

NUTRITION MANAGEMENT IN THE INTENSIVE CARE UNIT



Brian M. Hodges, Pharm.D., BCPS, BCNSP; and Joseph E. Mazur, Pharm.D., BCPS

Reviewed by Roland N. Dickerson, Pharm.D., FCCP, BCNSP; and H. William Kelly, Pharm.D., FCCP, BCPS

Learning Objectives

1. Distinguish between nutritional disorders occurring in starvation and critical illness.
2. Assess the nutritional status of adult patients in the intensive care unit (ICU).
3. Assess critically ill adults to determine the best route of nutrient delivery.
4. Develop an appropriate plan for the provision of enteral nutrition in critically ill adults.
5. Develop an appropriate plan for the provision of parenteral nutrition to critically ill adults.
6. Design a specialized nutrition support plan appropriate for the impact of common illnesses and/or injuries in the ICU.

Introduction

Malnutrition in the Intensive Care Unit

Nutrition management in the intensive care unit (ICU) is a vital part of the treatment of patients with critical illness and injury. Up to 50% of certain critically ill populations have preexisting nutritional disorders. Among the patients who are previously well nourished before ICU admission, nutritional disorders develop rapidly because of the metabolic demands of illness and healing, rapid fluid shifts, and the loss of specific vitamins and trace elements.

In the broadest sense, malnutrition in the ICU represents the deficiency or excess of energy, protein, vitamins, or minerals. These disorders may occur independently, or in any combination, depending on the clinical state of the patient. Malnutrition in critical illness results in loss of body cell mass, alterations in mineral homeostasis, and derangements in organ system function. Typical manifestations of these derangements in critically ill patients include impaired immune function, prolonged

dependence on mechanical ventilation, and increased rates of infection. These effects often are difficult to differentiate from the concurrent illness and injury, but attempts must be made by practitioners to identify and correct nutritional disorders because they render patients vulnerable to infectious complications, increased health care costs, and lead to increased patient morbidity and mortality.

Nutrition Support Goals

The provision of specialized nutrition support to patients in the ICU is a complex and sometimes daunting task. Nutrition support benefits critically ill patients by facilitating wound healing, ameliorating the maladaptive metabolic response to injury, maintaining the structure and function of the gastrointestinal tract, and decreasing overall morbidity. Although nutrition support can prevent the morbidity and mortality associated with prolonged malnutrition, the use of either parenteral nutrition (PN) or enteral nutrition (EN) can cause mechanical, infectious, and metabolic complications. Clinicians providing nutrition support in the ICU do so with the goals of improving patient outcomes. Surrogate markers used in assessing these outcomes include preserving lean body mass, treating or preventing micronutrient or macronutrient deficiencies, and preventing complications associated with the provision of nutrition support.

Physiological Changes

Starvation

Protein energy malnutrition varies greatly between healthy individuals and patients with critical illness or injury. Healthy individuals experiencing starvation adapt to this state through the use of nutritional reserves. Restricted access to nutrients results in a reduction in resting energy expenditure (REE) and urinary nitrogen excretion. The degree of decrease in REE is determined by the severity of

Abbreviations in this Chapter

BEE	Basal energy expenditure
EN	Enteral nutrition
ICU	Intensive care unit
PN	Parenteral nutrition
REE	Resting energy expenditure

calorie restriction and the duration of that restriction. Typically, human beings maintain stores of glycogen in the liver that may be used to provide the glucose vital to the function of the brain. However, these stores are depleted in about 24 hours. In unstressed patients, protein stores are sufficient to meet the body's needs for about 30 days, though this severity of restriction would cause death well before all this protein has been used. In the setting of caloric restriction, the only other source of energy to be used is fat, which is calorically dense and may be used without serious sequelae. In a starving patient, the oxidation of these fat stores provides energy. The use of fat for energy production allows for the relative sparing of protein use. However, fat cannot be used to produce glucose. Early in starvation, hepatic gluconeogenesis from protein breakdown is a major source of glucose. As the starved state continues over longer periods, the body acts to preserve muscle mass by decreasing nitrogen excretion and increasing the production of ketones that the brain can use as a source of energy. The use of lipids as a major source of energy continues until fat stores are greatly diminished. Because of the caloric density of fat, the loss of body weight for the degree of energy produced is minimized.

Critical Illness

Ebb and Flow Physiology

The metabolic response to critical illness or injury is quite different from the response to starvation. This response has classically been discussed in two phases, the ebb and flow. In the first hours to a couple of days after injury, the ebb phase is marked by hypometabolism and increases in the activity of the sympathetic nervous system and hypothalamic-pituitary axis. The flow phase of critical illness is characterized by hypermetabolism, increased REE, proteolysis, gluconeogenesis, and lipolysis. These adaptations to severe physiological stress represent the body's survival mechanisms, activated to use nutrients to maintain organ systems and promote healing processes. The degree of this response is variable and depends on factors such as the type of insult, severity of insult, prior nutritional state of the host, and temporal relationship to any previous illness or injury. Numerous changes in the activity of chemical mediators are involved in the stress response to critical illness and injury. These include increases in the counterregulatory hormones cortisol, adrenocorticotropic hormone, epinephrine, and glucagon. Increased production of proinflammatory cytokines, such as interleukin-1, interleukin-6, and tumor necrosis factor, also play a role in the occurrence and magnitude of the stress response. Energy

expenditure may be increased to 150–200% of normal in the most severely injured or ill patients, whereas most patients in the ICU maintain REEs of 100–150% of normal.

Protein Metabolism

Protein loss is accelerated by increases in proteolysis. Even in the critical care setting, where protein and nonprotein substrates are provided, negative nitrogen balance can be an expected result. Urinary nitrogen excretion can exceed 15–20 g/day. The excessive protein catabolism occurs because of not only gluconeogenesis, but also thermogenesis, immune function, acute phase protein synthesis, and tissue repair. These processes may result in a substantial loss of body protein within a relatively short duration of ongoing critical illness. Body composition studies in critical illness have revealed that a majority of these losses occur in skeletal muscle. Most experts recommend that protein be given as amino acids at a rate of at least 1.5–2.0 g/kg/day.

Carbohydrate Metabolism

As previously discussed, glucose is a primary source of fuel for the brain. It also provides energy for immune function, red blood cells, bone marrow, and for the healing wound. Hyperglycemia is highly prevalent among critically ill patients, which occurs because of resistance in peripheral muscle to the effects of insulin despite increased insulin secretion in concert with increased rates of gluconeogenesis and increases in counterregulatory hormones. The catabolism of protein is a major source of the glucose produced in critical illness. Administering exogenous carbohydrate to these patients does not suppress the gluconeogenesis as it does in healthy patients, and it may further exacerbate hyperglycemia. The degree and control of hyperglycemia in the ICU are being revealed as increasingly important to predicting outcomes related to critical illness. The maximum rate of glucose oxidation in critically ill patients is about 5 mg/kg/minute. Administering glucose in excess of this rate leads to lipogenesis, hepatic steatosis, and hyperglycemia. These effects are why carbohydrate administration should be limited to 50–60% of daily calories and delivered at no more than 5 mg/kg/minute.

Lipid Metabolism

Lipid metabolism also is altered in critical illness. Lipolysis is accelerated because of increased adrenergic stimulation. This increase in lipolysis is not suppressed by hypercaloric carbohydrate administration. The rate of turnover of glycerol and free fatty acids increases and reflects the degree of acceleration in lipolysis because of stress. The concentrations observed indicate increases in re-esterification of free fatty acids to triglyceride concentrations and increased lipolysis of triglyceride concentrations to free fatty acids. The contribution of fat oxidation to energy production is increased in critically ill patients. The fatty acids liberated by lipolysis are oxidized as a primary source of adenosine triphosphate during stress. In patients fed parenterally, lipid emulsion must be provided to prevent the development of essential fatty acid deficiency. In general, preventing such a deficiency requires

1.2–2.4 g/kg/week of lipid to maintain a triene-tetraene ratio greater than 0.2.

Fluid Changes

Fluid and electrolyte changes are a constant challenge to critical care practitioners. Critical illness predictably results in gains in total body water. Whether it is from fluid resuscitation or perioperative fluid loading, critically ill patients experience a 15–20% increase in extracellular water. The degree of fluid overload depends on the type and severity of illness or injury, the amount of exogenous fluid administered, and patient age. This change in volume status remains present even after patients have been stabilized. Older patients tend to take longer to resolve this excess extracellular water than younger patients.

Electrolyte Changes

Electrolyte derangements are common in patients in the ICU. The clinical manifestations of these abnormalities include arrhythmias, gastrointestinal dysfunction, and mental status changes. The goals of fluid and electrolyte therapies in the ICU are to maintain normal serum concentrations. Potassium, magnesium, and phosphorus are particularly important in critically ill patients because they are involved in processes that maximize protein anabolism.

Nutritional Assessment

With the ultimate goal of providing nutritional support and minimizing the loss of lean body mass in burns, major trauma, sepsis, acute respiratory distress syndrome, and other forms of critical illness, nutritional screening and assessment should take place in every patient in the ICU. Many complex processes occur simultaneously in critically ill patients, and they must be considered both clinically and metabolically.

Clinical Assessment

Weight History

Although difficult to obtain in critically ill patients, an accurate usual body weight and weight change history may be useful as prognostic markers. Fluid shifts, resuscitation, leaky capillary syndrome, and excess drainage contribute to inaccuracies that make weight a less useful monitoring parameter in patients in the ICU. Involuntary weight loss of more than 5% over 1 month or 10% over 6 months in critically ill patients is the most common marker used that correlates with increased morbidity and mortality. However, interpretation of weight history may be difficult in patients whose acute illness has prompted rapid fluid shifts before admission (vomiting, diarrhea, and heart failure). When an accurate body weight and height have been measured, the body mass index ($\text{weight [kg]} \div \text{height [m]}^2$) may be calculated. The body mass index provides clinicians with useful information in interpreting the patient's body composition, whether underweight (body mass index less than 18.5) or obese (body mass index of 30 or more). The body mass index also may serve as a prognostic indicator. For example, in a severely underweight patient, a body mass index less than 14 would be associated with a low

probability of survival. See the Overweight and Obesity chapter.

