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Chapter 45

METABOLIC SUBSTRATE REQUIREMENTS

What is *food* to *one man may be fierce poison* to *others.*
Lucretius

The fundamental goal of nutritional support is to provide individual patients with their daily nutritional requirements. This chapter explains how to determine the nutrient and energy needs of each patient in the ICU.

OXIDATIVE ENERGY CONVERSION

Oxidative Combustion

According to the Laws of Thermodynamics, energy can neither be produced nor destroyed. Therefore, the only way to obtain energy is to transfer it from an energy source in nature. Natural substances that are rich in stored energy are called *fuels,* and the device that performs the energy transfer is called an *engine.* The process of energy transfer by two types of engines is illustrated in Figure 45.1. The automobile has a mechanical engine that mixes oxygen with a fossil fuel (e.g., gasoline) at high temperatures, and this releases the energy from the fuel that is then used to power the automobile. Likewise, the human body has a biochemical engine (metabolism) that mixes oxygen with an organic fuel (e.g., carbohydrates) at high temperatures, and this releases energy from the fuel that is then used to power the human body. The process that allows the energy to be released from a fuel is called oxidation, or the chemical reaction between oxygen and a fuel. If the oxidation reaction is

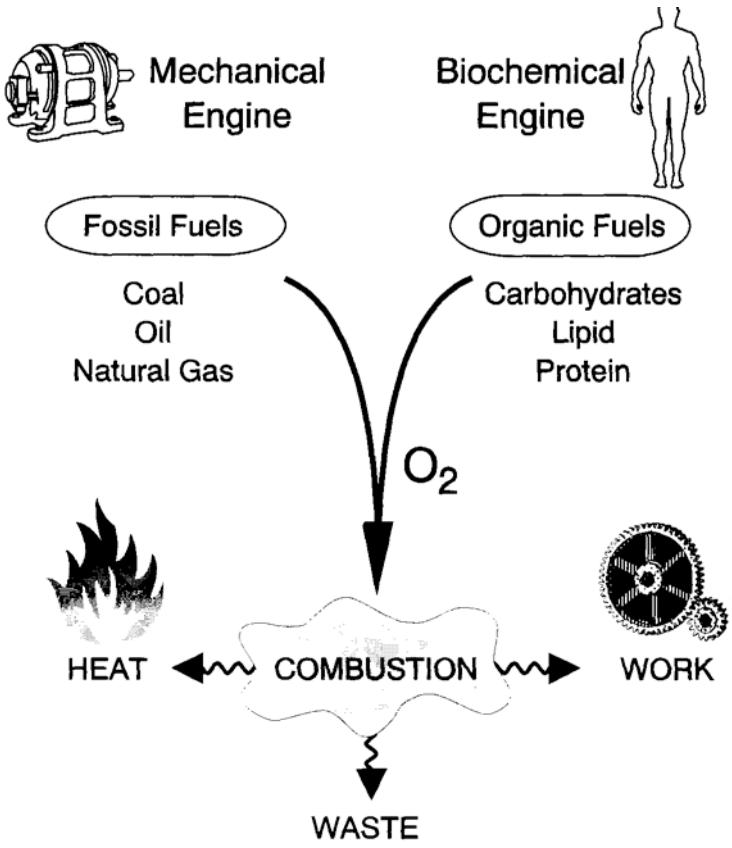

FIGURE 45.1 Energy conversion by two internal combustion engines. One engine is mechanical, and the other is biochemical.

conducted at high temperatures, the energy release from the fuel is more rapid. Such high-temperature oxidation reactions are called *combustion* reactions. Thus, both the automobile engine and oxidative metabolism are internal combustion engines that capture the energy stored in natural fuels.

