CHAPTER 65 ■ PRACTICAL ASPECTS OF NUTRITIONAL SUPPORT

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“If the gut works, use it. If it isn’t working, make it work.” This adage summarizes how a clinician should approach nutritional support in the intensive care unit. Although it may seem intuitive that parenteral nutrition should improve morbidity and mortality because the patient is “being fed,” conclusive data are sparse. On the contrary, much has been published on the benefits of enteral feeds, especially if the patient is fed early (1,2).

Being familiar with nutrition support is not just about calories and proteins the patient needs, but requires familiarity with the ordering, initiating, monitoring, and discontinuing processes of nutrition support as well. This chapter is meant to complement the previous chapter by taking the clinician through the practical aspects of nutritional support.

References


WRITING A TOTAL PARENTERAL NUTRITION ORDER

In 2003, the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) assembled a task force to look into the safe practice of parenteral nutrition practice. Out of this task force emerged the 2004 A.S.P.E.N. guidelines on Safe Practice for Parenteral Nutrition (3), as well as the 2003 A.S.P.E.N. Nutrition Support Practice Manual (2nd ed.) (4). The latter is considered to be one of the primary resources for nutritional support.

Life-threatening errors continue to occur in the preparation and delivery of parenteral nutrition (PN) admixtures to
patients. Many of these errors are related to the ordering process. One solution to this problem is to use a standardized PN form that is institution-specific. Research has demonstrated the benefits of a standardized order-writing process in reducing prescription errors (3). These forms, however, are not perfect themselves, as shown by one study, which reported an increase in prescriber errors after a standardized PN order form was introduced (3).

Providing nutrition support to critically ill patients is a complex but important task. The ultimate goal should be to minimize loss of lean body mass, especially in patients with burns, sepsis, acute respiratory distress syndrome, and trauma. Energy expenditure of the critically ill patient depends on the underlying disease state, as well as the nutritional status of the patient before the injury or illness. Although the Harris-Benedict equation is widely used to estimate the basal energy expenditure, the stress and activity factors used to adjust for the severity of illness may be excessive, and can lead to overfeeding (4). One recommendation from the A.S.P.E.N. guidelines, as well as from the American College of Chest Physicians (ACCP), is using a total energy requirement of 2.5 kcal/kg/day (4,6). If the patient is obese, then an adjusted body weight should be used in the calculation (4).

Protein requirements for critically ill patients with normal renal function can range from 1.3 to 2 g/kg/day (moderate to severe stress), using the preemorbid body weight or the adjusted body weight if obese (4). In patients with acute renal failure, the following amounts of protein are recommended: 0.8 to 1.2 g/kg/day if patients are not dialyzed, 1 to 1.4 g/kg/day in patients receiving dialysis, and 1.5 and 2.5 g/kg/day in patients undergoing continuous renal replacement therapy (CRRT) (4). For chronic kidney disease, the A.S.P.E.N. recommends 0.5 to 0.6 g of protein/kg/day (4). The ACCP, on the other hand, recommends no change in the amount of protein given to patients with acute renal failure versus patients with normal kidney function (i.e., 1.2–2 g/kg/day) (6). In chronic renal failure, the ACCP recommends 0.5 to 0.8 g of protein/kg/day (6).

There are at least three different ways PN can be ordered. If the patient has only peripheral venous access, peripheral parenteral nutrition (PPN) is used. Compared to total parenteral nutrition (TPN), PPN is lower in osmolarity (<900 mOsm/L) to minimize thrombophlebitis (7). For formulas to be given via central line, TPN can be administered in two ways. One is a two-in-one TPN formula, which is protein and dextrose in one bag, with the intravenous fat emulsions (IVFEs) hung separately. The other method is a three-in-one TPN formula, in which all three fuel substrates (amino acids [AAs], dextrose, and fats) are mixed in one bag. Each has advantages and disadvantages. The two-in-one formula allows visualization of particulate matter but takes up more nursing time and requires two different intravenous lines. The three-in-one is more user friendly since only one bag needs to be hung, but the cloudiness of the solution will not allow visualization of particulate matter. The A.S.P.E.N. guidelines do not favor one formula over another.

Most institutions have premixed PN formulas with known amounts of protein (g/L) and calories (kcal/L) to make it easier for order writing. For three-in-one formulas, once the caloric and protein needs have been assessed, the volume of PN needed is calculated to match the assessed needs. For instance, if 2 L of formula X from your institution is needed to meet needs, then the PN rate should be 83 mL/hour (i.e., 2,000 mL/day ÷ 24 hours/day). If your institution does not have premixed PN formulas or none of the formulas is appropriate for your patient, then a customized mixture will be necessary. This will be discussed later in the chapter.

For two-in-one formulas, fat is administered separately, usually three times a week. To calculate the total caloric contributions, the amount of calories per week from fat is totaled and then divided by 7 days per week to obtain the calories per day. For example, Intralipid 20% 500 mL containing 1,000 kcal is given three times a week. The caloric contribution per day would be 3,000 kcal/week ÷ 7 days/week, which equals 429 kcal/day from fat. This amount is then added to the known caloric contributions provided by the dextrose and amino acids in the two-in-one formula.

Most institutions have default amounts of additives (electrolytes) to facilitate the ordering process. The amounts are based on guidelines and may not suit every patient. For example, using default additives with potassium and phosphorus in a renal failure patient can lead to hyperkalemia and hyperphosphatemia, respectively.

