients 60 years or older with body mass index 30 kg/m^2 or higher, the overall accuracy of the Penn State equation increases to 73%.

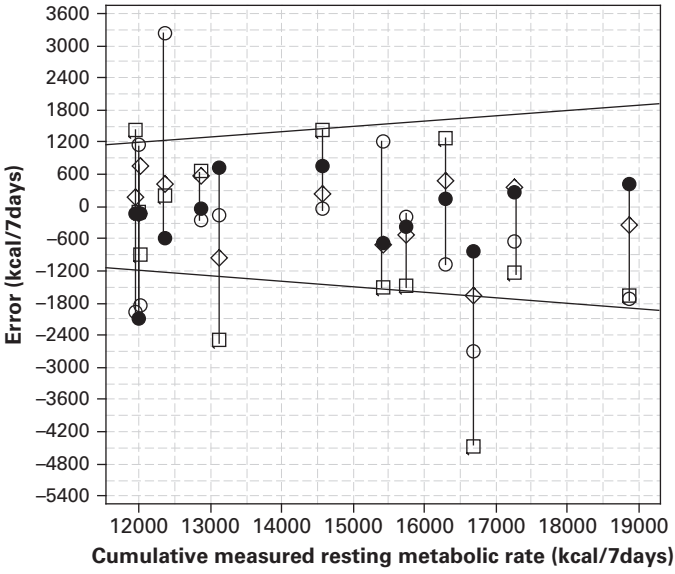

Figure 1.3 Cumulative errors in predicting resting metabolic rate in mechanically ventilated critically ill patients using the Penn State equation (closed circles), ACCP standard of 25 kcal/kg (open circles), a 7-day estimate extrapolated from a single measurement (open squares), and a 7-day estimate extrapolated from two measures on day 1 and day 4 (open diamonds). The vertical lines connect the four estimates for a single patient. Total number of patients studied was 13.

Protein

There is general agreement that protein needs are elevated in the critically ill patient, but there is little agreement as to the exact requirement. The critically ill patient experiences an increase in muscle proteolysis that is resistant to the usual attenuating effect of feeding. Nitrogen and muscle loss are moderately correlated with the degree of hypermetabolism (R^2 0.25 and 0.37 respectively). Proteolysis in critically ill patients is thought to occur in order to mobilize amino acids from muscle to be used in the viscera for gluconeogenesis, acute phase protein synthesis, RNA, and ATP. The availability of glutamine to the viscera may play an extraordinary role in this movement of amino acids from the periphery to the central tissues of the body, serving as a major fuel and cell component in the cells of the immune system and gastrointestinal tract, an antioxidant (glutathione), and a component of acid–base balance in the kidney.

Thus the critically ill patient is at once experiencing increased catabolism (muscle) and increased synthesis (viscera), but the net effect is a catabolic state resistant to feeding. Nutrition support is capable of stimulating the synthetic component but cannot eliminate the catabolic component.

Table 1.2 Nitrogen utilization at different levels of energy balance in critically ill patients

	Burge		Dickerson	Frankenfield		
Parameter	Hypocaloric	Eucaloric	Hypocaloric	Hypocaloric	Eucaloric	Hypercaloric
Percentage of kilo calories fed	73	113	63	75	105	124
Nitrogen intake (g/d)	18	21	21	19	19	20
Nitrogen output (g/d)	8	11	15	27	25	27
Balance (g/d)	+1	+3	+2	−8	−8	−8
Catabolic rate (g/d)	64	85	–	90	105	95

Data compiled from Dickerson RN, Rosato EF, Mullen JL. Net protein anabolism with hypocaloric parenteral nutrition in obese stressed patients. Am J Clin Nutr 1986;44:747–755; Burge JC, Goon A, Choban PS, Flancbaum L. Efficacy of hypocaloric total parenteral nutrition in hospitalized obese patients: a prospective, double-blind randomized trial. J Parenter Enteral Nutr 1994;18:203–207; Frankenfield DC, Smith JS, Cooney RN. Accelerated nitrogen loss after traumatic injury is not attenuated by achievement of energy balance. J Parenter Enteral Nutr 1997;21:324–329.

Another unique aspect of protein metabolism in the critically ill patient is its relationship with energy intake. In healthy people nitrogen balance can only be achieved when energy balance is also achieved and the protein intake is adequate. At a fixed but inadequate protein intake, nitrogen balance will improve as more total energy is fed but a plateau in nitrogen balance will occur before nitrogen equilibrium. At a fixed and inadequate energy intake, nitrogen balance will improve as more protein is fed but again a plateau in nitrogen balance will occur before equilibrium is achieved (unless so much protein is given that the requirement for total energy is satisfied). In critically ill patients, there are studies in which nitrogen balance has been demonstrated to be independent of energy balance (Table 1.2).