Organic Fuels

The three organic (carbon-based) fuels used by the human body are carbohydrates, proteins, and lipids. The energy yield from the combustion of these fuels is measured as heat production in kilocalories (kcal) per gram of substrate. The energy yield from the combustion of each of the organic fuels is shown in Table 45.1. The information in this table can be stated as follows:

$$1 \text{ g Glucose} + 0.74 \text{ L of } O2 \text{ yields } 0.74 \text{ L of } CO_2 + 3.75 \text{ kcal} \quad (45.1)$$

TABLE 45.1 The Oxidative Metabolism of Organic Fuels

Fuel	$V0_2$ *(L/g)*	$VC0_2$ *(L/g)*	Energy Yield RQ*	(kcal/g)
Lipid	2.00	1.40	0.70	9.1
Protein	0.96	0.78	0.80	4.0
Glucose	0.74	0.74	1.00	3.7

'Respiratory quotient: RQ = VCO./$V0_2$.

The summed metabolism of all three organic substrates determines the total-body 02 consumption ($V0_2$), CO_2 production ($VC0_2$), and energy expenditure (EE) for any given period. The 24-hour EE then determines the daily calorie requirements that must be provided by nutrition support.

DAILY ENERGY EXPENDITURE

The daily energy expenditure of each individual patient can be estimated or measured.

Predictive Equations

In the early part of the twentieth century, the daily energy expenditure of a group of healthy adults (136 men and 103 women) was measured (7). The results of this study were expressed as regression equations for daily energy expenditure based on sex, body weight (in kilograms), and height (in inches). These equations are known as the Harris-Benedict equations (named after the principal investigators in the study), and they are shown in Table 45.2. The daily energy expenditure is expressed as the basal energy expenditure (BEE), which is the heat production of basal metabolism in the resting and fasted state. Because the body weight in the Harris-Benedict equations does not allow for changes in body weight caused by obesity or edema fluid, the ideal body weight should be used in these predictive equations.

Another more simplified predictive equation for the BEE is as follows:

$$\text{BEE (kcal/ day)} = 25 \times \text{wt (in kg)} \qquad (45.2)$$

This relationship has proven to be equivalent to the more complicated Harris-Benedict equations (8). Although it has not been tested rigorously, this simple relationship provides a "ballpark" estimate of BEE for determining nutritional needs.

Adjustments in BEE

To allow for the thermal effect of food intake, the BEE is multiplied by 1.2 to derive the resting energy expenditure (REE), which is the energy

TABLE 45.2 Methods for Determining Daily Energy Expenditure

Basal Energy Expenditure (BEE):

Men:

BEE (kcal/24hr) = 66 + (13.7 x wt) + (5.0 x ht) - (6.7 x age)

Women:

BEE (kcal/24hr) = 655 + (9.6 x wt) + (1.8 x ht) - (4.7 x age)

(wt = weight in kilograms, ht = height in inches)

Resting Energy Expenditure (REE):

*REE (kcal/24hr) = [(3.9 x $V0_2$) + (1.1 x $VC0_2$) - 61] x 1440

tREE (kcal/24hr) = BEE x 1.2

'From Bursztein S, Saphar P, Singer P, et al. A mathematical analysis of etry measurements in acutely ill patients. Am J Clin Nutr 1989;50:227-230.
$VC0_2$ are measured in *mL/min*, and the multiplier 1440 is used to convert the to 24 hr.
tREE is equivalent to the BEE plus the thermal effect of food.

expenditure of basal metabolism in the resting but not fasted state. Other adjustments in the BEE that allow for enhanced energy expenditure in hypermetabolic conditions are shown below:

Fever: BEE X 1.1 (for each °C above the normal body temperature)
Mild stress: BEE X 1.2
Moderate stress: BEE X 1.4
Severe stress: BEE X 1.6

The actual adjustments for severe illness can vary widely in individual patients (9). Studies comparing predicted and actual energy expenditure in critically ill patients have shown that the predictive equations (with adjustments for degree of stress) overestimate daily energy needs by 20 to 60% (9-12). For this reason, measurements of energy expenditure are more accurate than predictive equations in patients in the ICU.