Because patient weight is an unreliable marker of changing nutritional status in the ICU, it would be useful to have a tool to assess body composition. Bioelectrical impedance analysis is a technique that uses the impedance of body tissue to a low magnitude alternating current. Mathematical manipulation of the measured impedance is used to estimate total body water, fat-free mass, body fat, and body cell mass. Other similar techniques have been studied to assess intracellular and extracellular water. Although bioelectrical impedance analysis is an evolving and promising technique for nutritional evaluation in the ICU, the sensitivity of this technique to detect short-term nutritional changes is still in question. It also is not appropriate in patients with renal dysfunction or with gross edema.

Clinical History and Physical Examination

Closely related to the weight history and body composition assessment is a thorough physical examination of patients in the ICU. A thorough examination can reveal numerous problems of nutritional relevance, such as abnormalities in skin and mucous membrane appearance reflective of vitamin and mineral deficiencies, decubitus ulcers, diabetic foot ulcers, or ascites. A good history of the patient's eating habits and changes which may have resulted recently is important, along with a closer examination of the musculoskeletal system, which may reveal muscle wasting indicative of underlying chronic illness.

Bowel Function

Before clinicians initiate any form of nutrition, they must determine whether diarrhea, constipation, emesis, ileus (surgical, functional, or medical/pharmacological), or gastrointestinal bleeding precludes oral feeding if patients are not mechanically ventilated or hemodynamically unstable. Constipation can have a serious impact on the ability to absorb macro- and micronutrients from EN, and can be extremely uncomfortable for the patient. Emesis, if severe enough, can cause malnutrition and impact long-term nutritional status, as can ileus. Postsurgical ileus usually is self-limiting and only lasts about 4 days in the average patient; however, there are reports of postoperative ileus lasting 7–14 days. The time lines on a medical/pharmacological ileus are variable, making it difficult to ascertain when to initiate EN. Active gastrointestinal bleeding may prevent initiation of EN as well.

Injury and Illness Type and Severity

Patients with comorbidities, such as cirrhosis or chronic liver disease, chronic renal failure, diabetes mellitus, congestive heart failure, chronic obstructive pulmonary disease, cancer, or human immunodeficiency virus, may be predisposed to even greater catabolic breakdown of protein and gluconeogenesis when a critical insult occurs. Sepsis or the systemic inflammatory response syndrome causes the release of inflammatory mediators or cytokines (tumor necrosis factor and interleukins), potentiating the observed metabolic alterations. It is the combination of these

derangements coupled with chronic disease(s) that makes nutritional assessment such a challenging part of supportive care. The most critical injuries, such as burns (second or third degree), major trauma (including long bone fractures and traumatic head injury), sepsis and septic shock, require nutritional intervention as expeditiously as clinically feasible with the goal of minimizing further protein loss.

Laboratory Assessment

Serum Proteins

Serum protein concentrations frequently are used as markers of nutritional state in the ICU. Proteins most frequently monitored are albumin, prealbumin (also known as transthyretin or thyroxine-binding prealbumin), retinol-binding protein and transferrin.

Albumin

Albumin, found both intravascularly and extravascularly, is the most widely studied serum protein marker. It is the only one of the monitored proteins for which a decreased concentration on admission (less than 2.5 g/dl) has been correlated with increasing mortality. Serum albumin is a good prognostic marker but a poor marker of nutritional recovery because of its long half-life (18 days) and large body pool. The normal concentration range of albumin is 3.5 g/dl to 5 g/dl.

Prealbumin

Prealbumin, with a normal range of 17 mg/dl to 40 mg/dl, is a transport protein for thyroxine and vitamin A. Prealbumin circulates as a complex with retinol-binding protein. With a half-life of 2–3 days, prealbumin is an effective short-term monitoring parameter for nutritional support. Factors which account for concentrations below 11 mg/dl or when prealbumin does not increase despite nutrition support are reprioritization of protein production by the liver during the stress response, concomitant diseases (hepatic failure), or inadequate caloric/protein provision. Drugs, such as corticosteroids, and renal failure may lead to increased concentrations of prealbumin that do not reflect nutritional repletion. Prealbumin concentrations also may be increased secondary to partial catabolism and impaired degradation in patients with renal dysfunction. These increases do not totally negate the value of monitoring prealbumin. The increase simply means that the evaluation of the trend in concentration is of more value than assessing individual measurements. Because of its favorable characteristics, feasibility of collection, and awareness of limitations, prealbumin is the currently preferred serum protein marker for assessing short-term nutritional changes in the ICU.

Retinol-binding Protein

Retinol-binding protein has a small body pool size and short biologic half-life (12 hours), which makes it a good short-term marker of nutrition. Retinol-binding protein circulates in plasma with plasma transthyretin, and has a binding site for one molecule of retinol. However, renal dysfunction affects the clearance of retinol-binding protein, thereby decreasing its usefulness in critically ill patients.

Transferrin

Transferrin binds and transports the ferric ion, is synthesized in the liver, and has a half-life of 8–9 days. Transferrin concentrations have been used as a predictor of morbidity and mortality, with concentrations less than 100 mg/dl indicative of severe serum protein depletion, 100–150 mg/dl suggestive of moderate depletion, and values of 150–200 mg/dl, indicating mild nutritional depletion. In periods of physiological stress, this marker may not be reflective of nutritional repletion because of reprioritization of hepatic protein synthesis. It also is important to note that transferrin is elevated in states of iron deficiency secondary to increased hepatic synthesis.

Overall, these serum protein markers can be used independently or in combination with nitrogen balance to assess the aggressiveness of protein repletion necessary. The usefulness of these serum protein markers in assessing nutritional status is limited by a lack of research correlating protein concentrations with clinically important outcomes, by decreased protein synthesis that may occur in patients with hepatic dysfunction, and by decreased protein clearance that may occur in patients with renal dysfunction.

Nutritional Requirements

Energy Requirements

Energy expenditure of critically ill patients depends on the underlying disease state of the patient, nutritional status before injury or illness, and the degree of stress incurred. For the patient with critical illness, increases in oxygen consumption and REE are to be expected. Critically ill patients typically have REEs up to 150% of predicted values, except for patients with head injury or thermal injury in whom even greater increases are observed.

Weight-based estimates or predictive equations for assessing energy needs for patients in the ICU traditionally have been used; however, they should be used with caution.

Predictive Equations

Basal energy expenditure (BEE) is the energy expended by the body in the resting state under basal conditions, varying with the weight of the individual and as a function of body surface area. Resting energy expenditure relates to BEE by adding the thermogenesis from nutrient assimilation, as well as from fever and sepsis. About 200 equations have been derived to predict BEE or REE. Age, height, weight, sex, and clinical condition are factors involved in predicting energy output in patients in the ICU. Studies have shown that most predictive equations tend to overestimate REE by an average of more than 1000 kcal/day. With the current emphasis on avoiding overfeeding, the clinical usefulness of these equations must be carefully considered.

Harris-Benedict Equations

The BEE can be estimated by using one of these two formulas, one for men and women.

$$\text{Men} \quad \text{BEE} = 66 + [13.8 \times \text{weight (kg)}] + [5 \times \text{height (cm)}] - (6.8 \times \text{age})$$

$$\text{Women BEE} = 655 + [9.6 \times \text{weight (kg)}] + [1.8 \times \text{height (cm)}] - (4.7 \times \text{age})$$

These equations do not take into consideration either activity or stress factors that vary based on injury type and infection, but were developed in healthy volunteers in a fasting, resting state. A commonly used method of estimating energy needs in an average patient in the ICU is 1.2–1.3 times the BEE. This estimate has limitations, including what effects drugs may have (neuromuscular blockers or sedatives may decrease REE), overestimation of actual energy expenditure (as determined by various studies of critically ill patients where time after acute injury may affect REE), and severity of illness (lack of correlation of Acute Physiology and Chronic Health Evaluation II score and estimated REE). The major criticism for use of the Harris-Benedict equations is their limited applicability to clinical practice in critically ill patients. Many modifiers to the Harris-Benedict equations have been developed to account for activity and stress. These stress factors are observer-dependent and do not accurately estimate patient needs compared to indirect calorimetry. It typically is not recommended that the Harris-Benedict equations, with or without modifiers, be used to estimate energy needs in the ICU.

Ireton-Jones Equations

Another set of predictive equations for energy expenditure assessment in critically ill patients is the Ireton-Jones energy equations. These equations provide a lower estimated caloric requirement than the modified Harris-Benedict equations and, in certain critically ill patient populations, have been validated as being more accurate. Their development also included obese patients (body mass index 27–40 kg/m²). These equations estimate energy needs based on patient sex, trauma or burn injury, and whether the patient is mechanically ventilated or spontaneously breathing.

$$\text{EEE(s) in spontaneously breathing patients} = 629 - 11 (\text{age in years}) + 25 (\text{weight in kg}) + 609 (\text{obesity})$$

$$\begin{aligned} \text{EEE(v) in ventilator-dependent patients} &= 1784 - 11 (\text{age in years}) + 5 (\text{weight in kg}) + 244 (0 = \text{female}, 1 = \text{male}) \\ &+ 239 (\text{trauma diagnosis}; 0 = \text{absent}, 1 = \text{present}) \\ &+ 804 (\text{burn diagnosis}; 0 = \text{absent}, 1 = \text{present}) \end{aligned}$$

EEE = estimated energy expenditure.