Ordering electrolytes and other additives is as much an art as it is a science. With practice, one can develop a “feel” for how patients will respond to the additives depending on their condition. The most difficult part of the ordering process is how much electrolyte to add initially. The subsequent adjustments are easier with adjustments to increase, decrease, or keep the additives the same, depending on the laboratory values. Table 63.1 summarizes how to determine the quantity of electrolytes to add to PN solutions.

### INITIATING PARENTERAL NUTRITION

The A.S.P.E.N. guidelines suggest no more than 150 to 200 g/day of glucose initially to ensure tolerance of PN (4). Thus, it may be prudent to infuse only 1 L of the TPN on the first day (i.e., 42 mL/hour) and reaching goal rate on day 2 or 3, depending on the patient’s tolerance of volume and macronutrients. It is imperative that central line placement be verified by radiography before initiating TPN, and that TPN be administered through a dedicated infusion port via an infusion pump that is equipped with protection from “free flow” and has reliable alarms. To reduce the chance for infusing particulates, microorganisms, and pyrogens, a 1.2-micron filter may be used (anything smaller than 1.2 micron may filter out the fat emulsions in a three-in-one formula). Alternatively, a 0.22-micron filter may be used for a two-in-one formula. PPN formula is not as calorie dense and contains less protein; therefore, it may be initiated at goal rate (assuming the patient is able to tolerate the fluid load). The PN administration set must be changed every 24 hours using aseptic techniques and universal precautions. An exception is if the PN does not contain fat emulsions (i.e., the two-in-one formulation); then the administration set may be changed every 72 hours (4). However, the administration set used in infusing the IVFE separately must be discarded after use or at least every 12 hours (4).
If problems occur with the TPN bag that render it not usable (e.g., a leak in the bag) and the patient is on a rate >42 mL/hour, dextrose 10% (D10W) or dextrose 10% with 0.9% sodium chloride (D10NS) should be infused at the same rate as the TPN to avoid rebound hypoglycemia. In the same scenario, dextrose 5% (D5W) may be substituted in place of PPN, not because of rebound hypoglycemia, but more for maintaining caloric intake.

**CYCLIC PARENTERAL NUTRITION**

PN that is infusing 24 hours a day means that the patient is tethered to the intravenous pole, limiting mobility. Getting the patient who is receiving PN to eat more may be problematic because the satiety center is constantly being stimulated. A reduced oral intake can be expected if more than 25% of caloric needs is provided by PN (9). In these two scenarios, transitioning over to cyclic PN may be a good option. Cyclic or nocturnal PN is almost like regular PN except that instead of infusing the PN over 24 hours, the same volume is infused over a shorter period (12 or 14 hours), starting in the evening and finishing in the morning. Cyclic PN allows patients to be more mobile during the day, as well as have more of an appetite. Other benefits of cyclic PN include less deterioration of liver function (10).
Before transitioning to cyclic PN, the nutritional goal needs to be defined: Full support versus supplemental to a diet. Full support means that the total amount of protein and calories will be provided. In this case, it is important to make sure that the TPN is already concentrated, since the patient will be receiving the same volume that was previously given over 24 hours over a shorter period of time. If the goal is to have the patient eat more but not get behind in nutrition, then one can provide 50% of assessed needs as cyclic PN while the patient is fed orally or enterally. An important aspect of cyclic TPN is calculating the tapered flow rate to minimize harmful fluctuations of blood sugar (i.e., hyperglycemia during initiation of PN and rebound hypoglycemia during cessation of PN). One simplified method of calculating the redius cyclic PN rate comes from Stanford University (11):

\[ v = r + 4t - 4r + 2r + t, \]  
\[ x = \text{volume infused}, \]  
\[ v = r \times \text{time}, \]  
\[ v = 6r + 4r - 16r \]  
\[ v = 4rt - 10r \]  
\[ v = r \times (4t - 10) \]  
\[ r = v / (4t - 10) \]  
\[ r = 1,500 \text{mL}/(4t - 10) \]  
\[ r = 39.47 \text{mL/hour} \]

For example, the patient will be receiving a total of 1,500 mL of PN formula X over 12 hours (t = 12). To calculate the cyclic TPN rate (r), the formula uses the model (r mL/hour × 1 hour) + (2r mL/hour × 1 hour) + (4r mL/hour × cyclic PN time – 4t) + (2r mL/hour × 1 hour) + (r mL/hour × 1 hour) + (2r mL/hour × 1 hour) + (4r mL/hour × cyclic PN time – 4t) + (2r mL/hour × 1 hour) + (r mL/hour × 1 hour). Therefore, the cyclic TPN will be ordered as follows: 40 mL/hour × 1 hour, then 80 mL/hour × 1 hour, then 160 mL/hour × 8 hour, then 80 mL/hour × 1 hour, then 40 mL/hour × 1 hour, then stop. It is important that there be a "ramp up" and "ramp down" during cyclic TPN infusion to avoid significant glucose fluctuations. Glucose may be drawn 60 minutes after the maximal infusion rate, or 60 minutes after discontinuation of cyclic PN to make sure the patient is tolerating (4).