Indirect Calorimetry

Because it is impossible to measure metabolic heat production in clinical practice, the metabolic energy expenditure is measured indirectly by measuring the whole-body V02 and VC02. This technique is called indirect calorimetry (2,3). The REE can be derived from the whole-body VO and VC02 by using the equation shown in Table 45.2 (13). The original REE equation, which incorporated a measurement of the daily urinary nitrogen excretion, was proposed by the Scottish physiologist J. B. de V. Weir in 1949 **(4)**. A number of adaptations of the original Weir equation have been proposed (15,16), but the REE equations used in the clinical setting do not include the urinary nitrogen excretion.

Method
Indirect calorimetry is performed with specialized instruments called metabolic carts that measure the exchange of O_2 and CO_2 across the lungs. These instruments can be placed at the bedside, and gas exchange measurements are obtained over 15 to 30 minutes. The $V0_2$ and $VC0_2$ are then extrapolated to a 24-hour period, and the 24-hour REE is calculated by using an equation similar to the one shown in Table 45.2.

Total Energy Expenditure
The REE obtained from indirect calorimetry is usually measured for 15 to 30 minutes, and then extrapolated to a 24-hour period. The total energy expenditure (TEE), measured over 24 hours, is equivalent to the extrapolated REE in patients who are not hypermetabolic (7), but the TEE can be as much as 40% higher than the extrapolated REE in hypermetabolic septic patients (7). Therefore, the REE measured over limited periods is not necessarily equivalent to the total daily energy expenditure in hypermetabolic patients in the ICD.

Limitations
Indirect calorimetry is the most accurate method for determining the daily energy requirements of individual patients in the ICD. However, several factors limit the popularity of indirect calorimetry in the clinical setting. First and foremost, the technique requires relatively expensive equipment and specially trained personnel, and it is not universally available. In addition, the oxygen sensor in most metabolic carts is not reliable at inspired oxygen levels above 50%, so indirect calorimetry can be unreliable in patients with respiratory failure who require inhaled oxygen concentrations above 50% (2). Because of all these limitations, daily caloric needs are often estimated using predictive formulas such as the Harris-Benedict equations, whereas indirect calorimetry (if available) is reserved for selected patients who require careful titration of daily energy intake (e.g., ventilator-dependent patients).

NONPROTEIN CALORIES
The daily energy requirement should be provided by calories derived from carbohydrates and lipids, and protein intake should be used to maintain the stores of essential enzymatic and structural proteins. The proportion of daily calories that is provided by lipids and carbohydrates is a matter of some debate, but no clear evidence shows one substrate to be superior to the other as a source of calories (2,3).

Carbohydrates
earbohydrates supply approximately 70% of the nonprotein calories in the average American diet. Because the human body has limited

TABLE 45.3 Endogenous Fuel Stores in Healthy Adults

Fuel Source	Amount (kg)	Energy Yield (kcal)
Adipose tissue fat	15.0	141,000
Muscle protein	6.0	24,000
Total glycogen	0.09	900
		Total: 165,900

Data from Cahill GF Jr. N Engl J Med 1970;282:668-

carbohydrate stores (Table 45.3), daily intake of carbohydrates is necessary to ensure proper functioning of the central nervous system, which relies heavily on glucose as its principal fuel source. However, excessive intake of carbohydrates can prove detrimental for the following reasons.

Carbohydrates stimulate the release of insulin, and insulin inhibits the mobilization of free fatty acids from adipose tissue. Because adipose tissue fat is the major source of endogenous calories (Table 45.3), excessive carbohydrate intake impairs the ability of the body to rely on endogenous fat stores during periods of inadequate nutrition.