Despite Ireton-Jones energy equations' greater validity than the Harris-Benedict equations, their use has decreased relative to other predictive methods and weight-based energy provision.

Other Equations

Other equations that have been compared to indirect calorimetry include the Frankenfield and Penn State equations (studied in trauma, surgical and medical ICUs, and patients with sepsis) and the Swinamer equation (mechanically ventilated critically ill patients). There are factors that should be considered with the use of any of these equations. The Frankenfield equation, developed in trauma and sepsis, tends to estimate higher energy requirements. The Swinamer and Penn State equations have variables that are common apart from height, weight, and age. Respiratory rate, tidal volumes, and temperature are used. The Swinamer equation includes body surface area as well, but is not widely used in clinical practice. The accuracy and precision of any of these equations in predicting energy needs compared to indirect calorimetry are open to question. Unless recalculated frequently, equations also do not take into account changes in patient condition and, therefore, energy requirements. With these limitations, and the data showing equations as a whole tend to overestimate patient needs, a careful assessment of the methods used to validate an equation and the population in which this was done would be necessary before using it clinically. Because of these factors, some clinicians avoid predictive equations.

Weight-based Estimates

Recommendations for estimating energy expenditure have been presented in numerous clinical trials, reviews, and clinical practice guidelines. The American College of Chest Physicians recommends administering 25 kcal/kg/day. Most clinicians implement total energy provision of 25–35 kcal/kg/day across different ICU populations. The current thinking on caloric provision to critically ill patients is to meet patients' needs, but to avoid overfeeding as long as adequate protein is provided to maintain or replenish lean mass. Complications such as fatty liver infiltration with cholestasis, hyperglycemia, and prolonged mechanical ventilation from excess carbon dioxide production are problems that can arise when more than 40 kcal/kg/day are administered. Patient obesity is a factor that needs to be addressed increasingly when estimating patient energy needs in the ICU. Traditionally, an adjusted body weight calculation of:

$$\text{ideal body weight} + 0.25(\text{actual body weight} - \text{ideal body weight})$$

has been used in patients weighing more than 120% of their ideal body weight. Recent data in obese patients have shown that an adjusted body weight equal to the ideal body weight plus 50% of excess body weight may be used to more accurately estimate energy needs. An increasingly accepted strategy for obese patients is to use a hypocaloric, high-protein nutritional feeding intervention, wherein goal

MacDonald A, Hildebrandt L. Comparison of formulaic equations to determine energy expenditure in the critically ill patient. *Nutrition* 2003;19:233–9.

Frankenfield DC, Smith JS, Cooney RN. Validation of 2 approaches to predicting resting metabolic rate in critically ill patients. *JPEN J Parenter Enteral Nutr* 2004;28:259–64.

Patino JF, Pimiento S, Vergara A, Savino P, Rodriguez M, Escallon J. Hypocaloric support in the critically ill. *World J Surg* 1999;23:553–9.

Barak N, Wall-Alonso E, Sitrin MD. Evaluation of stress factors and body weight adjustments currently used to estimate energy expenditure in hospitalized patients. *JPEN J Parenter Enteral Nutr* 2002;26:231–8.

energy provision is about 20 kcal/kg of adjusted body weight.

Indirect Calorimetry

A patient's energy expenditure is most accurately assessed by using indirect calorimetry by a metabolic cart. Indirect calorimetry measures oxygen consumption and carbon dioxide production. The measurements, taken at 30-minute intervals, are then extrapolated to determine 24-hour energy expenditure. The benefit of indirect calorimetry for critically ill patients is that energy expenditure is measured, rather than estimated as with predictive equations. In addition to the REE, the respiratory quotient also is calculated as carbon dioxide production ÷ oxygen consumption. This ratio is an indicator of substrate oxidation, ranging from about 0.7 to 1 or more. At least in part due to metabolic changes because of stress and increases in oxygen consumption in critically ill patients, it is unusual for observed respiratory quotients greater than about 0.9, which would be indicative of overfeeding total calories. Overfeeding may lead to prolonged mechanical ventilation because of the excessive production of carbon dioxide. Although many clinicians consider an elevated respiratory quotient to be the result of an excessive proportion of carbohydrate calories delivered, studies reveal that hypercaloric nutrition support leads to increased carbon dioxide production, regardless of the relative proportion or fat and carbohydrate calories delivered. This is in contrast to stable mechanically ventilated patients who received three eucaloric nutritional regimens with variable carbohydrate-fat ratios, and had no significant changes in carbon dioxide production. A respiratory quotient of 0.7 indicates predominant fat use. The usual target respiratory quotient, reflecting a state of mixed substrate oxidation, is about 0.85. Various analyses have shown that respiratory quotient reflected substrate use accurately in 77% of studies assessed by indirect calorimetry.

Indirect calorimetry has its limitations. It requires trained personnel and specialized equipment; therefore, interoperator differences need to be addressed. Indirect calorimetry should occur under steady-state conditions, avoiding involuntary skeletal muscle activity, occurring in a rested or thermoneutral environment for at least 30 minutes, and without changes to feeding formulas surrounding the study. Ventilator changes and fraction of inspired oxygen stability should be demonstrated, along with chest tube or other ventilatory leaks excluded, and any supplemental oxygen provided. Finally, drugs that can impact energy expenditure and nutritional supplementation during the study need to be noted.

Indirect calorimetry should be recommended to assess patients who may be receiving excessive total calories or in whom estimating energy needs is more difficult.

Protein Requirements

Each gram of nitrogen lost correlates to the loss of 30 g of lean tissue, with the majority of loss coming from skeletal muscle. The goal in providing protein to critically ill patients should be to limit protein catabolism.

Most patients in the ICU require the provision of at least 1.5–2 g/kg/day of protein. Protein needs of enterally fed critically ill patients should be addressed first, then the total calories determined. A controversy exists over whether to include protein calories or separate them from total energy requirements. Most practitioners would include the 4 kcal provided by each gram of protein as part of the total energy calculation.

Acute renal failure and renal replacement therapies require a careful assessment of the clinical state of the patient and the interventions being made to determine the best provision of protein. Patients with acute renal failure who are not dialyzed should be given 0.5–0.8 g/kg/day, with titration based on changes in blood urea nitrogen. Patients receiving hemodialysis should receive about 1.2 g/kg/day. With the increasing use of continuous renal replacement therapies, this mode of therapy leads to even greater loss of amino acids than other forms of dialysis. Patients receiving continuous renal replacement therapies should be given 1.5–2.5 g/kg/day, titrated based on changes in blood urea nitrogen and changes in nitrogen balance. Recent studies indicate that administering protein at doses that achieve positive nitrogen balance has a positive effect on patient outcome. Patients receiving continuous renal replacement therapies require fewer total calories from feeding regimens because of dextrose retention from dialysate. Therefore, it is recommended that they be given 20–25 kcal/kg/day.

Weight Determination

The patient weight that is used to calculate protein requirement depends on whether the patient is obese. For patients whose total weight is at or near their ideal body weight, then total weight should be used. For patients who are malnourished or below their ideal body weight, ideal body weight should be used. For obese patients, as discussed previously, the use of a hypocaloric, high-protein regimen can be used instead of debating adjusted body weight calculations. With these regimens, goal protein provision is about 2 g/kg of ideal body weight. This approach results in decreases in length of ICU stay and antimicrobial use, with no differences in nutritional markers or mortality when compared with traditional feeding regimens.

Nitrogen Balance

Nitrogen balance assessment is the standard technique used to assess the adequacy of protein provision. The goal of protein provision in critically ill patients is to maintain a positive nitrogen balance of 2–4 g/day; however, this frequently cannot be achieved. In many critically ill

Dickerson RN, Boschert KJ, Kudsk KA, Brown RO. Hypocaloric enteral tube feeding in critically ill obese patients. *Nutrition* 2002;18:241–6.

Scheinkestel CD, Kar L, Marshall K, et al. Prospective randomized trial to assess caloric and protein needs of critically ill, anuric, ventilated patients requiring continuous renal replacement therapy. *Nutrition* 2003;19:909–16.

patients, the goal is revised to minimize the degree of negative nitrogen balance.

Nitrogen balance requires a timed collection of urine over 24 hours, which is analyzed for urea nitrogen loss, and knowledge of the amount of protein provided to the patient during the collection period. From the results of the urine collection, clinicians may calculate a nitrogen balance by simply subtracting the amount of nitrogen lost from the amount provided. This balance is most commonly calculated as

$$\text{nitrogen balance} = (\text{protein intake [g/day]}) / 6.25 - \text{urine urea nitrogen (g/day)} - 4 \text{ (g/day)}.$$

This equation assumes that the protein source used is 16% nitrogen, which may need to be reassessed for different protein sources. The 4 g/day in the equation represents non-urea nitrogen lost through the urine (2 g) and through the stool, integument, and insensible losses (2 g). This 4 g/day factor must be reevaluated in certain clinical situations, wherein it may underestimate the true degree of nitrogen loss. Patients with diarrhea, enterocutaneous fistulae, and drain losses may lose significantly greater amounts of nitrogen than 2 g/day. Patients with thermal injury have increased integumentary nitrogen losses. In highly catabolic patients (more than 30 g urinary urea nitrogen loss/day), it has been recommended that non-urea nitrogen losses are more accurately estimated as 6 g/day. Finally, in patients with evolving renal dysfunction, the calculation of nitrogen balance requires that accumulation of urea nitrogen in the blood be accounted for in assessing the total daily nitrogen losses of the patient. The calculation for urea nitrogen accumulation over 24 hours is:

$$\text{urea accumulation (g/day)} = 0.6 \text{ (L/kg)} \times \text{initial weight (kg)} \times [\text{final BUN} - \text{initial BUN}] \times 0.01 + [(\text{final BUN} \times 0.01) \times (\text{final weight} - \text{initial weight})].$$

BUN = blood urea nitrogen.

