Nutritional Therapies in Critically Ill Patients

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Nutritional support of critically ill patients is aimed at preserving tissue mass and decreasing use of endogenous nutrient stores. In addition, we are attempting to decrease catabolism and maintain and improve organ function (i.e., immune, renal, hepatic, muscle). Major goals include improving wound healing, decreasing infection, maintaining the gut barrier (decreasing translocation), decreasing time of mechanical ventilation, and decreasing morbidities and mortality, which may also decrease ICU and hospital stay and hospital costs.

Outcome after injury is related to adequate metabolic and hemodynamic resuscitation of critically ill patients. Roles of optimal delivery and timing, techniques of early feeding, comparisons of parenteral and enteral nutrition, complications of nutritional therapies, nutrition for specific diseases, and a recommendation for an approach to feeding are covered in this chapter. Recently published guidelines from the Society of Critical Care Medicine (SCCM) and American Society of Parenteral and Enteral Nutrition (ASPEN) provide an extensive review of key issues related to critical care nutrition, and the reader is referred to them for more details and references.¹
NUTRITIONAL ASSESSMENT

Traditional nutritional assessment begins by obtaining the patient's history from information in hospital records, from family members, or from the patient. Recent weight loss, anorexia, surgical history, activity levels, nausea and vomiting, and diarrhea are important symptoms to elicit from the history. Physical examination findings suggestive of nutritional deficiencies (e.g., dermatitis, scaling of the skin, glossitis, poor wound healing) may be present.

Actual weights of critically ill patients may be of limited value because of water retention, and therefore weights may not correlate with nutritional status. Ideal body weights (IBWs) are typically more useful and are a practical estimate of lean body weight. Ideal body weight can be obtained from published actuarial tables and from nomograms based on height and body build characteristics or can be estimated by the following:

- Adult males: 106 lbs for the first 5 ft and about 6 lbs for each additional inch
- Adult females: 100 lbs for the first 5 ft and about 5 lbs for each additional inch
- Individuals over 50 years are allowed an additional 10% of the calculated weights

The ratio of actual body weight to ideal body weight for a given gender, height, and age may establish the degree to which the patient is underweight and further may reflect the degree of malnutrition: mild (80%-90%), moderate (70%-79%), and severe (<70%). Anthropometric measurements such as skinfold thickness and midarm muscle circumference are useful in less severe illness but are rarely useful in critically ill patients. Skinfold thickness (triceps or subscapular) measurements are a means of estimating body fat but are unreliable in the presence of fluid retention. Midarm muscle circumference is used to estimate body protein stores but is also unreliable in the presence of fluid retention.

For some clinical situations such as pharmacological volumes of distribution and drug dosing considerations, an adjusted body weight may be a better weight estimate to use. Adjusted body weight is typically calculated as follows:

\[
\text{Adjusted Body Weight} = \text{Adjustment Factor} \times (\text{Actual Weight} - \text{IBW}) + \text{IBW}
\]

where the adjustment factor ranges from 0.2 to 0.5; most commonly 0.25 is used for nutrition assessment purposes.

Laboratory tests used in nutritional assessment are measurements of visceral protein levels produced by the liver: albumin, transferrin, prealbumin, and retinol-binding protein. Monitoring these proteins has not been shown to improve outcomes. But many clinicians believe that these proteins have value as a monitor of responses to nutritional therapy. Important facts about each of these visceral proteins are provided next.

**Albumin**
- Half-life is 18 days.
- Levels decrease when vascular permeability is altered, protein synthesis is decreased, metabolism is increased, or resuscitation with fluid or blood products is required.

**Transferrin**
- Transports iron.
- Half-life is 8 to 10 days.
- Levels depend on the iron status of the individual and are affected by blood loss or replacement.
- Levels may be decreased by the acute phase response to injury.

**Prealbumin**
- Transports thyroxine; is not a precursor to the albumin protein.
- Half-life is 2 to 3 days.
- Kidney is major site of clearance.
- Expect levels to decrease during the acute phase response and to increase as patient improves if adequate substrate is present.

**Retinol-Binding Protein**
- Half-life is 10 to 12 hours.
- Kidney is major site of clearance.
- Levels may be altered by vitamin A levels and carbohydrate concentration of the diet.

Nitrogen balance studies may be helpful in assessing adequacy of nutritional protein intake. Nitrogen excretion amounts are best determined from 12- to 24-hour urine collections and measurements of total urinary nitrogen (more accurate than total urea nitrogen). These may be unreliable in patients with renal failure or if urine is not correctly collected by staff. Nitrogen balance is nitrogen intake minus nitrogen lost (in urine, through the skin and stool, or from fistulas, wounds, or dialysates). Common estimates for normal nonurinary nitrogen excretion are 2 g/d each for skin and stool losses but are difficult to estimate with severe wounds and protein-losing enteropathies. Indeed, negative nitrogen balance is not necessarily detrimental over the short term (ie, 1-2 weeks). Some patients, for example, those with spinal cord injury or on steroid therapy, will have high muscle protein turnover and increased nitrogen excretion. The belief is that a positive nitrogen balance of several grams per day is advantageous, but a simple improvement in sequential nitrogen balance studies can suggest that nutritional support is adequate. Still, be aware that nitrogen balance may improve as catabolism decreases despite inadequate nutritional support. In the care of dynamic patients, nitrogen balance studies can be difficult to interpret and may have limited value to the clinical team.