The oxidative metabolism of glucose produces an abundance of CO_2 relative to the oxygen consumed, as indicated by the respiratory quotients listed in Table 45.1. Furthermore, ingestion of excessive carbohydrates leads to de novo lipogenesis, which has a respiratory quotient of 8.0. Therefore, the ingestion of excessive carbohydrates can be accompanied by an exaggerated production of CO_2 **(8)**, and this could promote hypercapnia in patients with compromised lung function. In fact, excessive calories from any nutrient source can be accompanied by excessive CO_2 production **(9)**.

Lipids

Dietary lipids have the highest energy yield of the three organic fuels (Table 45.1), and lipid stores in adipose tissues represent the major endogenous fuel source in healthy adults (Table 45.3). Most nutritional regimens use exogenous lipids to provide approximately 30% of the daily energy needs.

Linoleic Acid

Dietary lipids are triglycerides, which are composed of a glycerol molecule linked to three fatty acids. The only dietary fatty acid that is considered essential (i.e., must be provided in the diet) is linoleic acid, a long chain, polyunsaturated fatty acid with 18 carbon atoms (20). A deficient

intake of this essential fatty acid produces a clinical disorder characterized by a scaly dermopathy, cardiac dysfunction, and increased susceptibility to infections (20). This disorder is prevented by providing 0.5% of the dietary fatty acids as linoleic acid. Safflower oil is used as the source of linoleic acid in most nutritional support regimens.

Protein Requirements

The goal of protein intake is to match the rate of protein catabolism in the individual patient. Protein intake can be estimated by using the following generalized predictions for normal and hypercatabolic patients (21):

Condition Daily Protein Intake

Normal metabolism 0.8 to 1.0 g/kg
Hypercatabolism 1.2 to 1.6 g/kg

The estimated protein intake in hypercatabolic patients is limited by the inability to determine the severity of protein catabolism. A more accurate assessment of daily protein requirements requires some measure of protein catabolism. This measure is the urinary excretion of nitrogen, as described below.

Nitrogen Balance

Two-thirds of the nitrogen derived from protein breakdown is excreted in the urine (21). Because protein is 16% nitrogen, each gram of urinary nitrogen (UN) represents 6.25 g of degraded protein. The total-body nitrogen (N) balance can therefore be determined as follows (22):

N Balance (g) = (Protein intake (g)/6.25) - (UUN + 4) (45.3)

where UUN is the urinary urea nitrogen excretion (in grams) in 24 hours, and the factor 4 represents the daily nitrogen loss (in grams) other than UUN. If the UUN is greater than 30 (g/24 hours), a factor of 6 is more appropriate for the daily nitrogen losses other than UUN (23). The goal of the nitrogen balance is to maintain a positive balance of 4 to 6 grams.

Total versus Urea Nitrogen

Under normal circumstances, approximately 85% of the nitrogen in the urine is contained in urea and the remainder is contained in ammonia and creatinine. However, in certain groups of patients in the ICU (e.g., post-operative patients), urea may contain less than 50% of the total nitrogen in the urine (24). Therefore, the UUN can underestimate urinary nitrogen losses in patients in the ICU. Measuring the urinary ammonia excretion in addition to the UUN will provide a more accurate assessment of the TUN (total urinary nitrogen) in these patients (25). However, the clinical significance of this added measurement is unknown at present.