Practical limitations to the accuracy of nitrogen balance assessment include inadequate urine collection, drugs that may alter nitrogen excretion in the urine, and inaccuracy in the estimation of non-urea nitrogen loss.

Fluid Requirements

Fluid needs in critically ill patients may vary greatly. The goals of fluid administration are to maintain adequate urine output and electrolyte concentrations. Daily fluid needs in adults are estimated to be 30–40 ml/kg/day, with decreasing needs as patients age. Fluid needs also may be calculated using the Holliday-Segar method where the minimal daily fluid requirement equals 100 ml/kg for the first 10 kg of weight, an additional 50 ml/kg for 11–20 kg, and an additional 20 ml/kg/day for every kg greater than 20 kg. However, many factors affect fluid needs. Fluid needs are increased in patients with fever, severe sweating, hyperventilation, and losses of fluid because of nasogastric suctioning or enterocutaneous fistula output. Third spacing of fluids also necessitates adjustment of total fluid replacement. Although total body water is unchanged, the

effective intravascular volume may be decreased. Hydration may be difficult to assess in many critically ill patients and invasive monitoring of hemodynamic parameters and fluid status may be necessary. Patients with renal, hepatic, or cardiac dysfunction may have reduced fluid needs because of volume overload inherent with the pathophysiology of organ system dysfunction. Because of the large volume of other intravenous fluids frequently required in the ICU, and the data showing the degree of fluid overload common in these patients, nutrition support formulations may frequently need to be maximally concentrated.

Electrolyte Requirements

Specific recommendations for electrolyte requirements in patients in the ICU cannot be made because of a lack of evidence. Therefore, electrolyte assessment must be conducted on an individual basis for each patient and should be based on established norms. The goal of electrolyte administration in the ICU is to maintain adequate serum concentrations. Specific attention must be paid to intracellular electrolytes, phosphorus, potassium, and magnesium, as they frequently are reduced in critically ill patients at initiation of nutrition support.

Vitamin and Trace Element Requirements

No specific guidelines are available for the requirements of vitamins and trace elements in patients in the ICU. As part of any nutrition support regimen, patients should be given vitamins and minerals, regardless of the administration route. These micronutrients should be administered in doses to meet recommended daily allowance, dietary reference intake, or the American Medical Association National Advisory Group parenteral vitamin and mineral recommendations. The goal of this supplementation is to optimize the use of macronutrients and support the integrity of the body's defenses.

There are critically ill populations that require alterations in trace element administration. Patients suffering from the most severe metabolic insults or who suffer excessive gastrointestinal fluid losses require additional zinc supplementation. Removing selenium from parenteral nutrition formulations is recommended for patients with renal dysfunction who are not receiving dialysis. Patients with cholestatic liver disease should not receive chromium or copper to avoid toxicities because of decreased hepatobiliary clearance.

Nutritional Intervention

Timing of Intervention

The optimal time to initiate nutrition support in critically ill patients is unknown. The American Society for Parenteral and Enteral Nutrition recommends that beginning nutrition support within 5–10 days is reasonable in critically ill patients, based on data extrapolated from studies of patients undergoing surgery.

Many studies have examined the utility of early initiation of EN in critically ill patients. Initiation of EN within 36 hours of admission to the hospital or within 36 hours after surgery is associated with a decrease in infectious

complications and a reduction in length of hospital stay. However, these data should be interpreted carefully because of significant heterogeneity in results among studies. Similar analyses have shown that EN started within 24–48 hours results in a trend toward decreased mortality when compared to delayed nutrient intake. Similarly, a trend toward a reduction in infectious complications has been observed in patients randomized to early EN when compared to delayed nutrient intake. In studies reporting nutritional indices, such as calorie intake, protein intake, percentage of goal feeding achieved, and improvement in nitrogen balance, early EN is associated with improved results relative to control groups. Therefore, it is recommended that critically ill adults be initiated on EN within 24–48 hours, assuming that they are adequately resuscitated and hemodynamically stable. However, starting later may be advantageous in certain patient populations. Although not uniformly, many studies comparing PN to intravenous fluids and progression to oral diet as tolerated have revealed no difference in mortality between the two groups. However, PN was associated with an increase in mortality and complications in studies of critically ill patients, as opposed to studies looking at postoperative patients. Preoperative PN is beneficial for malnourished patients undergoing surgery who cannot be fed enterally.

The initiation of PN early after surgery in patients who cannot be fed enterally and who have not received PN preoperatively has not been associated with improvements in clinical outcome. Indeed, some studies have shown a higher complication rate in patients fed parenterally compared to those who were not fed. Thus, some have suggested delaying the initiation of PN for 5 days after major surgery or presentation with acute pancreatitis. This recommendation is made to avoid complications of PN when initiated at the height of the stress response in these patient populations. However, the decision to delay PN must be made with serious consideration to the patient's preoperative nutritional status and severity of illness. It is inappropriate to delay feeding of a patient who is already malnourished or who is highly catabolic.

Route of Intervention

During the past 10–15 years, many studies have been conducted to determine the optimal route of nutrient administration in critically ill patients. These studies have resulted in a major push toward the use of EN whenever possible.

Physiology

Numerous studies in animals, and a small number in humans, have shown the detrimental effects of prolonged disuse of the gut that occurs in patients fed parenterally. The gut is a major immune organ, and dysfunction and disuse increase the incidence of numerous complications. Disuse of the gut results in atrophy of the villi lining the intestines, a decrease in gut motility, and decreased secretion of bile salts and secretory immunoglobulin A. These changes are associated with decreased barrier function and a greater degree of bacterial translocation from the gut to the systemic

circulation. In addition, hypoperfusion injury to the gut as a result of disuse leads to increased antigen exposure and gut macrophage activation. This priming of the immune system has been hypothesized as a means to increase the production of inflammatory mediators that are associated with sepsis and multiorgan failure. Through these mechanisms, feeding parenterally results in an exaggerated stress response relative to EN in volunteers who were subsequently exposed to *Escherichia coli* endotoxin. Parenterally fed patients also have increased protein catabolism compared to those fed enterally.

Clinical Studies Comparing EN to PN

Studies noting clinical differences between critically ill patients fed parenterally and enterally have been conducted in several different ICU populations. Differences in outcomes between these modes of nutrition support seem to depend on a variety of factors. The patient population being studied, the risk of malnutrition among study patients, and the degree of illness or injury of study patients all seem to affect the degree of benefit and/or risk measured for the different routes of nutrient administration.

Several studies have examined the impact of route of nutrition support in patients with acute pancreatitis. In this population, differences in clinical outcomes have been related to the severity of illness. In a study of patients with less severe pancreatitis (fewer local complications, fewer Ranson criteria present, and lower Acute Physiology and Chronic Health Evaluation II scores), no difference was observed in safety and nutritional outcomes. However, EN delivered into the jejunum has been associated with fewer infectious complications and with attenuating the acute phase response in patients with more severe pancreatitis. Feeding patients with pancreatitis enterally also is associated with lower costs than PN, regardless of disease severity.

A systematic review of randomized, controlled studies comparing EN and PN in the ICU also was published recently. It did not find a decrease in mortality in patients fed enterally, but EN was associated with a reduction in infectious complications compared to PN.

Overall, there appears to be a clinically significant benefit to feeding patients enterally. Improved outcomes have been demonstrated in a variety of populations, including major abdominal trauma, head injury, major surgery, and acute pancreatitis of varying degrees of severity. In addition, decreased costs, safety, and the feasibility of providing EN are cited as reasons to promote its use. Thus, the American College of Chest Physicians, the American Society for Parenteral and Enteral Nutrition, and the Canadian Critical Care Guidelines Committee all support the use of EN over PN, whenever adequate nutrient administration by EN is possible.

However, these recommendations do not mean that PN is universally detrimental or should not be used in appropriate patients. As previously discussed, there are studies in defined situations and populations in which PN decreased morbidity and mortality.

Marik PE, Zaloga GP. Early enteral nutrition in acutely ill patients: a systematic review. *Crit Care Med* 2001;29:2264–70.

In patients who cannot, or should not, be fed enterally, PN is preferred. The American Society for Parenteral and Enteral Nutrition has set forth criteria to help clinicians determine when patients should be fed parenterally. These criteria include patients who have not tolerated EN despite the placement of enteral access beyond the pylorus, disease states in which EN is contraindicated (high-output distal enterocutaneous fistulas or intestinal obstruction), and in patients who cannot be fed enterally in whom wound healing or recovery will be jeopardized if nutrition is not provided within 5–10 days.

Some experts also suggest that PN be used in combination with EN in patients who are not able to receive adequate nutrients by EN alone. Patients are more likely to receive a higher percentage of prescribed nutrients by PN than EN, for many clinical and practical reasons. The use of adjuvant PN in critically ill patients to achieve goal caloric intake for the first 4–7 days increased visceral protein concentrations and reduced overall length of hospital stay by an average of 2.5 days compared to EN alone. However, the PN group did incur almost twice the cost per treatment course. Morbidity in the ICU and short- and long-term mortality were not different between the two groups. Although the use of PN to supplement EN is intriguing, there are not enough data to support its routine use. There is no evidence to support starting EN and PN simultaneously in critically ill patients, and not enough evidence to make a recommendation about when supplementing EN with PN is appropriate. It is recommended that every effort to maximize EN should be made before beginning supplemental PN.

Enteral Nutrition

Enteral Access

One of the first considerations in initiating EN in the ICU is the type of enteral access that is best, which depends on the type of illness or injury sustained by the patient, presence of gastric motility disorders, and the anticipated length of nutrition support in a given patient. Choices for enteral access include nasal or oral tubes placed in the stomach, duodenum, or jejunum, as well as percutaneous tubes placed in the stomach, duodenum, or jejunum either endoscopically or surgically. The decision to use percutaneous enteral access usually is made because of a longer anticipated need for EN. Some authors have advocated that percutaneous access be used for patients requiring nutrition support for more than 30 days.