Indirect calorimetry (metabolic cart) is based on laws of thermodynamics; the use of energy involves the consumption of oxygen (ie, $V_{O_2}$) and the production of CO$_2$ (ie, $V_{CO_2}$), nitrogenous wastes, and water.$^1$ When matter is converted to heat by the body, measurement of $V_{O_2}$ and $V_{CO_2}$ indirectly reflects the metabolic energy expenditure.

Typical studies measure $V_{O_2}$ and $V_{CO_2}$ for 15 to 30 minutes, then estimate energy expenditure and respiratory quotient (RQ), and then extrapolate to 24 hours. These studies should be performed while the patient is resting, that is, not during baths, respiratory treatments, physical therapy sessions, or other events that will increase stress and energy expenditure. Because of the short test period and extrapolation of data to a 24-hour estimate, large errors can occur, so clinical judgment plays a key role in interpretation of the results. Following measurements over time may allow the clinician to recognize changes in the metabolic rate and tailor nutritional support to meet an individual's needs.

Indirect calorimetry can provide an estimate of the RQ, which reflects whole-body substrate utilization.

**Relationship between various fuels and their RQ:**
- Carbohydrate: 1.0
- Fat: 0.70
- Protein: 0.80

The RQ can vary between 0.70 and 1.2. Provision of excess carbohydrate calories results in net fat synthesis and leads to high CO$_2$ production (eg, RQ > 1.0), which should be avoided. The most obvious related problem is that excessive CO$_2$ production requires more ventilation for CO$_2$ elimination. This may increase work of breathing in tenuous patients and can increase the time on mechanical ventilation. Several problems are associated with indirect calorimetry; results can be inaccurate when the inspired oxygen fraction is greater than 0.40, any leak in the system can introduce error (eg, endotracheal tube cuff leak), and the test is labor-intensive because a steady state is needed for accurate measurements (this can take an extended period of time to obtain in a critically ill patient). In fact, some recommend that 3 to 5 measurements in a day be averaged to obtain a daily average of energy expenditure, and therefore indirect calorimetry can be associated with high cost, especially if measured frequently.
Functional tests of nutritional status are traditionally used. Skin tests of immune function (i.e., delayed cutaneous hypersensitivity) are frequently affected by critical illness, which limits their usefulness since many critically ill patients are anergic. Muscle strength assessment of grip or respiratory muscle function correlates with nutritional status but has limited utility in the ICU patient.

TIMING OF INSTITUTION OF NUTRITIONAL SUPPORT

Optimal timing of nutritional support cannot be determined by nutritional assessment indices since many are altered by critical illness. Therefore, it must be a clinical decision. Optimal timing remains controversial. Some patients tolerate short periods of starvation by using endogenous stores to support body functions. Well-nourished subjects (nonstressed) have actually survived without food for 6 weeks (ingesting only water). However, hypermetabolic and hypercatabolic critically ill patients can probably tolerate only a few weeks of starvation before death, and shorter periods of starvation are expected to contribute to organ dysfunction. Clearly, there appears to be no benefit of total starvation.

Data suggest that outcomes can be improved with early and optimal nutritional support. Extensive reviews of benefits of early nutritional support are found in guidelines published jointly by SCCM and ASPEN in 2009 as well as other guideline groups from varied parts of the world. Briefly, early enteral nutritional support blunts the hypercatabolic and hypermetabolic response to injury. In numerous studies, patients randomized to receive early versus delayed feeding had decreased infection rates, fewer complications, and shorter length of stay in the hospital.

Animal studies in injury models report improved wound healing, renal function, hepatic function, and even mortality with early enteral feeding.

NUTRIENT REQUIREMENTS (QUANTITY)

Energy

Energy needs are met by the caloric content of the major nutrients (lipids provide 9 kcal/g, carbohydrates 4 kcal/g, and proteins 4 kcal/g). Studies show that most critically ill patients expend 25 to 35 kcal/kg/d. One can measure energy expenditure with indirect calorimetry or more simply by estimating resting metabolic expenditure (RME) using the Harris-Benedict equation:

Men: RME (kcal/d) = 66 + (13.7 × W) + (5 × H) - (6.8 × A)

Women: RME (kcal/d) = 665 + (9.6 × W) + (1.7 × H) - (4.7 × A)

where W = weight in kilograms, H = height in centimeters, and A = age in years.

Historically, some recommended adjusting RME by multiplying by a correction factor based on stress factors for burn injury, sepsis, or activity levels; however, correction factors frequently overestimate energy needs and are currently not recommended.

Current recommendations are to initially administer 25 kcal/kg/d (~20% protein, ~30% lipids, ~50% carbohydrates, where % refers to percentage of total daily calories). Patients with organ failure or disease states may have increased or decreased needs and should be considered individually. Overfeeding (with either enteral or parenteral nutrients) is associated with more adverse side effects than is slightly underfeeding during most critical illnesses.