### HIDDEN SOURCES OF KCALS

Inadvertent hypercaloric feeding can result in increased carbon dioxide production, hyperglycemia, and hepatomegaly, all of which may be detrimental to the critically ill patient. It is important to pay attention to medications that can inadvertently lead to excessive calories. Propofol, which is suspended in 10% Intralipid, contributes 1.1 kcal/mL. A patient on a relatively high dose of 50 µg/kg/minute (assuming a 70-kg patient) can easily receive an extra 554 kcal/day.

Another hidden source of calories is the dextrose concentration in the dialysate fluid of patients receiving CRRT. Diffusion greatly influences dextrose absorption across the hemofilter. It has been reported that the daily caloric contribution ranges from 123 to 2,188 kcal depending on the dextrose concentration of 0.5% to 4.25% in the dialysate solution. Approximately 43% to 45% of dextrose can be absorbed by the body across the hemofilter (12). Other factors that affect the degree of dextrose absorption are the dialysate flow rate, blood flow rate, ultrafiltration rate, arterial blood glucose concentration, and integrity of the hemofilter (12-14). Using the lowest possible concentration of dextrose in the dialysate is the best way to avoid hyperglycemia.

### FLUID RESTRICTION

In institutions that use electronic admixing equipment (e.g., Baxter’s Autumix/Micromix), formulating the TPN is virtually just a touch of a button. Reformulating PN formulas to maximize caloric density and minimize fluids is not labor intensive. Although mixing standard or nonstandard formulas makes little difference from an admixing standpoint when using the automatic mixing machines, the calculation of a nonstandard PN formula can be tedious and requires knowledge of base solution stabilities used by the pharmacy to admix the PN (see calculations below).

### ESTIMATING PROTEIN, FAT, AND CARBOHYDRATE REQUIREMENTS

As discussed earlier, most institutions will likely have premixed standard PN formulas for ease of ordering. However, there are times when the clinician has to formulate a PN formula for special cases. One instance could be if the assessed calories and proteins do not match up to any of the premixed formulas. Another instance could be if the patient has hypertriglyceridemia, and the PN formula has to be adjusted so that the fat is taken out and the dextrose is increased to compensate for the absence of fat. To better understand how to formulate a three-in-one PN formula, a sample case will be presented.

#### Base Solutions (may vary with different institutions)

- **Amino acids base solution:** Travasol 10%
- **Dextrose base solution:** 70%
- **Intralipid base solution:** 20%

#### Assessed caloric needs: 2,000 kcal/day

**Assessed protein needs: 130 g/day**

**STEP 1:** Assess calories and volume provided by protein (4 kcal/g).

\[ 4 \text{kcal/g} \times x = 130 \text{g} \quad (\text{see Table 65.2}) \]

**STEP 2:** Assess amount of nonprotein calories required. Nonprotein calories should be 15% to 30% fat based, and

<table>
<thead>
<tr>
<th><strong>TABLE 65.2</strong></th>
<th><strong>Respiratory Quotient (RQ) and Calories per Gram of Different Fuel Substrates</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fuel substrates</strong></td>
<td><strong>RQ</strong></td>
</tr>
<tr>
<td>Fats</td>
<td>0.7</td>
</tr>
<tr>
<td>Proteins</td>
<td>0.8</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>1</td>
</tr>
</tbody>
</table>
the rest (70%–85% of nonprotein calories) should be dextrose based (4).

2. $000 \text{ kcal (total caloric needs)} - 520 \text{ kcal (calories from proteins)} = y$

$y = 1,480 \text{ kcal (nonprotein calories needed)}$

$1,480 \text{ kcal} \times 0.2 (\text{ i.e., } 20\% \text{ calories from fat})$

$\sim 300 \text{ kcal (fat calories)}$

$1,480 \text{ kcal} - 300 \text{ kcal} = 1,180 \text{ kcal (dextrose calories)}$

STEP 2: Assess volume contributed by dextrose (3.4 kcal/g) and fat calories, rounding up the numbers.

Fat calories = 300 kcal

Intralipid = 20% or 2 kcal/mL (see Table 65.2)

Therefore, 300 kcal = 150 mL fat volume

Since 20% is $20 \text{ g/100 mL} = 150 \text{ mL} = 30 \text{ g fat}$

Dextrose calories = 1,180 kcal = 3.4 kcal/g

$= 347 \text{ g (see Table 65.2)}$

Dextrose 70% = 70 g/100 mL = 347 g/z

$z = 495.7 \text{ or } 496 \text{ mL (volume from dextrose)}$

STEP 4: Add up the protein, fat, and dextrose volume to calculate minimum amount of fluid needed to make the TPN formula.

1,300 mL (from AA) + 150 mL (from fat) + 496 mL (from dextrose) = 1,946 mL

1,946 mL/day = 24 hour/day = $\sim 81 \text{ mL/hour}$.

The 1,946 mL volume represents the minimum amount of volume needed to make the TPN (i.e., the TPN is “concentrated”).

STEP 5: Put it all together. The PN order would look something like this:

Amino acids = 130 g

Dextrose = 347 g

Fat emulsion = 30 g

Rate = 81 mL/hour (i.e., 1,946 mL over 24 hours)

This formula will provide 1,997 kcal + 130 g protein over 24 hours

If the clinician wanted 100 mL/hour of fluids, the rate can simply be changed to 100 mL/hour (i.e., 2,400 mL over 24 hours; sterile water is added to make up the balance) without affecting the amount of calories and proteins given to the patient. Since 81 mL/hour (1,946 mL) represents the minimum volume needed to make the above TPN, it is not possible to go below 81 mL/hour without decreasing the calories and proteins given to the patient.