Deciding whether gastric or small bowel feedings are best requires careful patient assessment. The placement of a large bore nasal or oral feeding tube into the stomach requires relatively little technical expertise and is less likely to result in tube blockage with the administration of EN or drugs. However, some patients should not or cannot be fed intragastrically. For example, patients with acute pancreatitis should not be fed intragastrically because gastric feeding stimulates the pancreas and is likely to cause worsening pancreatitis. In providing EN to patients with acute pancreatitis, enteral access distal to the ligament of

Treitz should be used for feeding. In addition, patients with impaired gastric motility should be monitored carefully for tolerance of nasogastric feeding.

Because a high proportion of critically ill patients have, or are at risk for impaired gastric motility, some clinicians routinely seek small bowel enteral access in patients in the ICU. The goal of this practice is to maximize caloric delivery by decreasing interruptions of EN because of gastric intolerance and to potentially decrease the incidence of pneumonia because of aspirated gastric contents. Many studies have sought to assess this practice by comparing the safety and effectiveness of routine use of nasoduodenal or nasojejunal EN in the ICU with nasogastric EN.

Initial trials failed to detect differences in cumulative gastric residuals and other indices of EN intolerance between nasogastric and nasojejunal placement. Because of the higher level of expertise needed to place enteral access into the jejunum, the mean time to achieve the desired access was significantly longer in the nasojejunal feeding group. However, no differences were noted in the clinical outcomes of the two groups. Cumulative caloric deliveries also were not different.

More recent systematic reviews also revealed no differences in nutrient delivery. However, there was conflicting evidence concerning risk of infection, with small bowel EN being associated with a decreased incidence of infection that was largely influenced by a single study.

Despite being controversial, routine use of small bowel EN is recommended in ICUs where the resources and facilities needed are available with relatively little difficulty. In institutions where gaining small bowel access is feasible, but with some difficulty, patients at high risk for EN intolerance should preferentially receive small bowel EN. These patients may include those receiving inotropes, continuous sedation, neuromuscular blockade, or with large volumes of nasogastric drainage. Small bowel access also should be considered in patients who are at a high risk for aspiration, such as patients with central nervous system injuries, those who are required to remain supine, or after gastrointestinal surgery. Finally, in institutions where small bowel enteral access is possible only with great difficulty, it should be sought only in patients with consistently high gastric residual volumes and those not tolerating intragastric EN.

Enteral Administration Techniques

Most institutions routinely administer EN, whether in the stomach or small bowel, by continuous infusion. Although intermittent EN is not feasible into the small bowel, it is a consideration for gastric feeding. Some experts have questioned whether intermittent EN administration may cause less pneumonia. The potential decrease in pneumonia incidence is thought to be because of rest periods between feeding episodes, allowing gastric acid production to resume and preventing the overgrowth of pathogenic bacteria in the stomach. Clinical studies to date have not demonstrated this benefit of continuous infusion intragastric EN. Another factor that may affect any differences in the

Bauer P, Charpentier C, Bouchet C, Nace L, Raffy F, Gaconnet N. Parenteral with enteral nutrition in the critically ill. *Intensive Care Med* 2000;26:893–900.

Marik PE, Zaloga GP. Gastric versus post-pyloric feeding: a systematic review. *Critical Care* 2003;7:R46–R51.

method of EN administration is the widespread use of antisecretory drugs to prevent upper gastrointestinal bleeding. There is not enough evidence to date to support any specific administration technique in patients receiving EN intragastrically.

Enteral Formula Selection

Most critically ill patients can be fed formulas with intact polymeric protein. Studies conducted comparing polymeric protein formulas with more elemental peptide-based formulas have failed to show a difference in clinical outcomes. No differences in caloric delivery have been observed with peptide-based formulas compared to polymeric EN. Although a meta-analysis of available studies revealed no difference in the incidence of diarrhea with peptide-based formulas, individual study results have noted a decrease in stool frequency with these more elemental products. Some authors advocate the use of peptide-based or semielemental formulas in patients who develop refractory diarrhea while receiving polymeric EN. Critically ill geriatric patients who are at a greater nutritional risk, as indicated by an albumin concentration less than 2.5 g/dl, tolerate a semielemental formula with fiber better than a polymeric formula. There is also a potential benefit for peptide-based formulas in patients with gastrointestinal complications, such as short bowel syndrome or pancreatitis. When considering the paucity of documented benefit in light of the increased cost of elemental or semielemental formulas, polymeric formulas should be used as long as they are tolerated.

Immune-enhancing Formulations

Throughout the past several years, many enteral feeding formulas have been developed that include ingredients that enhance immune function. These include the amino acids arginine and glutamine, nucleotides, such as antioxidants, fish or borage oils, and omega-3 fatty acids.

Arginine

The most commonly studied of these immune-enhancing products in ICU population are those enriched with arginine. Arginine is a nonessential amino acid that may become conditionally essential during periods of severe physiological stress. It also is a precursor to the production of nitric oxide, which is important for gastrointestinal function, vascular tone, and immune function.

Glutamine

Glutamine is the most abundant amino acid in healthy patients, but rapid depletion occurs during periods of physiological stress. Glutamine may become conditionally essential in critically ill patients. It functions by serving as a source of energy for enterocytes and colonocytes. It further enhances immune competence by promoting lymphocyte trophism. Finally, glutamine is involved in glutathione function as an antioxidant.

Several products with immune-enhancing ingredients, including arginine or arginine and glutamine, are

commercially available. Preliminary studies showed that arginine does affect immune function, support nitrogen retention, and modulate vascular perfusion. Early clinical trials of immunonutrition with arginine revealed no mortality benefit with these products, but decreased infectious complications, ventilator dependence, and length of hospital stay were noted. These benefits primarily were seen in patients undergoing surgery, and not in critically ill patients.

A meta-analysis of arginine-enhanced EN showed a decrease in infectious complications, but no difference in mortality. When studies with critically ill patients were analyzed as a separate subgroup, again no difference in mortality or infectious mortality was noted. Lower arginine-containing formulas were associated with increased mortality relative to studies with higher arginine content. When studies were analyzed based on methodological quality, studies of higher quality revealed an increase in mortality associated with immunonutrition.

On publication of this previously discussed immunonutrition meta-analysis, an interim review of an ongoing trial also reported increased mortality in patients with severe sepsis. Thus, the randomization of patients with sepsis was stopped and use of these products in patients with sepsis should be avoided. Some authorities recommend against the use of formulas supplemented with arginine in critically ill patients, but many clinicians continue to use these products in severely ill patients before the development of sepsis.

Not enough evidence exists to make specific recommendations about the general use of other immune-modulating supplements in critically ill patients.

Complications of EN

Mechanical Complications

Mechanical complications associated with EN include inadvertent tube removal, as well as tube kinking and clogging. Although numerous substances have been recommended for opening clogged tubes, warm water is preferred and is as effective as cranberry juice or cola. However, preventing clogged tubes is much more important. Fastidious tube care and flushing are vitally important. Careful selection of nutrient formulations and drugs to be put through tubes also is essential. Recent recommendations from the British Association for Parenteral and Enteral Nutrition aid clinicians in making sound decisions about drug administration by enteral feeding tubes. These recommendations include using soluble tablet, liquid, and injectable drug formulations when appropriate, and minimizing the use of crushed tablets, especially in smaller diameter postpyloric feeding tubes. Feeding tubes should be flushed with 30 ml of water before and after administering each drug. Finally, drugs should not be administered directly with enteral feeding.

Mechanical complications also occur that are related to the placement of enteral feeding tubes. Inadvertent intubation of the tracheobronchial tree has been reported to occur in up to 16% of naso- or orogastric tube placement

Bertolini G, Iapichino G, Radrizzani D, et al. Early enteral immunonutrition in patients with severe sepsis. Results of an interim analysis of a randomized multicentre trial. *Intensive Care Med* 2003;29:834–40.

procedures. The most serious procedural complication in enteric tube placement is leakage of gastric contents into the abdomen after percutaneous access procedures. This technical complication has been observed in up to 4% of patients, and is associated with a high level of morbidity and mortality.

Infectious Complications

Aspiration of gastric contents and the subsequent development of pneumonia are among the most serious infectious complications of EN. Aspiration pneumonia requiring antimicrobial therapy occurs in 1–4% of enterally fed patients. Recognizing risk factors for aspiration (altered mental status and gastrointestinal motility disorders), monitoring patients carefully, and maintaining patients in a head-up, inclined position are important to minimizing the occurrence of aspiration. The use of prokinetic drugs and small bowel EN should be considered in patients with a history or risk of aspiration. The routine use of coloring agents to aid in the detection of aspiration is not recommended because of a lack of sensitivity and the potential toxicity of dyes in patients with impaired gastrointestinal perfusion.

Other infectious complications of EN include percutaneous tube site infections and upper respiratory infections in patients with nasoenteric tubes. Percutaneous tube site infections have been observed in as many as 23% of patients. Attentive tube site care is the most important factor in minimizing this complication. Sinusitis and related upper respiratory infections, which are reported in 10–15% of patients fed through nasoenteric tubes, are best avoided by discouraging long-term use of nasal tubes.

Underfeeding and Therapy Interruptions

Underfeeding, although not exclusive to EN, is more likely to occur with this mode of nutrition support. Numerous studies report that reaching goal caloric delivery is less likely in patients fed enterally when compared to patients receiving PN. One recent study reported that about 76% of prescribed calories were delivered to critically ill patients receiving EN. Although this degree of underfeeding has not adversely affected patient outcomes or diminished the relative advantage of EN over PN, every reasonable effort should be made to achieve prescribed EN delivery. Underfeeding results in greater protein loss, loss of lean body mass, and slowed wound healing. Minimizing interruptions in EN delivery are necessary to achieve nutritional goals.