Protein

Most critically ill patients need 1.2 to 2.5 g of protein per kilogram of body weight per day. Protein requirements are often highest in patients with severe trauma, burns, and protein-losing enteropathies (Table 1 on page 683).
Table 1.
Macronutrient Nutritional Requirements of the Adult

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>% of Total Calories</th>
<th>Quantity of Nutrients</th>
<th>Example for 70-kg (154-lb) Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total calories</td>
<td>25 kcal/kg/d</td>
<td>1750 kcal/d</td>
<td></td>
</tr>
<tr>
<td>Protein/amino acids</td>
<td>15-25</td>
<td>1.2-2.0 g/kg/d (based on 1.35 g/kg/d)</td>
<td>95 g/d (380 kcal/d)</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>50% of calories (average patient)</td>
<td>220 g/d (880 kcal/d)</td>
<td></td>
</tr>
<tr>
<td>Fats</td>
<td>30-65</td>
<td>30% of calories (average patient)</td>
<td>55 g/d (495 kcal/d)</td>
</tr>
</tbody>
</table>

Water

Needs for water vary greatly between patients primarily because of differences in insensible losses, gastrointestinal (GI) losses, and urine losses. It is reasonable to initially estimate water needs as 1 mL of water per kilocalorie of energy expended in adults.

Vitamins

Vitamins A, D, E, and K are fat soluble. The water-soluble vitamins are ascorbic acid (C), thiamine (B₁), riboflavin (B₂), niacin, folate, pyridoxine (B₆), B₁₂, pantothenic acid, and biotin. Published recommended daily intakes (RDIs) are based on oral intake in healthy individuals. Vitamin needs for critically ill patients have not been determined. Commercial enteral formulas generally supply the RDI (or more) of vitamins if patients are given sufficient quantities of formula to meet their caloric needs. An adult parenteral vitamin formulation was approved by the US Food and Drug Administration (FDA) in 1979 and is available for addition to total parenteral nutrition (TPN) solutions; this should be added just before administration since degradation can occur. Recent drug shortages have included this IV vitamin preparation. When shortages occur, patients on TPN more than a week are at greatest risk of deficiencies, and available vitamins should be rationed to these patients if necessary (Table 2 on page 684).

Minerals (Sodium, Potassium, Calcium, Phosphate, Magnesium)

Minerals are present in sufficient quantities in enteral products (special formulas limit electrolytes for renal failure); however, they must be supplemented in TPN (Table 2 on page 684).

Trace Elements (Iron, Copper, Iodine, Zinc, Selenium, Chromium, Cobalt, Manganese)

Needs for trace elements in critically ill patients have not been determined (Table 2 on page 684). Sufficient quantities are thought to be present in enteral products, but they must be supplemented in TPN (all except iron can be added to solution). Deficiency states have been reported in patients receiving long-term TPN (e.g., copper, chromium). Specifics are best managed by specially trained nutritional support teams.

COMPARISON OF ENTERAL VERSUS PARENTERAL NUTRITION

Enteral nutrition is required for optimal gut function (i.e., maintenance of gut barrier, gut-associated lymphoid tissue, immunoglobulin A secretion, mucus layer). Total parenteral nutrition is associated with immunosuppression (thought to be related to IV lipids, which are high in ω-6 long-chain fatty acids) and increased infection rates (compared with enteral) in patients following trauma, burns, surgery, and cancer chemotherapy and radiotherapy. Total parenteral nutrition is associated with a higher mortality in patients receiving chemotherapy or radiotherapy and after burn injury. Extensive reviews of enteral nutrition versus TPN studies are found elsewhere. Historically, TPN was used in patients with inflammatory bowel disease or pancreatitis,
### Table 2.
Micronutrient Nutritional Requirements of the Adult