Research on this topic has focused either exclusively on obese patients or included non-obese and obese patients. Obese patients were not as catabolic as the non-obese patients (consisting of blunt trauma patients studied in the first week after injury). The nitrogen losses in obese patients were lower than in non-obese patients, and thus nitrogen balance was positive. Non-obese patients reached similar nitrogen intake to the two studies on obese patients but had much higher nitrogen losses and thus did not achieve nitrogen balance. However, over a wider range of energy intake, nitrogen balance was not more negative in underfed than in overfed patients. Muscle catabolic rate was likewise found to be independent of energy intake, though it must be made clear that none of the patients studied were completely unfed during the study and all received protein. Studies of catabolic

rate in which only low concentration dextrose (5%) was given show a higher catabolic rate than demonstrated in studies of fed patients.

Balance studies

Bartlett published perhaps the first study of the effect of negative energy balance on outcomes in the critical care unit. In an observational study of 57 critical care patients whose resting metabolic rate was measured once or twice each day of their intensive care unit stay, mortality rate was 27% in 15 patients achieving positive energy balance, 39% in 28 patients with an energy balance of 0 to –10 000 kcal, and 86% in 14 patients with an energy deficit greater than 10 000 kcal. Subsequent observational studies have disputed this finding, showing detrimental outcome associated with more aggressive provision of energy. Most recently, however, several studies indicate an outcome advantage to meeting the energy and protein demand of critically ill patients via nutrition support.

One prospective randomized clinical trial has been conducted to examine the question of energy balance in critically ill patients. The study used indirect calorimetry to monitor actual energy expenditure in 112 critically ill patients. One group was assigned a study coordinator to adjust feeding rates to compensate for interruptions so that energy intake matched (actually exceeded) the measured energy expenditure (cumulative balance +2008 ± 2177 kcal over 14 days) while the other group was randomized to standard care in which the feeding interruptions common in critical care were not compensated for by rate adjustment, resulting in negative energy balance of –3550 ± 4591 kcal over 14 days. Length of stay in the critical care unit was significantly longer in the group in positive energy balance (16 vs 11 days) as were days on mechanical ventilation (17 vs 12 days), but overall hospital mortality rate was reduced from 48% to 29%. It should be noted that the positive energy balance group also received a higher protein intake than the negative energy balance group. Besides the prospective randomized nature of design of this study, another unique aspect was the extension of the examination of outcomes of critical care interventions in the post-critical care environment.

In a study of 50 septic patients requiring continuous renal replacement therapy it was found that positive nitrogen balance conferred a survival advantage (a 21% increase in survival probability was noted for a 1 g/day increase in nitrogen balance). Increasing protein intake was associated with an improvement in nitrogen balance, but not directly with an improvement in survival. This may be because some septic patients are less able to utilize the dietary protein than others. Those who can utilize the protein more efficiently are more likely to achieve positive nitrogen balance, and the data indicate that this ability results in a survival advantage. Therefore it was recommended a protein intake > 2.0 g/kg body weight (ideally 2.5 g/kg body weight).

A larger (n=886) study of general critical care patients found that achieving protein and energy intake goals reduced the 28-day and overall hospital mortality

risk. The reduction in risk was even more pronounced when the data were controlled for age, body mass index, admitting diagnosis, APACHE score, hyperglycemia index, and time to reach target intake. Notably, energy balance alone did not reduce the mortality risk.

Water

In healthy people, water intake should balance losses both sensible and insensible. A general rule is 30 mL/kg body weight. In the critically ill patient the same is often but not always true, and fluid needs can change as the illness evolves. Early on in the illness and during septic shock while the vascular system is dilated, the need for water and volume are increased. If acute renal failure has occurred, then water requirements can be decreased. On the other hand water loss during continuous renal replacement therapy can be many liters per day and require extra replacement. Chronic illness such as congestive heart failure may continue to dictate fluid restriction even during a period of critical illness. High water loss through the gastrointestinal tract as gastric drainage or diarrhea, or high fluid loss through surgical drains will increase the need for fluid replacement. It is important to realize that water needs often need to be met not simply with water but with crystalloid or colloidal fluids. Remove these from the dietary fluid needs of the patient, and further subtracting the obligatory fluid intake from medications, and the water content of a nutrition support regimen may actually need to be restricted even though the patient's overall requirement for fluid is increased.

Nutrition and inflammation

Injury and infection elicit inflammatory responses from the host that help create the conditions to resolve the insult and return the body to a state of homeostasis. This is accomplished through orchestration of anti-inflammatory and pro-inflammatory processes. However, if multiple insults occur, or if the response to a single insult is severe, the inflammatory response becomes dysregulated and maladaptive, leading to hemodynamic and other organ and metabolic dysfunction, and ultimately to increased morbidity and mortality. Many of the mediators of inflammation are produced from dietary components, especially fatty acids. A change in diet can be rapidly detected in the fatty acid composition of cell membranes and enteral feeding formulas containing n-3 fatty acids have been shown to improve outcomes in patients with inflammatory lung disease and sepsis. Specifically, a prospective randomized clinical trial has been conducted on critically ill patients with sepsis or septic shock. All of the patients also met criteria for acute respiratory distress syndrome. The patients were randomized to one of two high-fat diets. The control diet was based on canola oil while the treatment diet contained canola, borage, and fish oil, nearly doubling the ratio of n-3:n-6 from 1:3.8 to 1:1.85. Starting at the fourth day of the study, PaO_2/FIO_2 ratio fell in the study group compared to the

control as a result of increased PaO_2 as well as decreased FIO_2. Accompanying this improvement in oxygenation was a fall in positive end-expiratory pressure (PEEP) and minute ventilation. In the 28-day study period the treatment group had more ventilator-free days (13 vs 6) and more ICU-free days (11 vs 5). Mortality risk was reduced by 19% in the treatment group.