Feeding Protocols. Many professional bodies advocate the initiation of well-defined EN protocols as a means of optimizing delivery. Institutions implementing feeding protocols should ensure that the protocol selected uses parameters that optimize the delivery of EN to critically ill patients. For example, in one trial comparing two feeding protocols, one with a higher threshold for gastric residual volume in combination with prokinetic drugs achieved significantly fewer high residuals than a protocol with a lower threshold. No differences in complications were

Table 1-1. Antimotility Drugs

Drug	Mechanism	Adverse effects
Codeine	Opioid agonist	Sedation
Diphenoxylate/ atropine	Opioid agonist/ anticholinergic	Sedation, tachycardia, and dry mouth
Loperamide	Cholinergic/ noncholinergic neuronal alterations	Fatigue, nausea, and dry mouth
Tincture of opium	Opioid agonist	Sedation

noted. Others have stated that protocols that advance EN relatively rapidly are more effective and equally tolerated compared with slower titration. In addition to protocol use, interventions to maximize EN tolerance should be aggressively pursued to minimize time periods during which patients are not receiving nutrition support.

Diarrhea. Diarrhea is one of the more frequent causes of EN interruption. It is difficult to estimate the incidence of diarrhea in critically ill patients because reported definitions of diarrhea are widely variable. However, the most widely accepted definition uses the Stool Output Assessment Tool to quantify stool consistency and volume. However, patients in the ICU rarely develop diarrhea as a direct result of EN formula delivery. Systematic assessment of patients with diarrhea is important to prevent prolonged interruption of feeding. Other drugs being administered enterally should be reviewed carefully. Many patients in the ICU receive prokinetic drugs, magnesium supplements, or liquid preparations with high osmolarity or sorbitol content that may contribute to diarrhea. Patients also should be assessed for the presence of *Clostridium difficile*-induced pseudomembranous colitis. If these factors are not present, then consideration should be paid to changing the EN formulation. Switching to a peptide-based or a semielemental formula may be attempted in patients not tolerating polymeric formulas. Also, the addition of fiber to EN acts to add bulk to the stool and may have favorable effects on colonocytes. Finally, the addition of drugs that slow gastrointestinal motility may be used to increase contact time and absorption of nutrients and fluids. Table 1-1 lists some of the most commonly used drugs to slow gastrointestinal motility.

Delayed Gastric Emptying. Impaired gastric emptying is another common barrier to EN delivery. Most interruptions related to gastroparesis are avoidable with careful monitoring and management. Fear of aspiration has led many clinicians to enact policies that require temporary cessation of feeding for gastric residual volumes lower than that which has a deleterious effect on patient outcomes. Residual volumes of up to 200 ml are not associated with increased morbidity relative to lesser volumes. Also, the use of residual volume alone as a marker of feeding intolerance should be avoided. An isolated residual volume of 200 ml should not serve as a trigger for withholding EN. Gastric residuals must be considered in context with the abdominal examination, the presence of nausea and vomiting, and the passing of flatus and stool. Consistently high residual

De Jonghe B, Appere-De-Vechi C, Fournier M, et al. A prospective survey of nutrition support practices in intensive care unit patients: what is prescribed? What is delivered? Crit Care Med 2001;29:8–12.

Table 1-2. Prokinetic Drugs Used to Promote Gastric Feeding Tolerance

Drug	Mechanism of action	Dose
Erythromycin	Motilin receptor agonist	200–250 mg IV 3–4 times/day
Metoclopramide	Dopamine antagonist	10–20 mg IV 3–4 times/day

IV = intravenously.

volumes and/or other abnormalities in gastrointestinal function may necessitate further action.

Prokinetic Drugs. Prokinetic drugs may be given to patients with altered gastric emptying. Erythromycin and metoclopramide are two prokinetic drugs that have been studied in patients in the ICU receiving EN. Table 1-2 contains the mechanism of action of these drugs in promoting gastric motility, and commonly used dosages. Although both have been effective in promoting gastric motility, the use of prokinetic drugs has not yet been proven to decrease the incidence of pneumonia or decrease length of stay. The Canadian Critical Care Guidelines Committee recommends that metoclopramide be the preferred prokinetic drug in critically ill patients. This recommendation is based on the concern for the development of bacterial resistance with widespread use of erythromycin in the ICU. Some clinicians use erythromycin primarily, or in patients who do not respond to metoclopramide, but limit its duration of use to minimize patient exposure to antibiotic drugs.

Postpyloric Tube Placement. Another intervention that should be considered in patients with gastric intolerance of EN is the placement of a postpyloric feeding tube. The American Society for Parenteral and Enteral Nutrition and the Canadian Critical Care Guidelines Committee recommend this approach.

Parenteral Nutrition

Parenteral Access

Parenteral nutrition may be delivered through either central or peripheral intravenous access. Because of the nature of critical illness, patients in the ICU typically receive PN through central venous access. Numerous types of intravenous access devices and sites of insertion may be considered for central administration of PN. Common sites of insertion include the subclavian, internal jugular, and femoral veins. Each is associated with different levels of technical difficulty, patient discomfort, risk of infection, and risk of noninfectious complications.

Peripheral PN is less frequently used in the ICU, despite recommendations from some advocating the use of peripheral PN using rotating sites. To date, no evidence has been published to support an advantage to this method of administration. Peripheral PN also is limited by the tolerance of peripheral veins to formulations with high osmolarities. Peripheral PN formulations should not exceed 900 mOsm/L. In critically ill patients who are already hypervolemic, the amount of fluid needed to meet patients' needs with peripheral PN is likely to be prohibitive.

Administering PN

No definitive evidence exists to guide clinicians in the best way to administer PN, or how to advance PN to reach feeding goals. It has been recommended that no more than 150–200 g of carbohydrate should be given in the first day, and that this may be advanced as patients demonstrate metabolic tolerance. It is further recommended that, in patients with preexisting hyperglycemia, the initial PN not provide more than 100 g of carbohydrate in the first 24 hours, and that adding a basal amount of insulin therapy is reasonable. The amount of carbohydrate should not be advanced until blood glucose concentrations are consistently controlled for 24 hours.

Complications of PN

Administering PN through central venous access is associated with several mechanical and procedural complications. These include catheter obstruction, venous thromboembolism because of the presence of the venous access device (more common with femoral placement), and pneumothorax.

Catheter-related infection is a commonly encountered problem in patients receiving central PN. The size, type of material, and position of the catheter influence the probability of blood stream infection. Controversy exists about whether the use of single versus multiple lumen venous access devices results in different rates of infection. Strict aseptic technique is essential to minimize catheter infection, as is fastidious care of catheters already in place. Another practice aimed at decreasing bloodstream infection is the use of dedicated ports for PN administration, which is done to minimize the disruption of the intravenous line, which may allow a greater opportunity for bacterial contamination and growth.

Metabolic Complications

Overfeeding

Overfeeding, which may occur with any form of nutrition support, is a distinct risk in patients receiving PN.

Overfeeding Protein

Excessive protein administration is associated with azotemia and elevations in blood urea nitrogen. Patients with preexisting renal insufficiency, hepatic dysfunction, or hypovolemia are particularly at risk. The response to these changes is addressing the primary disease process if possible, but moderation of protein provision may be necessary. Periodic assessment of serum prealbumin concentration and nitrogen balance are recommended to help monitor the appropriateness of protein delivery.

Overfeeding Carbohydrates and Hyperglycemia

Carbohydrate intolerance can manifest in numerous complications in patients in the ICU. The liver may be affected, manifesting as hepatic steatosis or cholestasis. Lipogenesis and excessive carbon dioxide production also may result, which may lead to difficulty discontinuing mechanical ventilation.

Hyperglycemia is the most common complication of carbohydrate administration in the ICU, especially when rates of carbohydrate infusion exceed 5 mg/kg/minute. The

occurrence of hyperglycemia has had great impact outcome in the past several years. In the past, glucose concentrations typically were tolerated until they reached 180–220 mg/dl, where osmotic diuresis and volume depletion are likely to occur. However, intensive insulin therapy to maintain blood glucose between 80 mg/dl and 110 mg/dl has been associated with decreases in mortality, the percentage of patients requiring more than 10 days of antibiotic therapy, transfusion requirements, the length of ICU stay, and mechanical ventilation when compared with standard therapy.

It is recommended that intensive insulin to maintain blood glucose between 80 mg/dl and 110 mg/dl be considered in critically ill surgery patients, particularly after cardiovascular surgery. Although the results with intensive insulin therapy to maintain tight glucose control have not yet been replicated in other critically ill populations, they emphasize the importance of good glycemic control. It is recommended that a reasonable goal in these populations is to maintain blood glucose between 100 mg/dl and 150 mg/dl until further data are available.

Overfeeding Lipid

Overfeeding of fat calories is associated with dysfunction of the reticuloendothelial system, leading to the development of hypertriglyceridemia. Other potential complications include immunosuppression and hepatic steatosis. Some elevation in triglyceride concentrations is to be expected with nutrition support, especially PN, but excessive elevation requires moderation of fat delivery. Although the exact concentration requiring intervention has not been defined, the American College of Chest Physicians recommends that serum triglyceride concentrations be maintained at 500 mg/dl or less. The rate, and not just total daily dose, is associated with symptoms of lipid intolerance. It is recommended that the rate of lipid infusion not exceed 0.1 g/kg/hour. If significant hypertriglyceridemia occurs, lipid-free PN can be given or limiting the administration of lipids to 1–2 days/week may be appropriate. It also is important to evaluate whether other sources of lipid administration are present, such as propofol.