<table>
<thead>
<tr>
<th>Micronutrient</th>
<th>Enteral Nutrition</th>
<th>Parenteral Nutrition</th>
<th>Example for TPN for a 70-kg (154-lb) Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minerals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>60-140 mmol/d</td>
<td>60-120 mmol/d</td>
<td>80 mmol/d</td>
</tr>
<tr>
<td>Potassium</td>
<td>50-140 mmol/d</td>
<td>50-120 mmol/d</td>
<td>50 mmol/d</td>
</tr>
<tr>
<td>Magnesium</td>
<td>8-15 mmol/d</td>
<td>8-12 mmol/d</td>
<td>10 mmol/d</td>
</tr>
<tr>
<td>Phosphorous</td>
<td>25 mmol/d</td>
<td>14-16 mmol/d</td>
<td>15 mmol/d</td>
</tr>
<tr>
<td>Calcium</td>
<td>20 mmol/d</td>
<td>7-10 mmol/d</td>
<td>10 mmol/d</td>
</tr>
<tr>
<td>Trace elements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron</td>
<td>10 mg/d</td>
<td>1-2 mg/d</td>
<td>None</td>
</tr>
<tr>
<td>Zinc</td>
<td>15 mg/d</td>
<td>2-5 mg/d</td>
<td>5 mg/d</td>
</tr>
<tr>
<td>Copper</td>
<td>2-3 mg/d</td>
<td>0.5-1.5 mg/d</td>
<td>1 mg/d</td>
</tr>
<tr>
<td>Chromium</td>
<td>50-200 µg/d</td>
<td>10-20 µg/d</td>
<td>10 µg/d</td>
</tr>
<tr>
<td>Selenium</td>
<td>50-200 µg/d</td>
<td>80-150 µg/d</td>
<td>100 µg/d</td>
</tr>
<tr>
<td>Iodine</td>
<td>150 µg/d</td>
<td>120 µg/d</td>
<td>120 µg/d</td>
</tr>
<tr>
<td>Manganese</td>
<td>2.5-5.0 mg/d</td>
<td>0.2-0.8 mg/d</td>
<td>0.5 mg/d</td>
</tr>
<tr>
<td>Vitamins*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin A</td>
<td>RDA = 4,000-5,000 IU/d</td>
<td>ND</td>
<td>3,300 IU/d</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>RDA = 200-400 IU/d</td>
<td>ND</td>
<td>200 IU/d</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>RDA = 12-15 IU/d</td>
<td>ND</td>
<td>10 IU/d</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>RDA = 60-80 µg/d</td>
<td>ND</td>
<td>10 mg/wk(^b)</td>
</tr>
<tr>
<td>Thiamine</td>
<td>RDA = 1.1-1.4 mg/d</td>
<td>ND</td>
<td>3 mg/d</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>RDA = 1.2-1.7 mg/d</td>
<td>ND</td>
<td>5 mg/d</td>
</tr>
<tr>
<td>Niacin</td>
<td>RDA = 13-19 mg/d</td>
<td>ND</td>
<td>40 mg/d</td>
</tr>
<tr>
<td>Pantothentic acid</td>
<td>4-7 mg/d(^c)</td>
<td>ND</td>
<td>15 mg/d</td>
</tr>
<tr>
<td>Pyridoxine</td>
<td>RDA = 1.6-2.0 mg/d</td>
<td>ND</td>
<td>4 mg/d</td>
</tr>
<tr>
<td>Folic acid</td>
<td>RDA = 0.4 mg/d</td>
<td>ND</td>
<td>0.4 mg/d</td>
</tr>
<tr>
<td>Vitamin B(_{12})</td>
<td>RDA = 3 µg/d</td>
<td>ND</td>
<td>5 µg/d</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>RDA = 40 mg/d</td>
<td>ND</td>
<td>100 mg/d</td>
</tr>
<tr>
<td>Biotin</td>
<td>RDA = 30-100 µg/d</td>
<td>ND</td>
<td>60 µg/d</td>
</tr>
</tbody>
</table>

Abbreviations: ND, not defined; RDA, recommended daily allowance; TPN, total parenteral nutrition.

\*Enteral requirements should always exceed parenteral requirements; most recommend supplying 1-3 times the RDA of each vitamin to patients with critical illness (requirements are probably increased by stress, infection, disease). However, the exact requirements are not known.

\(^b\)None if anticoagulation is used.

\(^c\)RDA not established.
but current data demonstrate that enteral nutrition is preferred for both.

Total parenteral nutrition may be beneficial in patients with short-gut syndromes, some types of GI fistulas, adynamic small bowel, or chylothorax, or patients who after a week have failed to tolerate enteral feeding. Enteral nutrition is the preferred method of feeding in patients receiving chemotheraphy or radiotherapy and following surgery, burns, trauma, sepsis, renal failure, liver failure, and respiratory failure. Parenteral nutrition is indicated when enteral nutrition is not possible (ie, inadequate small bowel function). US guidelines recommend that for most patients (ie, specifically those who are not severely malnourished already), TPN should be deferred in the first days while enteral nutrition is initiated, and TPN use should be limited to those patients who cannot tolerate enteral nutrition. Total parenteral nutrition should not be used as a supplement to enteral nutrition. A recent multicenter trial compared early enteral nutrition plus TPN to early enteral nutrition alone and reported higher morbidities as well as a higher mortality rate in patients who received supplemental TPN administered to meet energy expenditure. Of note, enteral nutrition is less expensive than parenteral nutrition. Table 3 on page 686 compares the nutrient sources available in both enteral and parenteral nutrition in the United States.

ENTERAL NUTRITION SPECIFICS

Enteral nutrition is the preferred route of nutritional support in both pediatric and adult patients. Delivery of enteral nutrition can be achieved by several routes: oral, gastric tube (ie, nasogastric, gastric), or small bowel feeding tube (ie, nasoduodenal, gastroduodenal, jejunal). Optimal route of administration varies per individual patient. For many ICU patients, gastric feeds can be used with success if judiciously managed. If a patient has high aspiration risk or has shown intolerance to gastric feeds, small bowel feeds may be preferred. Studies report contradictory results as to risks of pneumonia with gastric versus small bowel feeds, although small bowel feeds are often associated with earlier delivery of nutritional targets enterally. We prefer small bowel feeding in mechanically ventilated patients who have frequent trips to operating rooms. We have a protocol that allows small bowel feeds to continue until the patient leaves the ICU for the operating room; this diminishes nutritional deficits that otherwise develop following cumulative hours without feeds from unexpected delays in scheduling of operative procedures and frequent nutritional holds. In a study of burn patients, small bowel feeds in patients who were already intubated (ie, mechanically ventilated patients) were safe without common preoperative nutrition holds and with continued intraoperative enteral feeding.