ELECTROLYTE ABNORMALITIES

Refeeding syndrome is an imbalance of electrolytes as well as vitamins, micronutrients, and fluids that occurs within the first few days of refeeding malnourished patients as nutrients replete the intracellular space (15). The hallmark biochemical findings include hypophosphatemia (intracellular shift plus depletion of phosphorus substrate to synthesize adenosine triphosphate [ATP]), hypomagnesemia (intracellular shift plus magnesium is a cofactor in many enzymatic functions), and hypokalemia (intracellular shift of potassium with insulin secretion as a response to dextrose infusion). Patients may exhibit respiratory distress, cardiac arrhythmias, congestive heart failure, hemolytic anemia, or paresthesias, or they may die (16). The three most important steps in preventing refeeding are (a) high-risk patients (chronic alcoholism, kwashiorkor, marasmus, rapid refeeding) and those receiving high TPN rates must be identified (17); (b) baseline electrolytes must be checked before the initiation of PN (4,17), and low magnesium, phosphorus, or potassium levels must be corrected immediately; (c) the TPN rate should be advanced slowly (<110 g/day of carbohydrates) as tolerated over several days before going to the goal rate (4,17). In patients receiving enteral nutrition (EN), the rate could be advanced more aggressively if needed, provided that electrolytes are monitored closely and replaced in a timely manner (18).

Replacing electrolytes is both a science and an art, because patients respond differently. Table 65.3 will help guide the clinician in managing electrolyte imbalances that occur. There are two things to remember when adjusting the electrolytes in PN: First, the degree of metabolic derangements must be determined before any adjustments are made. Second, PN should not be used to replace electrolytes rapidly, but should be used for maintenance.

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MONITORING

The potential for serious complications is high in patients receiving PN unless careful monitoring is conducted by clinicians. Furthermore, appropriate monitoring can be cost effective by avoiding complications. Suggested protocols for monitoring PN in adults are shown in Table 65.4.

WRITING ENTERAL ORDERS

Ordering enteral feedings is less complex than ordering PN, but it could be just as confusing with many different formulas. Enteral feeding should be started as early as possible since it is a “pharmacotherapy” for the gut (improves mesenteric blood flow and maintains gut integrity). Feeding early, which is defined as 48 hours within mechanical ventilation onset, is associated with a 20% decrease in intensive care unit (ICU) mortality and a 25% decrease in hospital mortality, according to a recent retrospective, multi-institutional study looking at 4,409 patients (1). When choosing enteral formulas, consideration depends on the patient’s digestive capability, fluid restriction status, electrolyte balance, nutrient requirements, disease state, and possible routes available for administration.

Enteral formulas may be categorized into the monomeric (which contain free amino acids with or without peptides, with modified fat) and the polymeric formulas. Most enteral formulas fall in the semi-synthetic polymeric formulas, which are more cost effective but require patients to have digestive capability. Monomeric formulas are for patients with malabsorption, such as short-gut syndrome. Because of the cost associated with monomeric formulas, polymeric formulas should be tried first. For instance, in patients with pancreatitis, instead of using monomeric formulas, adding pancreatic enzyme tablets may help with polymeric tube feed tolerance. If the patient
TABLE 65.3
AN EXAMPLE OF MANAGEMENT GUIDELINES FOR METABOLIC COMPLICATIONS IN ADULTS INDUCED BY PARENTERAL NUTRITION