Refeeding Syndrome

Refeeding syndrome is another complication observed when severely malnourished patients or patients with cardiac or pulmonary failure receive nutrition support. The response to aggressive feeding in these populations is increased insulin release, leading to acute sodium and fluid retention; cellular uptake of glucose; and rapid intracellular movement of phosphorus, potassium, magnesium, and thiamine. Hypophosphatemia and hypokalemia often result, which may cause cardiac arrhythmias, neuromuscular abnormalities, and respiratory failure. Management of refeeding syndrome begins with identification and conservative initiation of nutrition support in patients at risk. Close monitoring of phosphorus, potassium, magnesium, and glucose are imperative in patients in the ICU being started on nutrition support.

Monitoring Nutrition Support

Monitoring for Effectiveness

To adequately monitor nutrition support in the ICU, patient-specific goals of therapy must be developed and frequently reviewed. Once nutrition support has been initiated, the trend in visceral protein markers may be followed as part of the assessment of nutritional maintenance or repletion. The American College of Chest Physicians recommends that prealbumin be assessed on a weekly basis. If the trend is not positive, C-reactive protein concentrations may be collected to associate this with an increase in physiological stress. Many clinicians combine protein assessment with baseline urinary urea nitrogen and routine nitrogen balance assessment to monitor the appropriateness of nutritional intervention. Clinical markers of nutritional status, such as wound healing and respiratory function, also should be used to determine the effectiveness of the nutrition support regimen. Patients in whom nutritional goals are not being met may benefit from indirect calorimetry and/or nitrogen balance studies to better define nutritional needs.

Monitoring for Complications

Fluid and electrolyte status should be monitored closely, with the frequency determined by the severity of patient illness and risk factors for abnormalities. Daily weight measurement is an important marker for fluid status, as rapid changes likely reflect changes in total body water. More invasive measures, such as central venous pressure monitoring and pulmonary artery catheterization, should be used as appropriate. Complete blood cell counts with white cell differentials and international normalized ratio should be monitored frequently to monitor for infectious complications, hematopoietic function, and coagulopathy. Electrolyte concentrations should be monitored at least daily in critically ill patients and maintained within normal ranges. Particular attention should be paid to potassium, phosphorus, magnesium, and ionized calcium. Similarly, arterial blood gases should be used as necessary to monitor acid/base status.

Baseline and weekly monitoring of triglyceride concentrations and liver function tests also are important to avoid adverse outcomes. Routine monitoring of trace element concentrations are not normally necessary, but should be evaluated in patients with, or at risk for, specific deficiencies.

Blood glucose monitoring should be conducted frequently with initiation of nutrition support in the ICU. Frequency of monitoring should be based on severity of illness, presence of drugs, such as corticosteroids, which can cause hyperglycemia, and prior history of diabetes or hyperglycemia. In a typical patient being fed parenterally, it is reasonable to begin monitoring glucose every 6 hours to allow for corrective insulin therapy and determination of baseline insulin needs. When the glucose concentration stabilizes, glucose monitoring may be done less frequently, but changes in the clinical status of the patient may necessitate reassessment of the monitoring plan.

van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001;345:1359–67.

Gastric residual volumes should be collected every 6 hours in patients being fed intragastrically. This should be done in conjunction with evaluation of the patient's respiratory and abdominal examination and frequency of gas or stool passage. These assessments may need to be conducted every 4 hours in patients with a history of EN intolerance.

Specific Disease States

Burns

Hypermetabolism and thermal dysregulation are physiological responses characteristic of a severe burn. Understanding nutritional and fluid support centers on changes that occur postinjury. A severely burned patient's care will be outlined by first reviewing the metabolic response to injury, describing the effects of burn injury on the nutritional support of the patient, then commenting on complications related to either enteral or parenteral support.

Metabolic regulation is influenced by the degree of body surface area burned, with a characteristic hyperadrenergic surge occurring postburn. Catecholamines with β -adrenergic stimulation are the driving stimulus of the hypermetabolic response. Norepinephrine, glucagon, and glucocorticoid release all compound the hyperglycemia observed in hypermetabolic states. Central temperature regulation appears to affect internal warmth of patients together with water evaporation through dermal loss. The concern of hypermetabolism and catabolism postinjury mirrors the lean body mass loss of up to 40 g/day of nitrogen. Peripheral amino acid turnover from alanine and glutamine leads to a depletion of lean body mass that is significant biochemically through muscle proteolysis and nitrogen transfer from muscle to the liver. Skeletal muscle breakdown ultimately affects wound healing, indirectly through lactate production and Cori cycle metabolism.

Enteral nutrition is an important part of burn care. The earlier the EN is begun (within 12–48 hours postpylorically), the better the clinical outcomes (e.g., length of stay and physiological wound healing). Fluid management is key for patient resuscitation and prevention of complications such as acute renal failure.

For the first 48 hours after a burn, the Parkland Formula may be used to design patient fluid resuscitation regimens. Lactated Ringer's solution is given for the first 24 hours (estimated amounts of 4 ml/kg/per percentage of total burn surface area). This strategy of volume resuscitation is subdivided into six 4-hour periods of various volumes. The period from 24–48 hours after a burn allows for plasma administration for two of the first similar six 4-hour periods to the amount of 0.5 ml/kg/per percentage of total burn surface area. This period is followed by 5% glucose for the remainder of the formula.

When the resuscitation phase is completed, the patient's nutritional status should be reassessed. One of the primary goals is to minimize loss of protein stores and promote immunocompetence to assist in skin grafting and wound

healing. Protein requirements range from 2.0 g/kg/day to 2.5 g/kg/day, although some patients may require even more. Numerous formulas have been derived to estimate energy needs for the burn patient. The Milner equation and the Xie equation are two that are considered most appropriate. The Xie equation is an estimated energy expenditure which is easy to use in daily practice:

$$(1000 \text{ kcal} \times \text{body surface area}) + (25 \times \% \text{ total burn surface area}).$$

Other formulas that have been used include the Curreri formula and the Galveston formula. The Curreri formula calculates the daily caloric requirement in kilocalories to be equal to 25 times the body weight in kilograms plus 40 times the percentage of the total body surface area burned. A criticism of this formula has been its lack of emphasis on burn size. The Galveston formula uses absolute burn sizes, is more applicable to caloric requirements for burned pediatric patients, and tends to overestimate energy expenditure, which contributes to overfeeding in adults. Because of its accuracy and simplicity of use, the Xie equation is becoming the preferred method for the estimation of energy needs in thermally injured adults.

Micronutrient support in burn patients has prompted study of vitamins A, C, and E; glutathione; selenium; zinc; and arginine for antioxidant effects. The oxygen-free radical scavengers vitamins A, C, and E are contained in preparations used for PN support; however, they may have to be supplemented separately from EN. Glutathione tissue depletion may lead to oxidative damage. Selenium and zinc deficiency may contribute to impaired wound healing as these trace elements may be excessively lost in burn patients. Zinc losses differ from selenium losses as zinc concentrations are depleted in physiological stress, whereas selenium deficiency is the result of physical destruction of the dermis. An area of ongoing burn research is micronutrient replenishment coupled with arginine and glutamine supplementation. Both animal and human data using arginine as a protein source have demonstrated improved immunocompetence and survival, as well as reductions in length of stay and wound infections. Glutamine has the theoretical advantage of preserving gut mucosa; however, this has not yet translated into improved outcomes in burn patients. Plasma trace mineral concentrations are unreliable in stress; however, increased losses have been demonstrated for some of those minerals during thermal injury.

Immune-enhancing EN refers to formulas enriched with arginine, fish oils, and uracil as ribonucleic acid. Comparisons of standard EN (35% fat preparations) to formulas supplemented with omega-3 fatty acids have demonstrated lower pneumonia rates as well as shorter hospital stays and fewer infections with the omega-3 product. The problems with immunonutrition in burn injury patients are the paucity of studies and the conflicting results when compared to different control formulas. Thus far, use of immune-enhancing formulas has not yet resulted in a

Dickerson RN, Gervasio JM, Riley ML, et al. Accuracy of predictive methods to estimate energy expenditure of thermally-injured patients. *JPEN J Parenter Enteral Nutr* 2002;26:17–29.

clinically significant improvement in outcomes in patients with thermal injury.

Postresuscitation EN (Timing, Complications, and Overall Need for PN)

Burn patients should be initiated on nutrition support within the first 24–48 hours postburn. Transpyloric feeding tubes may result in better tolerance, although nasoenteric or nasogastric tubes can be used. Various studies support early enteral feeding with the recognition that ileus formation may limit EN advancement to patient-specific goals. Diarrhea used to be a common complication further exacerbated by antimicrobial use, prokinetic drugs, hyperosmolar EN formulas, and excess fat content with decreased vitamin A content. However, the incidence of diarrhea has been decreased with improved enteral formulations and more aggressive management of this complication. Parenteral nutrition should only be given if EN is contraindicated or the patient will not meet nutritional goals within 4–5 days.

Indirect calorimetry is useful in determining energy requirements in patients with significant thermal injuries. Converting from the hypercatabolic state to an anabolic state is a primary goal. There are newer modalities in burn care that are being attempted which focus on the anabolic conversion. Oxandrolone, an oral anabolic steroid, increases weight and elevates serum protein stores in burn patients in the rehabilitation phase with no major adverse effects. However, it has not been effective in the acute phase of thermal injury. Recombinant human growth hormone has been used with mixed results in adult patients with burns. Improved wound healing was countered by increased incidence of hyperglycemia, increased cost, and studies showing increased mortality.

Trauma

Traumatic injury is characterized by the destruction of lean body mass and protein. The overall goal is to provide energy and protein to assist in healing and recovery. These goals can be met with either EN or PN, depending on the clinical condition of the patient. The major consideration in feeding patients is to slow or stop the maladaptive processes that may lead to multiple organ failure after the original insult.