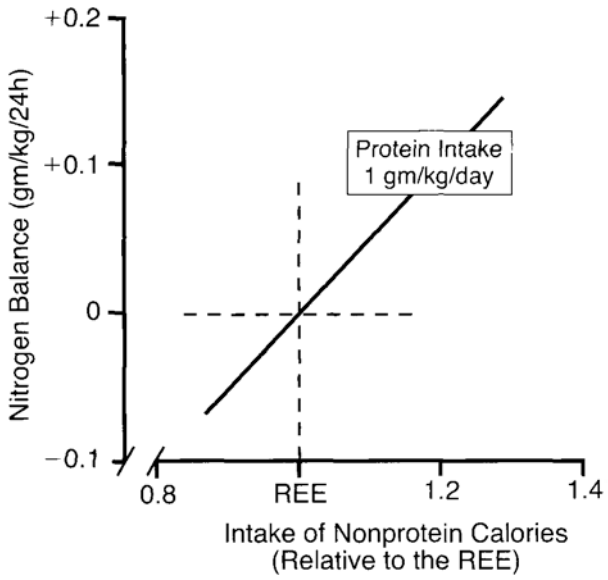

FIGURE 45.2 Graph showing that, when protein intake is constant, the nitrogen balance is directly related to the daily intake of *nonprotein* calories relative to the resting energy expenditure (REE).

Nitrogen Balance and Caloric Intake

The first step in achieving a positive nitrogen balance is to provide enough nonprotein calories to spare proteins from being degraded to provide energy. This is demonstrated in Figure 45.2, which shows the relationship between the intake of nonprotein calories and the nitrogen balance. When the daily protein intake is constant, the nitrogen balance becomes positive only when the intake of nonprotein calories is sufficient to meet the daily energy needs (i.e., the REE). If the nonprotein calorie intake is insufficient, some of the protein provided in the diet will be broken down to provide calories, which will produce a negative nitrogen balance. Therefore, when the daily intake of nonprotein calories is insufficient, increasing the protein intake becomes an inefficient method of achieving a positive nitrogen balance.

VITAMIN REQUIREMENTS

Twelve vitamins are considered an essential part of the daily diet. The recommended daily dose of individual vitamins in enteral and parenteral nutritional regimens is shown in Table 45.4 (2,3). It is important to emphasize that the daily vitamin requirements may be much higher than indicated in this table in seriously ill, hypermetabolic patients. In fact, deficiencies in several vitamins have been documented in hospitalized patients, despite the daily provision of vitamins in nutritional support

TABLE 45.4 Recommended Daily Requirements for Vitamins

Vitamin	Enteral Dose	Parenteral Dose
Vitamin A	1000 μg	3300 IU
Vitamin 8'2	3 μg	5μg
Vitamin C	60 mg	100 mg
Vitamin D	5 μg	200IU
Vitamin E	10 mg	10IU
Vitamin K*	100 μg	10 mg
Thiamine (B_1)*	2 mg	3 mg
Riboflavin (B_2)'	2 mg	4 mg
Pyridoxine (B_6)'	2 mg	4 mg
Pantothenic acid'	6 mg	15 mg
Biotin*	150 μg	60 μg
Folate	400 μg	400 μg

Adapted from Dark DS, Pingleton SK. Nutritional support in critically ill patients. Care Med 1993;8:16-33. Doses for vitamins indicated by asterisks (*) are rounded off to the nearest whole

regimens (26,27). The normal vitamin levels in blood are included in the section on Reference Ranges in the Appendix at the end of this text. Although it is impossible to comment on the importance of each of the vitamins in ICU patients, the following comments on thiamine and the antioxidant vitamins are deserved.

Thiamine

Thiamine (vitamin B_1) is a component of thiamine pyrophosphate, an essential cofactor in carbohydrate metabolism. Thiamine deficiency is likely to be common in patients in the ICU for the following reasons. First, the normal body content of thiamine is only approximately 30 mg (28), so assuming a daily thiamine requirement of 3 mg in patients in the ICU (Table 45.4), lack of thiamine intake could result in depletion of endogenous thiamine stores after just 10 days. Second, the use of thiamine is increased beyond expected levels in hypercatabolic conditions (29) and may also be increased in patients receiving nutritional support with glucose-rich formulas. Third, urinary thiamine excretion is increased by furosemide (30) which is a commonly used diuretic in the ICU. Finally, magnesium is necessary for the conversion of thiamine into thiamine pyrophosphate, so magnesium depletion (which is common in patients in the ICU) causes a "functional" form of thiamine deficiency (31).