<table>
<thead>
<tr>
<th>Complication</th>
<th>Target Value</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycemia</td>
<td>&gt; 200 mg/dL</td>
<td>Once daily requirements of insulin are known from the insulin sliding scale. Add 30–60% of total insulin dose to TPN. Consider insulin drip if blood glucose is uncontrolled, or if patient is edematous with unreliable absorption of subcutaneous insulin. Goal blood sugar is 80–110 mg/dL in critically ill surgical patients.</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>&lt; 80 mg/dL</td>
<td>If related to sudden discontinuation of TPN, administer D10W or D10NS at the same rate as the TPN. If related to insulin in TPN, initiate continuous glucose supplement (e.g., D10W). If glucose is still below desirable level, discontinue TPN and hang D10W or D10NS at the same rate as the TPN.</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>&gt; 150 mEq/L</td>
<td>If hypovolemic, give isonatremic or hypertonic fluid depending on degree of hypovolemia. If euvoletic or hypervolemic, reduce sodium in TPN and other sources. Increase symptomatic protein content.</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>&lt; 130 mEq/L</td>
<td>If hypervolemic, restrict fluid intake ± diuretics; if euvoletic/hypervolemic, increase sodium content in TPN; if hypovolemic, give additional isotonatremic fluid.</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>&gt; 5 mEq/L</td>
<td>If TPN related and patient symptomatic, discontinue TPN and initiate D10W or D10NS at the same rate as the TPN. If patient is asymptomatic, decrease K+ in TPN and other sources.</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>&lt; 3.5 mEq/L</td>
<td>Give KCl bolus either IV or enterally (4 mEq for each 0.1 mmol/K+; maximum IV KCl concentration is 20 mEq/50 mL via central venous access and 10 mEq/50 mL via peripheral vein). Add K+ in TPN.</td>
</tr>
<tr>
<td>Hypermagnesemia</td>
<td>&gt; 2.6 mEq/L</td>
<td>If TPN related and patient is symptomatic, discontinue TPN and start D10W or D10NS at the same rate as the TPN. If patient is asymptomatic, decrease Mg2+ in TPN.</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>&lt; 1.8 mEq/L</td>
<td>Give magnesium bolus either IV or enterally (1 g MgSO4 = 8 mEq; 1 tablet magnesium oxide = 6 mEq). Maximum rate of IV infusion is 1 g in 7 min. (If level is &lt;1 g/l, give 4-6 g IV or enteral equivalent; if level is &gt;1 but &lt;1.8, give 2-4 IV or enteral equivalent). Increase Mg2+ in TPN.</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>&gt; 10.2 mg/dL</td>
<td>If TPN related and patient is symptomatic, discontinue TPN and initiate D10W or D10NS at the same rate as the TPN. If patient is asymptomatic, decrease Ca2+ in TPN. Check ionized calcium in critically ill patients.</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>&lt; 8.5 mg/dL</td>
<td>Correct for hyperalbuminemia [True Ca2+ = Ca2+ observed + 0.8 (4 – albumin observed)]. Increase Ca2+ in TPN if corrected Ca2+ is trending low. If hemodynamically unstable and/or critically ill, obtain an ionized calcium level (normal range 1.05–1.35 mg/dL). Give calcium chloride bolus i/v or enterally (1 g CaCl2 = 13.6 mEq; 1 g calcium gluconate = 4.7 mEq).</td>
</tr>
<tr>
<td>Hyperphosphatemia</td>
<td>&gt; 4.8 mg/dL</td>
<td>If TPN related and patient is symptomatic, discontinue TPN and run D10W or D10NS at the same rate as the TPN. If patient is asymptomatic, decrease P (PO4)3– in TPN.</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>&lt; 2.4 mg/dL</td>
<td>Phosphorus replacement should be given over 6 h to avoid hypophosphatemia. If level is &lt;1, give 30 mmol P (PO4)3– × 2 doses IV plus check phosphorus level 1 h after end of infusion; if level is &gt;1 but &lt;1.8, give 30 mmol P (PO4)3– × 1 dose or enteral equivalent and check phosphorus level 1 h after end of infusion; if level is ≥1.8 but &lt;2.4, give 15 mmol PO43– or enteral equivalent. One packet of Neutra-Phos enterally = 8 mmol of PO43–. Increase phosphorus in TPN.</td>
</tr>
</tbody>
</table>

**Metabolic acidosis**
- **pH** < 7.4
- **HCO3–** < 23

**Metabolic alkalosis**
- **pH** > 7.4
- **HCO3–** > 29

*Consider increasing acetate-to-chloride ratio.*

*TPN, total parenteral nutrition; D10W, dextrose 10%; D10NS, dextrose 10% with 0.9% sodium chloride.*

Continues to have absorption issues, then monomeric formulas could be substituted.

Enteral formulas also vary by caloric density. In patients with chronic renal failure who require fluid restrictions, choosing polymeric formulas with high caloric density (high caloric-to-fluid ratio) may be helpful. Enteral formulas also differ in the amount of protein, the carbohydrate-to-fat ratio, and the fiber content.

Each enteral feed formula has known amounts of kcal/mL, as well as g/L of protein. Once caloric and protein needs are assessed, the volume needed can be calculated. Unlike PN, in which the amounts of protein, dextrose, and fat can be easily modified, enteral feeding formulas are fixed. However, there are protein powders available if supplemental protein is necessary.

Before starting any enteral feeds, feeding tube placement must be confirmed by abdominal radiography and documented...
in the orders. Once the enteral feeding formula has been selected, indicate initial strength (e.g., full or half-strength), initial rate in mL/hour, and desired progression regimen, followed by the goal rate. The rate can be started at 10 to 20 mL/hour and be advanced by 10- to 20 mL/hour every 8 hours as tolerated until goal (as long as residual is <200 mL via nasogastric tube or <100 mL via gastrostomy tube in 4 hours) (19). Many institutions have converted to a “closed system” to reduce the risk of microbial contaminations by minimizing the number of times the formula is manipulated. Enteral feedings start at full strength since a “closed system” will make it difficult to order partial-strength formulas.

When the patient is ready to transition over to a regular diet, similar strategies employed with the cyclic PN can be used. The patient may be converted to bolus feeding of the full-strength enteral formula with increases of 60 to 120 mL every 8 to 12 hours as tolerated up to goal volume. This simulates meals plus snacks (4). Bolus feedings are more physiologic, allowing the brain to stimulate sensations of hunger and satiety. When the patient is able to consume 60% of nutritional needs by mouth, the tube feeding can be discontinued (4).

**“DESIGNER” ENTERAL FEEDINGS: FACTS AND MYTHS**

Designer enteral feedings or specialized formulas contain modified protein and other ingredients to assist patients in stressed states. Sometimes the ratio of carbohydrate to fat, and the sources of fat, may also be altered to achieve desired effects.