Two major studies serve as the foundation of evidence that EN is preferred in patients with traumatic injury. Both studies showed fewer major infections with EN compared to PN. Another common denominator was the placement of needle catheter jejunostomy tubes or a Witzel jejunostomy intraoperatively, which facilitated aggressive feeding.

Conversely, there are studies that have demonstrated no difference in the incidence of multiple organ failure syndrome between enteral and parenteral nutrition. These studies have shown greater rates of complications and slowed nutritional recovery in patients fed enterally. Overall, the results demonstrate the complex interplay between hypermetabolism and multiple organ failure.

Immunonutrition has been evaluated for specific benefits in the trauma ICU population. Some evidence suggests a reduced risk of infection, fewer ventilator days, and shortened length of hospital stay, but no effect on mortality.

There also is conflicting data as to the incidence of multiple organ failure syndrome after septic insults. Multiple prospective studies have shown trauma patients benefit from immune-enhancing diets when compared with standard EN formulas. The immunonutrition formulas have been supplemented with branched-chain amino acids, glutamine, and arginine, whereas others have linolenic acid, beta-carotene, and hydrolyzed protein. End points assessed included infection rates (pneumonias and bacteremias), serum protein markers, acute phase reactants, plasma amino acid concentrations, lymphocyte blastogenesis, total lymphocyte counts, and stimulated cytokine production. Although the data appear promising for immunonutrition in trauma, improvements have occurred in rates of surrogate clinical outcome indicators, and not mortality. Therefore, use in critically ill trauma patients should be determined on a case-by-case basis. Many clinicians use immune-enhancing formulas in seriously injured trauma patients as long as they are not septic.

Acute Lung Injury and Acute Respiratory Distress Syndrome

Patients with acute lung injury or acute respiratory distress syndrome suffer from pulmonary edema that is the result of increased membrane permeability at the parenchyma level. Decreased compliance (stiff lungs), increased dead space, and shunt physiology are all hallmarks of acute lung injury. Nutrition support of these patients requires minimizing increases in the partial pressure of carbon dioxide, minimizing carbon dioxide production, and preventing worsening ventilation-perfusion mismatches at the bronchiolar level. Promising nutritional interventions include limiting total caloric intake, increasing the fat substrate, and fluid restriction. A preliminary trial comparing a high-fat (55%) formula to a typical fat (31%) EN formula reported less intensive mechanical ventilation in the high-fat group with reductions in the partial pressure of carbon dioxide, tidal volumes, and peak inspiratory pressures.

The goal of therapy in acute respiratory distress syndrome is to decrease pulmonary neutrophil migration and cytokines involved in the arachidonic acid cascade. It has been theorized that these pathologic mediators may be decreased by using eicosapentaenoic acid and gamma-linolenic acid, or by substituting omega-6 polyunsaturated fatty acid with omega-3 and medium-chain fatty acids. One major well-controlled trial evaluated the EN with eicosapentaenoic acid plus gamma-linolenic acid compared to a high-fat, low-carbohydrate EN formula. The eicosapentaenoic acid plus gamma-linolenic acid decreased length of ventilatory support, decreased length of ICU stay, and decreased total cells and neutrophils in bronchoalveolar lavage fluid. This type of research stimulates opportunities to evaluate more specialized EN nutrition products in various critically ill populations.

Another study comparing eicosapentaenoic acid plus gamma-linolenic acid formula with an isonitrogenous, isocaloric diet resulted in increased amounts of total protein, ceruloplasmin, and transferrin in patient bronchoalveolar lavage fluid who received control formula as opposed to the eicosapentaenoic acid plus gamma-linolenic acid EN,

indicating lower alveolar capillary membrane permeability. Although there also were improvements with eicosapentaenoic acid plus gamma-linolenic acid, the study does not provide sufficient data to recommend this formula in all patients with acute lung injury and acute respiratory distress syndrome. Patients were excluded with the most severe form of acute respiratory distress syndrome (partial pressure of oxygen-fraction of inspired oxygen ratios less than 100). Patients receiving the study formula were weaned from mechanical ventilation more quickly and had decreased length of hospital stay.

The nutritional support of acute lung injury or acute respiratory distress syndrome should focus on avoiding initial calorie provision of more than $1.3 \times \text{BEE}$, provision of carbohydrates and lipids by not exceeding the maximum glucose use rate and by monitoring triglyceride concentrations to ensure adequate plasma triglyceride clearance. In addition, fluid restriction is used to limit lung water accumulation from either PN or EN, and ensuring normal serum phosphorous concentrations to prevent muscle weakness. If predictive equations are used, the initial caloric provision should be no more than $\text{BEE} \times 1.3$ and initial protein provision should be 1.25–1.5 g/kg/day. Indirect calorimetry should be reserved for malnourished patients who are not gaining weight or patients who are losing weight despite goal nutritional support or when overfeeding is suspected because of carbon dioxide retention.

Conclusion

Nutrition management is a vital part of the care of critically ill patients. The changes in metabolic state that occur to patients in the ICU put them at risk for morbidity and mortality. Pharmacists should focus on appropriate nutritional assessment, accurate estimation of needs, and reevaluation and adjustment based on reasonable monitoring parameters. The enteral route of nutrition support should be used whenever possible, and feeding should typically begin within the first 24–48 hours after resuscitation after hemodynamic stability is achieved. Those in whom parenteral nutrition is necessary should be fed conservatively initially to ensure metabolic tolerance and prevent hyperglycemia. Pharmacists working as part of the ICU team should seek to minimize complications associated with nutritional intervention, and should keep in mind that the primary goal of nutrition support is to improve the clinical outcome of the patient.

Annotated Bibliography

1. ASPEN Board of Directors and the Clinical Guidelines Task Force. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. *JPEN J Parenter Enteral Nutr* 2002;26(suppl):1SA–138SA.

This publication is an important guideline set related to the provision of nutrition support. These guidelines were developed based on the best available evidence; if no evidence existed, expert consensus was used. For the critical care practitioner, recommendations are made for adults with critical illness, burns, pancreatitis, and perioperative nutrition support. The guidelines are referenced, and this is important because although the document provides a wide breadth of information, readers desiring more specific information may need to refer to the primary literature.

2. Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P; Canadian Critical Care Clinical Practice Guidelines Committee. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adults. *JPEN J Parenter Enteral Nutr* 2003;27:355–73.

This systematic review contains guidelines and recommendations relating specifically to the nutritional support of critically ill adult patients. The article is different from other guideline sets in that recommendations are only made based on the results of prospective trials, and not from a combination of clinical research and consensus opinion. In addition, the authors conducted analyses combining available studies in making recommendations to make stronger recommendations. The result is a guideline set that is somewhat limited in the number of recommendations that can be made definitively, but those that are made are specific and practical. This paper is highly valuable for the application of evidence-based principles to specialized nutrition needs of the general ICU population.

3. McClave SA, Mallampalli A. Nutrition in the ICU, part 1. Enteral feeding: when and why? *J Crit Illness* 2001;16:197–204.

This review is the first in a three-part series looking at the nutritional needs of critically ill patients. This paper lays an excellent foundation on which to build in assessing the benefits of enteral nutrition (EN) and parenteral nutrition (PN). The physiological changes that occur with prolonged gut disuse are discussed at length. Of importance, the authors address the valid criticisms of some of the proposed mechanisms of benefit and harm, and they acknowledge areas where little literature supports their hypotheses. This publication, the first in an excellent series of papers, serves as a refresher on the major issues surrounding the decision to feed enterally or parenterally.

4. Btaiche IF, Khalidi N. Metabolic complications of parenteral nutrition, part 1. *Am J Health-Syst Pharm* 2004;61:1938–49.

This paper is the first in a two-part series reviewing the metabolic complications of PN. This well-written paper details the problems that may be encountered in feeding patients parenterally. Complications specifically discussed include hyperglycemia, hypoglycemia, hypertriglyceridemia, and the refeeding syndrome. The authors do a nice job of providing not only the scientific foundation for the development of complications discussed, but also some practical recommendations for preventing and attempting to reverse complications in susceptible patients. They further enforce the principles guiding the appropriate use of PN.

Gadek JE, DeMichele SJ, Karlstad MD, et al. Effect of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in patients with acute respiratory distress syndrome. *Crit Care Med* 1999;27:1409–20.

5. Woodcock NP, Zeigler D, Palmer D, Buckley P, Mitchell CJ, MacFie J. Enteral versus parenteral nutrition: a pragmatic study. *Nutrition* 2001;17:1–12.

The authors of this paper conducted a randomized, controlled trial of EN and PN in 64 patients. These patients were chosen because the physicians caring for them were certain about the adequacy of their gut function to tolerate EN. In addition to the randomized analysis, a concurrent observational study followed patients for whom physicians felt more confident about whether EN or PN was more appropriate. The patients were evaluated for the percentage of patient-days when 80% or more (nutritional adequacy) of prescribed calories were given, and for the incidences of morbidity and mortality. The investigators reported that the incidence of inadequate nutrition was statistically significantly higher among patients randomized to EN (78.1% vs. 25%; $p < 0.001$). They further reported that while no significant differences were observed in septic morbidity, that significantly more complications related to nutritional access occurred in patients fed enterally. The design of this study is a real strength. In comparing different routes of nutritional access by randomizing patients in whom physicians are sure the gut is working, the authors make the case that in patients in whom gut function is in question, PN should be preferred. One area that could have been further clarified was the severity and clinical consequences of noninfectious complications occurring between groups. Although the authors state the total numbers in each group and recount some of the most serious complications in the enteral feeding group, it can be questioned whether the average complication related to a feeding tube is of equivalent severity to that of a central venous line. In addition, there are nominal differences in some important demographic data between the two randomized groups. Although not reaching statistical significance, the group randomized to PN had more patients recovering from surgery, with inflammatory bowel disease, or pancreatitis, whereas the EN group had more patients with nonsurgical diagnoses, such as respiratory failure.