Major complications encountered with administration of enteral nutrition are as follows:

- Aspiration (pneumonia, chemical pneumonitis, acute respiratory distress syndrome [ARDS])
- Metabolic derangements (eg, electrolyte disturbances, hyperglycemia) — less common than with parenteral nutrition
- Diarrhea
- Misplaced feeding tubes (eg, pneumothorax, empyema, bowel perforation)
- Overfeeding

RECOMMENDATIONS FOR USE OF TOTAL PARENTERAL NUTRITION

Simply stated, TPN should be used only when enteral nutrition is not possible (eg, short gut syndrome, chylothorax). Failure of the stomach to empty is not an indication for TPN but rather for a small bowel feeding tube. Most patients with diarrhea can be managed with enteral nutrition. Overall TPN management is best performed by specially trained nutritional support teams. Initial TPN orders may be based on recommendations in Tables 1 on page 683 and 2 on page 684. Total parenteral nutrition can be delivered via peripheral vein but more
Table 3.
Comparison of Nutrients in Enteral Versus Parenteral Nutrition

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Enteral</th>
<th>Parenteral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrogen source</td>
<td>Intact proteins, peptides, or amino acids</td>
<td>Amino acids*</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>Simple sugars or complex carbohydrates (ie, starch and fiber)</td>
<td>Simple sugar (dextrose)</td>
</tr>
<tr>
<td>Lipids</td>
<td>Long- and medium-chain triglycerides or long-chain fatty acids (ω-3 or ω-6)</td>
<td>Intravenous lipids*: 50%-65% linoleic acid (ω-6) and 5%-10% linolenic acid (ω-3)</td>
</tr>
<tr>
<td>Vitamins</td>
<td>Present</td>
<td>Can be added</td>
</tr>
<tr>
<td>Minerals and trace elements</td>
<td>Present</td>
<td>Can be added</td>
</tr>
</tbody>
</table>

*Lacks some conditionally essential amino acids (ie, glutamine and cysteine).

*Other IV lipid mixtures available in some countries but not in the United States.

commonly is administered in a concentrated preparation by central vein.

Major complications associated with TPN administration are as follows:

- Central line placement complications (pneumothorax, hemothorax, carotid artery perforation)
- Metabolic derangements (hyperglycemia, electrolyte disturbances)
- Immune suppression
- Increased infection rates (catheter-related sepsis, pneumonia, abscesses)
- Liver dysfunction (fatty infiltration, cholestasis, liver failure)
- Gut atrophy (diarrhea, bacterial translocation)
- Venous thrombosis
- Overfeeding

In addition, TPN lacks some conditionally essential amino acids that are not stable in solution (ie, glutamine, cysteine).

The glucose to fat ratio is usually 60:40 to 40:60 (ratio of calories from each source).

Large amounts of glucose (>60% of calories) can have undesirable effects:

- Increase energy expenditure
- Increase CO₂ production and increase pulmonary workload (may delay ventilator weaning)
- Produce liver steatosis
- Lead to immune compromise

**ROLE OF SPECIFIC NUTRIENTS USED IN ENTERAL NUTRITION**

**Nitrogen Sources**

Evidence suggests that peptides generated from the diet have specific physiological activities. Nitrogen is best delivered as intact protein if digestion and absorption are intact or as hydrolyzed protein or peptides when digestion is impaired. Protein is absorbed in the small bowel primarily as peptides (60%) and amino acids (33%). Essential amino acid formulas should not be used because they have been associated with worse outcomes when
compared with either intact protein or peptide-based formulations.

Some typically nonessential amino acids become essential during critical illness, and these are called conditionally essential amino acids (e.g., glutamine, cysteine, arginine, and taurine). In addition, some amino acids appear to have specific physiological roles:

- Glutamine is a fuel for the GI tract and immune system.\(^{17}\)
- Arginine is required for optimum wound healing and is important in immune function.\(^{18}\)
- Cysteine is needed for synthesis of glutathione.
- Branched-chain amino acids may improve mental status in patients with hepatic encephalopathy because these amino acids are primarily metabolized by peripheral muscle instead of liver.
- Glutamine and cysteine are not stable (or present) in TPN solutions in the United States; IV glutamine dipeptides are available in some parts of the world for use in TPN.

**Lipids**

Linoleic acid is an essential fatty acid that should make up 7% to 12% of total caloric intake for humans. It is an \(\omega-6\) polyunsaturated, long-chain fatty acid (a type of fatty acid that has been shown to be immunosuppressive) and is a precursor to membrane arachidonic acid. The lipids used in IV formulations are primarily \(\omega-6\) fatty acids. The \(\omega-3\) polyunsaturated fatty acids are found in fish oils and linolenic acid (an essential fatty acid). They decrease production of dienoic prostaglandins (i.e., \(\text{PGE}_2\)), tumor necrosis factor, interleukin-1, and other proinflammatory cytokines. The medium-chain triglycerides are water-soluble and are a good energy source. Medium-chain triglycerides enter the circulation via the GI tract. Short-chain fatty acids (e.g., butyric and propionic acid) are a major fuel for the gut (especially the colon) and are derived from metabolizable fibers such as guar and pectin.