**Hepatic Formula**

Specialized hepatic formulas (e.g., NutriHeal) differ from the standard formulas in two ways: the actual protein content is usually lower (around 40-46 g/L) and the ratio of branched-chain amino acids (BCAAs) to aromatic and ammonia-forming amino acids (AAAs) is higher in the hepatic formula. The theory is that when patients present with grade II or higher encephalopathy, or whose grade of encephalopathy has worsened, nutrient-controlled trial from 2003 demonstrated improvement in patients with acute overt encephalopathy, restriction or withdrawal of proteins may be necessary. Once encephalopathy has been reversed, adequate protein may be administered to target a positive nitrogen balance. Based on the available studies, and cost consideration of up to 20 times more, the “hepatic formula” should be restricted to patients who present with grade II or higher encephalopathy, or whose grade of encephalopathy worsens with the advancement standard enteral formulation.

**Renal Formula**

Enteral formulas in this class (e.g., Nepro) tend to be more calorie dense and low in electrolytes and mineral contents (especially potassium and phosphorus). The purpose of these modifications is to provide adequate nutrients but at the same time minimize complications such as uremia, fluid overload, and electrolyte accumulation. The older renal formulas differ from standard amino acids in that they were designed for patients...
who could not tolerate dialysis or for whom dialysis was being avoided; thus, the formulas tend to be enriched with essential amino acids (EAA). The rationale with this admixture is that the urea from EAAs would be recycled to produce nonessential amino acids. Evidence supporting the use of the older renal formulas is scant and of poor quality. In addition, the cost of the older renal formulas is 10 to 15 times that of standard polymeric formulas. These formulas have now been replaced with standard polymeric formulas since most patients with acute renal failure are now being dialyzed or are receiving CRRT. The new renal formulas continue to be more calorie dense (usually 2 kcal/ml) with minimal electrolytes or additives (K⁺, Mg²⁺, PO₄⁻) that could accumulate in renal failure. They are appropriate for patients whose serum electrolyte and mineral levels are difficult to control.

**Pulmonary Formula**

Respiratory quotient (RQ) is defined as the molecule of carbon dioxide produced per molecule of oxygen consumed (VCO₂/VO₂). Pulmonary formulas (e.g., PulmoCare) are designed to decrease carbon dioxide by providing the fuel substrate with the lower respiratory quotient (see Table 63.2). To achieve this, the manufacturer decreases the carbohydrates-to-fat ratio to achieve fat calories of about 38% to 55%. By decreasing the carbohydrates (RQ = 1.0)–to–fat (RQ = 0.7) ratio, the assumption is that the carbon dioxide production is reduced as well. Studies looking at the benefit of high-fat enteral feeds have been criticized as having a small sample size. One trial looking at high-fat enteral formula in 12 patients with chronic airflow obstruction suggests that the higher-fat formulas may be less likely to impair work performance in patients with chronic airflow obstruction (23). Another trial looking at 20 artificially ventilated patients demonstrated that the high-fat group spent 62 hours less time on the ventilator and the result was clinically significant (24). More recent evidence suggests that reducing total calories is more important than the source of calories, in terms of reducing carbon dioxide production (since the RQ of lipogenesis or overfeeding is 1.4–2.0) (25). The source of fat has also changed over the years. Many formulas marketed today use canola oil and medium-chain triglyceride (MCT) oil as the primary sources of fat, compared to fat formulas containing higher omega-6 fatty acids (precursor of arachidonic acid) that were used in the clinical trials. Whether the data from the earlier studies can be extrapolated to reflect the effect of the modern formulas on CO₂ remains to be answered.

**Metabolic Stress (Critical Care) Formula**

The critical care formulas (e.g., Perative) are somewhat similar to the hepatic formulas in that both have a high percentage of BCAAs, which are the preferred substrate of muscles during critical illness. Differences include higher protein content and fewer aromatic amino acids in the critical care formulas compared to the hepatic formulas. The clinical trials looking at these formulas are small, and have been equivocal from the standpoint of nutritional markers. Overall, BCAA-enriched enteral formulas are not the current standard of practice. Because this class of enteral formula, like the immunomodulating formulas, may contain immune-enhancing agents (i.e., arginine), they must be used cautiously in critically ill septic patients (see next section on immunonutrition timing).

**Immunomodulating Formula**

This class of enteral feedings is a subset of the metabolic stress formulas. Compared to the hepatic, renal, or pulmonary formulas, the formula designed to reduce inflammatory response (e.g., acute respiratory distress syndrome [ARDS]) is a more recent development. These so-called immunomodulating formulas are standard enteral formulas fortified with omega-3 fatty acids, nucleotides, arginine, and/or glutamine. The enteral feeding Opepa contains no glutamine and arginine, but does contain 55% of calories as fat, of which the omega-6-to-omega-3 ratio is optimized to 2:1. Formula Impact has 23% of calories as fat, has arginine and glutamine, and contains 17.1% BCAAs in protein, and the omega-3-to-omega-6 ratio is 1.4:1. Formula Immun-Aid has 36% protein as BCAAs, contains arginine and glutamine, has 26% fat calories, and has an omega-6-to-omega-3 ratio of 2.1:1 (ratio similar to Opepa). The theory behind this class of enteral feeds is that by minimizing omega-6 fatty acids and optimizing the ratio of omega-6 to omega-3 fatty acids, the inflammatory response is reduced, resulting in less lung injury.