However it should be mentioned that the control group feeding was higher in long-chain fat than most standard feedings (i.e. septic patients with ARDS (acute respiratory distress syndrome) can be fed standard diets with either a low total fat content or a high-fat content that is largely medium-chain fatty acid, and it is unknown how these diets would compare with the n-3 fatty acid feeding) and the results could not be replicated in a larger study. The n-3 fatty acid in this study was delivered in bolus fashion twice daily rather than by continuous infusion as part of a feeding regimen, and this could be an important difference influencing the outcomes. Furthermore, the two feeding formulas were not as similar to one another in terms of carbohydrate, fat, and protein, leaving open the possibility that other dietary differences in the studies interfered with the results.

Several evidence-based nutrition support guidelines for critically ill patients have concluded that enteral feeding formulas with n-3 fatty acids should be used in patients with acute respiratory distress syndrome. Some of these guidelines extend that recommendation to sepsis and more general critical care populations.

Metabolic dysregulation in critically ill patients

The changes in metabolism and nutrient requirement brought about by the inflammatory response to critical illness are thought to be adaptive, liberating fuels and stimulating pathways to produce glucose, acute phase proteins, and other components to return the patient to homeostasis. However, if infection intervenes, or other insults are sustained, the carefully orchestrated interplay between pro-inflammatory and anti-inflammatory signals that comprise the inflammatory response can become dysregulated and actually cause tissue damage leading to shock and organ failure. In such patients metabolism also becomes dysregulated, characterized by a further increase in catabolic rate, hyperglycemia, hypertriglyceridemia, and sometimes increased energy expenditure (although the change in energy expenditure still seems to follow changes in body temperature and minute ventilation). Provision of carbohydrate and fat are made more problematic by these changes. A higher portion of dietary protein is used ineffectively in some of these patients so that improvements in nitrogen balance are not realized from increasing the protein intake. If this metabolic defect occurs there seems to be a detrimental effect on outcome. The organ damage resulting from hyperinflammatory states may limit the tolerance to feeding, although with proper organ support the impact can be minimized. Nutrient intake in these patients should be characterized by increased protein intake, using urinary nitrogen loss when possible to determine if nitrogen balance is improved. Carbohydrate intake should be coordinated with insulin dosing to ensure that blood glucose does not exceed

150 mg/dL. A change in fat intake to an n-3 fatty acid based mixture should be considered, and minimizing negative energy deficits seems to be important.

Feeding routes and energy and protein requirements

One important area of disagreement in the recommendations of the published guidelines is the role of supplemental parenteral nutrition for patients who cannot be fed enterally or whose enteral feeding cannot be advanced to goal because of gastrointestinal intolerance. The ASPEN (American Society of Parenteral and Enteral Nutrition) guideline reserves early use of parenteral nutrition to patients with pre-existing malnutrition and inability to use enteral nutrition. If nutritional status is adequate, parenteral nutrition should not be considered until after 5 to 7 days inability to feed enterally. The Canadian guideline refrains from making a recommendation on the use of supplemental parenteral nutrition but does emphasize several strategies to maximize enteral feeding so that supplemental parenteral nutrition does not need to be considered. The European guideline on the other hand supports the early use of parenteral nutrition as a supplement to tube feeding if the tube feeding cannot be advanced. A recent study published after all of the guidelines seems to support the early use of parenteral nutrition to supplement enteral feeding if enteral feeding cannot be advanced. A randomized clinical trial was conducted on 275 patients started on early enteral feeding. On day 3 the patients were randomized to continue enteral feeding alone or to be supplemented with parenteral nutrition. Energy demand was determined by indirect calorimetry. Energy intake from day 4 to day 8 was 73 ± 27 vs 100 ± 16% of target in the enteral vs supplemental parenteral nutrition group. Being in the supplemental parenteral nutrition group reduced the risk of new infection, reduced antibiotic use, reduced the hours of mechanical ventilation, and reduced length of stay in the critical care unit. This study not only is evidence for the use of supplemental parenteral nutrition in the first week of critical care but is also further evidence favoring achievement of energy and protein intake targets.

Summary points

- Nutrition plays an important role in improving outcomes in critically ill patients.
- Evidence is accumulating that reaching protein and energy balance carries important benefits to these patients, including less infection, shorter length of stay, and reduced mortality.
- Energy requirements are predictable in about 75% of patients. It is not known whether this is sufficient accuracy or whether indirect calorimetry should be the standard way of determining energy needs. If indirect calorimetry is to be used, it needs to be repeated every 3 to 4 days to be more accurate than estimation methods.