Some enteral formulas were designed as high-fat formulas and are marketed for decreasing the respiratory quotient (RO). However, if a patient is not overfed, these have little effect on \(\text{CO}_2\) production. A problem with these formulas is that they are associated with poor GI tolerance (bloating, diarrhea).

**Carbohydrates**

Starches and sugars are a good energy source. Fiber has several benefits. Metabolizable fiber is converted to short-chain fatty acids in the colon by bacteria, and data suggest that these fatty acids are beneficial to colonic health. Other fiber sources that are insoluble add bulk, which increases stool mass, softens stool, adds body to stool, and provides some stimulation of gut mass.

**Antioxidants**

A number of antioxidants are likely to benefit critically ill patients.\(^{19}\) Glutamine and cysteine can be rate-limiting substrates for synthesis of glutathione, which is believed to be the body’s major antioxidant. Parenteral glutamine supplementation is associated with improved outcomes and is advocated for use in patients requiring parenteral nutrition. However, parenteral glutamine formulations are not FDA approved in the United States (although they are marketed in other parts of the world, including Europe).\(^{20}\) It is not established that enteral glutamine supplementation is as beneficial as parenteral administration. Vitamin C and E are antioxidants as well and are likely needed in higher quantity during critical illness. Selenium was reported to be deficient in some critically ill patients, and continuous infusion of selenium improved survival in one randomized trial of patients with severe sepsis.\(^{21}\) Specific optimal doses of antioxidants are unknown, but several clinical studies reported improved outcomes and smaller rates of organ dysfunction for patients treated with antioxidant formulations.\(^{22,23}\)
NUCLEIC ACIDS

Dietary nucleic acids (e.g., ribonucleic acid) may be important for immune function and are added to some specialty formulations.

GASTROINTESTINAL FUNCTION DURING CRITICAL ILLNESS

Oral nutrition remains the best form of nutritional support; however, many critically ill patients cannot be fed by mouth. Decreased motility of the stomach and colon are common in critically ill patients and typically last 5 to 7 days (longer if a patient remains critically ill). Gastric paresis is best assessed and monitored by measuring gastric residuals. Gastric residuals of 250 mL or greater are often considered abnormal. Controversies surround the gastric residual volume that limits safety of gastric feeds, but McClave and colleagues reported safety with residual volumes as high as 500 mL. Many critical care teams still monitor gastric residual volumes as a method of decreasing aspiration risk. It is reasonable to consider small bowel (postpyloric) delivery of enteral feeds in patients with gastric residuals greater than 300 mL to decrease risk of aspiration. Another option for patients with gastroparesis is to administer a promotility agent such as erythromycin or metoclopramide. If promotility agents are used, a trial off the agent should be considered after a few days of successful feeding at goal rate. In critically ill patients, motility and nutrient absorptive capability of the small bowel are usually at least partially preserved even after severe trauma, burns, or major surgery. Bowel sounds are a poor index of small bowel motility and thus should not be used to decide whether enteral nutrition should be attempted. Use of protocols is associated with better delivery of nutritional support, but implementation can be challenging.

Recommended Approach to Enteral Feeding

A. Enteral nutritional support should be initiated within 12 to 48 hours of admission to ICU.

B. Gastric route is second choice (oral is first choice) and should be tried before placing a small bowel tube in most patients.

C. Patients at high risk for aspiration or known gastric paresis should be fed with a small bowel tube.

D. Feeding formulas should not be diluted.

E. Keep head of bed elevated 30° or more to decrease risk of aspiration.

F. In adults, feeding should be started at 25 to 30 mL/h and increased by 10 to 25 mL/h every 1 to 4 hours as tolerated by gastric residuals and other signs of tolerance until the calorie goal (25 kcal/kg/d) is reached.

G. Protein goals can be achieved by using a formula with a higher protein/calorie ratio or administering protein to the patient separately.

H. Gastric residuals should be monitored every 4 hours.

I. If gastric residual (in adults) is greater than 300 mL, hold feeds for 2 hours and then resume.

J. Feeds (for adults) can be increased at a slower rate (i.e., 10 mL/h every 6-12 hours) for patients expected to have more intolerance, but often this is not necessary.

K. Promotility agents such as metoclopramide or erythromycin may be added if gastric emptying is problematic; alternatively, small bowel tubes can be placed for feeds.

L. Goal rate of infusion should be met by the third day of nutritional therapy (frequently earlier).

M. Formula osmolality

1. 300-600 mOsm/kg H2O

2. Rarely causes intolerance or diarrhea
GENERAL CONCERNS REGARDING OVERFEEDING

Potential complications from overfeeding have led to recent recommendations of lower total daily caloric intakes (i.e., initial goal of 25 kcal/kg/d) in adult critically ill patients. Indirect calorimetry is potentially useful in prevention of overfeeding. Complications can occur from overfeeding:

- Liver compromise can occur.
- Increased CO₂ production from lipogenesis results in increased ventilatory requirements.
- An association with worsened outcome was noted in a number of animal models and some human studies.