Based on the early clinical trials and meta-analyses, which have mainly looked at Immun-Aid and Impact, it appears that surgical patients benefited most from this class of enteral formula. There was no effect on mortality in the meta-analyses, but there were significant reductions in infection rate, ventilator days, and hospital length of stay (26). More recent trials in this class of enteral feeds have focused on formula (i.e., Ox-e-pa) enriched with eicosapentaenoic acid (EPA) from sardine oil and γ-linolenic acid (GLA) from borage oil plus antioxidants (vitamin E, vitamin C, β-carotene, taurine). One prospective, double-blind, placebo-controlled, randomized trial in 165 critically ill patients with severe sepsis found that this formula decreased mortality (19.4% absolute risk reduction), as well as decreased the number of days on the ventilator (27). Another prospective, randomized, controlled trial looking at nutritional support enriched with EPA + GLA in 100 patients with acute lung injury concluded that the formula reduced the length of time on the ventilator (28). Despite the many pieces of evidence pointing toward the benefit of immunomodulating formulas, it does have to be used with caution and at the right time. This will be discussed later in the chapter.

**Glycemic Control Formula**

The glycemic control enteral formulas are very similar to the pulmonary formulas in their design. The carbohydrate (35%–40%–to–fat (40%–50%–) ratio is reduced compared to standard formulas, with varying ratios of omega-6 to omega-3 fatty acids (e.g., Glucerna). This modification results in a greater proportion of fat calories than recommended (American Dietetic Association recommends ≤30% of calories from fat [29]). Various soluble fibers and/or soy polysaccharides are also added to the glycemic enteral formulas.
Clinical trials looking into the use of these specialty formulas in critically ill patients are limited. As with the pulmonatory formulas, the high fat content in the glycemic formulas can decrease stomach emptying, which could decrease tolerance to these formulas even more in patients with diabetic gastroparesis. If glycemic control is needed, consider insulin drip. More studies are needed before these formulas can be recommended.

### TIMING OF SPECIALIZED ENTERAL FEEDING (IMMUNONUTRITION) AND MANIPULATION OF IMMUNE AND INFLAMMATORY SYSTEM

Immunonutrition enteral feedings (e.g., Impact and Immun Aid) are formulas containing nutrients that have been shown to influence immunologic and inflammatory responses in humans. These so-called immune-enhancing agents usually include the following glutamine, arginine, omega-3 fatty acids, nucleotides, and antioxidants. Heyland et al. did an extensive meta-analysis to determine whether immunonutrition is safe and effective in critically ill patients (30). Although they were not able to find any mortality benefit, immunonutrition was associated with a statistically significant decrease in infectious complications and shorter length of hospital stay. When subgroup analyses of critically ill patients versus elective surgical patients were done, the results were surprising. There was a trend toward higher mortality in the critically ill patients, leading to the recommendation that immunonutrition not be used in critically ill patients until more clinical trials are conducted.

Bertolini et al. conducted a randomized multicenter trial comparing parenteral and early enteral nutrition containing immune-enhancing formula (Perative) in patients with and without severe sepsis (31,32). Results of an interim analysis indicated that mortality in severely septic patients receiving immune-enhancing enteral formulas was significantly higher than in those receiving parenteral nutrition (44.4% vs. 14.3%), and the study was aborted. Interestingly, in patients without sepsis, there was no 28-day mortality difference between the patients receiving parenteral nutrition versus immune-enhancing enteral formulas. However, those receiving immunonutrition had fewer episodes of septic shock, and the ICU length of stay was 4 days shorter.

Based on these studies, immunonutrition formulas should be used with caution in critically ill septic patients. Based on expert opinions, the immune-modulating nutrient likely to be responsible for the excess harm is arginine (see later), which has not been well studied in a randomized, clinical fashion in critically ill patients (33). In the critically ill nonseptic patients, immune-enhancing formulas appear to be beneficial if started within 48 hours.

### IMMUNOMODULATORS

#### Glutamine

Normally nonessential, glutamine becomes conditionally essential during times of high stress as evidenced by a decrease in glutamine concentration in the body during this period (34). Glutamine comes in the free form (unstable in solution, so only found in dried form) and protein-bound form as seen in all protein sources used in enteral formulas. Glutamine is an important amino acid because of its involvement in many vital functions, such as (a) gluconeogenesis; (b) synthesis of glycogen, nucleotides, nucleic acid, and urea; (c) ammoniagenesis; and (d) ammonia reduction (34). Glutamine is also the preferred fuel substrate for rapidly dividing cells in both the small intestine mucosa and the immune system (34). Furthermore, glutamine plays a big part in the antioxidation process, since it is the precursor of glutathione, a strong antioxidant (35). In critically ill patients, about 30 g/day or 0.5 g/kg/day of glutamine is needed to meet both basal and increased enterocyte requirements (35).

A meta-analysis looking at 14 randomized trials concluded that glutamine supplementation in critically ill patients may be associated with a reduction in complication and mortality rates (35). In the same meta-analysis, glutamine supplementation in surgical patients may be associated with a reduction in infectious complication rates and shorter hospital stay without any adverse effect on mortality. Evidence from this meta-analysis also suggests that parenteral glutamine is more effective than enteral glutamine. The effectiveness and benefits of glutamine supplementation are still not conclusive. A recent prospective but unblended study examining the benefit of enteral glutamine supplementation in 185 surgical ICU patients failed to detect a mortality difference between the control and treatment group (36).