NUTRITION FOR SPECIFIC DISEASE PROCESSES

Immune Function

Numerous commercial enteral formulas are marketed with the aim of modulating immune function as a nutritional therapy. Specific nutrients that may improve immune function include arginine, glutamine, ribonucleic acid, ω-3 fatty acids, and vitamins A, C, and E. The ω-3 fatty acids are considered immunostimulatory, whereas ω-6 fatty acids are immunosuppressive. Therefore, increasing the ω-3 fatty acids while decreasing the ω-6 fatty acids (i.e., providing a more balanced mixture) may improve overall immune function. More than 35 clinical studies have compared immune-modulating formulas to standard formulas and reported benefits (e.g., decreased infections and length of stay). Multiple metaanalyses found decreases in morbidities but not mortality. Only 2 randomized trials (which studied patients with sepsis) reported improved mortality with immune-modulating formulas. Subgroups that appear to have greatest benefits from these formulations are patients with trauma, GI surgery, and burns. The optimal amounts and combinations of immune-modulating nutrients remain unclear, as does whether different stages in illness and recovery require varied formulations. Further research is anticipated to clarify these issues.

Acute Lung Injury and Acute Respiratory Distress Syndrome

Several clinical trials have explored the effects of a specialized enteral formulation containing eicosapentaenoic acid, γ-linolenic acid, and antioxidants in patients with ARDS. Patients randomized to receive the study formula had faster resolution of ARDS, decreased sequential measures of inflammatory responses, less time on mechanical ventilation, and decreased development of additional organ injury compared with patients on a control formulation. Therefore, formulations with altered fat blends like this are recommended for adjunctive treatment of patients with acute lung injury or ARDS.

Acute Kidney Injury

Animal studies have demonstrated that early nutritional therapy improves outcomes after severe injury. In humans, recommendations for enteral nutrition in acute kidney injury (AKI) include use of an intact protein or peptide formula with moderate fat. Many critically ill patients with AKI are hypermetabolic secondary to their comorbid conditions and also have excessive losses of nutrients through dialysis techniques. Additionally, dialysis procedures themselves may increase nutritional demands. Protein intake should not be restricted; adequate nitrogen is required for healing and for other organ functions. Patients with AKI who are not on dialysis should receive a minimum of 1.0 g of protein per kilogram of body weight per day. Critically ill patients with AKI on hemodialysis should receive 1.2 to 1.5 g of protein per kilogram per day to compensate for expected losses via hemodialysis (i.e., 3-5 g of amino acid per hour). Patients on continuous renal replacement therapies may need more than 1.5 g of protein per kilogram per day. Fluid intake may be the major concern and can be limited with use of a caloric-dense formula (2 kcal/mL). Electrolyte levels (potassium, magnesium, phosphate) should be monitored carefully, and special enteral formulas with limited electrolytes may be indicated.
Hepatic Failure

Current recommendations are to use an intact protein or peptide formulas for patients with liver dysfunction. Usually 1.0 to 1.2 g of protein per kilogram per day is needed to support repair and immune function; further limitation of protein is likely detrimental. Branched-chain amino acids may be of value in selected patients if encephalopathy persists following an initial trial of intact protein or peptide diets. Branched-chain amino acid formulations are more expensive and have not been proven efficacious but may improve mental function in individual patients. Data regarding enteral nutrition in fulminating liver failure caused by viral hepatitis or drugs are insufficient to allow specific recommendations.

Inflammatory Bowel Disease

Patients with inflammatory bowel disease frequently have decreased nutrient intake, malabsorption, protein-losing enteropathies, and drug-nutrient interactions. Postpyloric enteral feeding of a peptide-based diet is usually well-tolerated in patients with inflammatory bowel disease. Bowel rest is not necessary to achieve remission. Enteral nutrition should be attempted early and TPN used only when patients fail to tolerate enteral nutrition.

Acute Pancreatitis

Numerous nutritional and metabolic alterations are induced by pancreatitis. Energy expenditure is widely variable. Pancreatic rest by withholding enteral nutrients was a common therapy for pancreatitis in the past. However, its benefit was never proven in acute or chronic pancreatitis. Oral ingestion of nutrients may lead to symptom recurrence and elevation of lipase and amylase levels. A randomized trial by Kalfarentzos and colleagues in 1997 showed that early enteral feeding in the distal small bowel is associated with improved outcomes versus TPN in patients with acute pancreatitis. Other trials reported similar results, and enteral nutrition should be attempted before initiating TPN.

Wound Healing

Sufficient quantities of specific nutrients are needed for healing. Nutrients believed to be important in wound repair include vitamin A, vitamin C, zinc, arginine, and copper. Vitamin A provided at 7 to 8 times the RDI blunted impairments of wound healing induced by diabetes or steroids in animals but did not enhance wound healing in normal animals. Similarly, zinc and vitamin C are needed in sufficient quantities, but "pharmacological" or excessive amounts do not appear to further enhance healing. Pharmacological quantities of arginine improved wound healing in numerous animal studies and increased collagen deposition in humans. Copper is a required cofactor for collagen cross-linking. Requirements of most of these nutrients are believed to increase in critical illness; however, precise requirements are not established.

Morbid Obesity

The incidence and severity of obesity continue to increase worldwide. Critically ill patients with morbid obesity should be provided high-protein hypocaloric nutrition during critical illness. Specific details are reviewed elsewhere. Common initial goals are typically described as 14 to 18 kcal per kilogram of adjusted body weight per day and 2.5 g of protein per kilogram of adjusted body weight per day. Provision of this ratio of calories to nitrogen generally requires use of high-protein formulations as well as additional supplementation with modular protein.

Postbariatric Surgery

In addition to specific goals for morbidly obese patients just described, additional challenges can occur if the patient previously had bariatric surgical interventions, as these involve varied anatomical modifications. Such patients may have altered absorptive capabilities or vitamin deficiencies. Consideration of fluoroscopic placement of feeding tubes in such patients may be prudent to avoid complications if they are unable to receive oral nutrition, especially if detailed surgical records are not readily available.
Multiple Organ Failure

Nutritional support is usually of marginal value in patients with multiple organ failure. For optimal benefits, nutritional therapy needs to be started before organ failure develops.

MONITORING RESPONSES TO NUTRITIONAL SUPPORT

Visceral protein levels may be useful. Prealbumin levels are expected to respond to short-term nutritional repletion after about 7 days. Transferrin and albumin levels are slower to improve given their longer half-lives. Of note, visceral protein levels are affected by nutritional intake as well as the clinical state (eg, inflammation, renal or hepatic dysfunction). Increasing levels of visceral proteins suggest that nutritional intake is adequate. Levels usually normalize in 1 to 2 weeks if the disease process is controlled and nutritional support is sufficient. If levels fail to increase, one should consider potential underlying infection, inflammation, or other disease processes. In addition, the clinician should reevaluate the adequacy of nutritional support and consider the utility of obtaining nitrogen balance and indirect calorimetry studies for the individual patient.

Nitrogen balance studies can determine the level of catabolism and may provide better estimates of protein needs. Improvement in nitrogen balance over time suggests that nutritional support is adequate. However, nitrogen balance may improve as catabolism decreases despite inadequate nutritional support. Reasonable indirect calorimetry (metabolic cart) goals are to keep RQ between 0.8 and 1. A respiratory quotient greater than 1 suggests lipogenesis from excessive caloric intake; values of approximately 0.7 are found in starvation and reflect fat oxidation.

DIARRHEA

Diarrhea is encountered in patients on enteral and parenteral nutrition. It is generally defined as greater than 500 mL of stool output per day (not merely as “loose

Table 4.
Causes and Evaluation of Diarrhea

<table>
<thead>
<tr>
<th>Causes</th>
<th>Examples</th>
<th>Workup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs</td>
<td>Sorbitol, antacids, H₂ blockers, antibiotics, lactulose, laxatives, quinidine, theophylline</td>
<td>No specific workup; discontinue any of these medications that aren’t absolutely necessary.</td>
</tr>
<tr>
<td>Infections</td>
<td><em>Clostridium difficile</em></td>
<td>Specific stool culture, <em>C difficile</em> toxin assay, sigmoidoscopy/colonoscopy for evidence of pseudomembranes</td>
</tr>
<tr>
<td>Infections</td>
<td>Infectious diarrhea (eg, typhoid fever, shigellosis)</td>
<td>Fecal leukocytes, culture</td>
</tr>
<tr>
<td>Other</td>
<td>Other: bacterial overgrowth, parasites, systemic infection, HIV</td>
<td>As relevant (eg, look for ova and parasites—rarely cause new diarrhea in critically ill).</td>
</tr>
<tr>
<td>Osmotic</td>
<td>May be secondary to narcotics</td>
<td>Measure stool osmotic gap; value &gt;100 suggests osmotic diarrhea.</td>
</tr>
<tr>
<td>Impaction</td>
<td></td>
<td>Rectal exam</td>
</tr>
<tr>
<td>Other causes</td>
<td>Inflammatory bowel disease, pancreatic insufficiency, short gut syndrome</td>
<td>See other references for workup.</td>
</tr>
</tbody>
</table>

*Stool osmotic gap = stool osmolality – 2(stool sodium + potassium).
stools”). See Table 4 on page 691 for recommendations for evaluation of diarrhea. The most common causes are medications and infections. Many elixir forms of medications contain sorbitol, which can cause diarrhea, especially if multiple doses are given. Once the specific causes of diarrhea have been evaluated, it can be treated with antimotility agents (ie, narcotics). Treatment with probiotic agents such as Lactobacillus can be considered, but evidence of its benefit in this setting is lacking.

SUMMARY

For optimal benefits and improved outcome, enteral nutrition should be initiated within 48 hours of ICU admission in most critically ill patients.

Most critically ill patients should be given 25 kcal per kilogram of IBW per day and 1.5 g of protein per kilogram of IBW per day as initial goals. An exception is patients with morbid obesity, for whom hypocaloric high-protein strategies are recommended.

Total parenteral nutrition is indicated only when enteral nutrition is not possible. Many studies have shown superiority of enteral nutrition over TPN. Supplemental TPN administered with enteral nutrition aimed at meeting energy expenditure goals is expensive and has not shown benefit; indeed a recent large, multicenter trial reported worse outcomes with early supplemental TPN.

Numerous studies suggest that early enteral feeding using immune-modulating formulas is associated with improved outcome in specific ICU populations (trauma, burns, and GI surgery patients).

REFERENCES