#### Arginine

Like glutamine, many would consider arginine also to be a conditionally essential amino acid. About 5% to 6% of arginine comes from intake of proteins, and the rest is synthesized by the body via the urea cycle. Arginine is important in ammonia detoxification, as well as producing nitric oxide, which, among other things, mediates vasodilatory effects of endotoxin (37). Arginine supplementation has been purported to enhance wound healing in humans, mainly via improvements in in vitro markers of immune function (e.g., CD4 count), rather than outcome measures like infection rates (38).

Most human studies have largely been conducted using immune-enhancing diets containing relatively high amounts of L-arginine. The optimal dose of arginine in the critically ill patient is unknown, but a dose of up to 30 g/day is generally well tolerated by relatively healthy people (39).

Although evidence is not robust, arginine supplementation is capable of promoting an increase in nitric oxide production, which can lead to vascular smooth muscle dilation (36). Given this theoretical potential for harm, the clinician should use arginine-containing formulas with caution in critically ill septic patients (31,33,40).

#### Nucleotides

Nucleotides are structural units for nucleic acids and various enzymes involved in energy transfer. They are essential for the formation of new cells (e.g., intestinal epithelium) and...
in the synthesis of protein, lipids, and carbohydrates. Nutri-
cleotides are of interest because supplementation of infant for-
mulas with nucleotides was noted to enhance bifidobacteria growth in the gastrointestinal tract. Bifidobacteria decrease the colonic lumen pH and inhibit growth of enteric bacteria (41).

Studies involving nucleotide use in humans are very limited, and like arginine, the studies available often involve immune-enhancing diets fortified with nucleotides, making it difficult to determine the effects of the nucleotides per se. One prospective, controlled trial studied the effects of nucleotide-supplemented formula in 26 severely malnourished children (younger than 4 years old). Insulin-like growth factor (IGF-1), growth fac-
tor binding protein-3 (IGFBP-3), leptin, soluble leptin receptor (sOB-R), and other hormonal biomarkers were measured. En-
teral formulas enriched with nucleotides were shown to have a notable effect on IGF-1 and IGFBP-3, which could stimu-
late the catch-up growth of severely malnourished infants and toddlers (42).

## Structured Lipids

Triglycerides are three fatty acid chains attached to a glycerol backbone. Structured lipids are triglycerides with combinations of long-, medium-, and short-chain fatty acids on a single glyce-
rol backbone not found in nature. The intent of this chemical manipulation is to make a product that has improved absorp-
tion (compared to long-chain triglycerides), minimizes immune dysfunction, and can provide essential fatty acids (43). Struc-
tured lipids are not yet commercially available in intravenous forms, although it has been a component of immunomodulat-
ing enteral formulas.

## Antioxidant Therapy

Antioxidants such as vitamin C, vitamin E, selenium, and β-
carotene are often found in immunomodulating formulas. The role of antioxidant supplementation during critical illness is un-
clear. Studies have shown that critically ill patients often have low serum concentrations of some antioxidants, the signifi-
cance of which is still not clear (44,45). However, there is good evidence now to suggest that reactive oxygen species (ROS) in-
duce direct oxidative tissue injury by means of peroxidation of cellular membranes, oxidation of critical enzymatic and struc-
tural proteins, and induction of apoptosis (44,45). Thus, the importance of antioxidants seems obvious. Nathens et al. con-
ducted a prospective, observational clinical trial looking at 595 critically ill surgical patients (91% trauma patients) who were conducted a prospective, observational clinical trial looking at 595 critically ill surgical patients (91% trauma patients) who were

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Poisonings are recognized in the earliest recorded history. The word *toxicology* is derived from the Greek terms *toxin*os (*"bow"*) and *toxikon* (*"poison into which arrowheads are dipped"*) (1, 2). In the 16th century, scholar Paracelsus made the astute observation that still holds strong: "What is there that is not poison? All things are poison and nothing is without poison. Solely, the dose determines that a thing is not a poison" (3). Today, we share Paracelsus’ appreciation of the dose-response relationship. One need not look farther than ba-sic elements such as oxygen or water to see that all substances can act as a poison at a specified dose. In modern medicine, the unique challenges posed by poisoned patients were recognized with the opening of the first poison control center in Chicago in 1953 (4); today, all 50 states are served by poison control centers. Medical toxicology, the care of poisoned patients, was recognized as a subspecialty by the American Board of Medical Subspecialties in 1992.

The American Association of Poison Control Centers (AAPCC) maintains the National Poisoning and Exposure Database (NPED), consisting of data from every case reported to poison centers in the United States. This database suffers from many obvious limitations. Many exposures go unre-ported. One investigator found that only 12% of poisoning deaths identified by the medical examiner were reported to poison centers (5). Those that are reported are usually uncon-firmed. Nevertheless, the database is a useful source of epidemi-oologic information, giving us an estimation of the incidence of various exposures. The NPED categorizes exposures based on outcome, designating effects as minor, moderate, or major. Maior effects are those where the patient exhibits signs or symp-toms as a result of exposure that is life threatening or results in increased lipid peroxidation in patients with septic shock and secondary organ dysfunction. Crit Care Med. 1995;23:646–651.


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