Clinical Features

Four clinical disorders are associated with thiamine deficiency (28,32-34): *(0)* cardiac dysfunction (beriberi heart disease), *(b)* a metabolic (Wernicke's)

TABLE 45.5 Laboratory Evaluation of Thiamine Status

Plasma Thiamine'

Thiamine Fraction	Normal Range
Total	3.4-4.8 μg/dL
Free	0.8-1.1 μg/dL
Phosphorylated	2.6-3.7 μg/dL

Erythrocyte Transketolase Activityt

Enzyme activity measured in response to thiamine pyrophosphate (TPP).

1. <20% increase in activity after TIP indicates normal thiamine levels.
2. >25% increase in activity after TIP indicates thiamine deficiency.

'From Reference 33.
tFrom Reference 35.

encephalopathy, (c) lactic acidosis (see Chapter 29), and *(d)* a peripheral neuropathy. Similar disorders, such as cardiac dysfunction and metabolic encephalopathy, are common in patients in the ICU, and thiamine deficiency should be considered in each case in which one of these disorders is unexplained.

Diagnosis

The laboratory evaluation of thiamine status is shown in Table 45.5. Although plasma levels of thiamine can be useful in detecting thiamine depletion, the most reliable assay of functional intracellular thiamine stores is the erythrocyte trans keto lase assay (35). This assay measures the activity of a thiamine pyrophosphate-dependent (transketolase) enzyme in the patient's red blood cells in response to the addition of thiamine pyrophosphate (TPP). An increase in enzyme activity of greater than 25% after the addition of TPP indicates a functional thiamine deficiency. I use the plasma thiamine levels to screen for thiamine depletion and reserve the transketolase assay for determining the end-point of thiamine repletion in patients with documented thiamine deficiency.

Antioxidant Vitamins

Two vitamins serve as important endogenous antioxidants: Vitamin C and Vitamin E. Vitamin E is the major lipid soluble antioxidant in the body, and Vitamin e is water-soluble and serves as one of the major antioxidants in the extracellular fluid. Considering that oxidant-induced cell injury may play an important role in multiorgan failure (see Chapter 40), it is wise to maintain adequate body stores of the antioxidant vitamins in critically **ill** patients. The increased rates of biological oxidation that are common in critical illness are likely to increase the daily requirements for Vitamin C and Vitamin E far above those listed in Table 45.4. Therefore, it is important to monitor Vitamin C and Vitamin E status carefully in seriously ill patients in the ICU (see the Appendix for the normal plasma levels of Vitamins C and E).

TABLE 45.6 Daily Requirements for Essential Trace Elements

Trace Element	Enteral Dose	Parenteral Dose
Chromium	200 μg	15 μg
Copper	3 mg	1.5 mg
Iodine	150 μg	150 μg
Iron	10 mg	2.5 mg
Manganese	5 mg	100 μg
Selenium	200 μg	70 μg
Zinc	15 mg	4mg

Doses represent the maximum daily maintenance doses for each element.

Pingleton SK. Nutrition and nutritional support in critically ill patients. Intensive 1993:8: 16-33.

ESSENTIAL TRACE ELEMENTS

A trace element is a substance that is present in the body in amounts less than 50 μg per gram of body tissue (36). Seven trace elements are considered essential in humans (Le., associated with a deficiency syndrome), and these are listed in Table 45.6 along with their recommended daily maintenance doses (2). As with the vitamin requirements, the trace element requirements in Table 45.6 are for healthy adults; the requirements in hypermetabolic patients in the ICU may be far greater. The following trace elements are mentioned because of their relevance to oxidationinduced cell injury.

Iron

One of the interesting features of iron in the human body is how little is allowed to remain as free, unbound iron. The normal adult has approximately 4.5 g of iron, yet there is virtually no free iron in plasma (37). Most of the iron is bound to hemoglobin, and the remainder is bound to ferritin in tissues and transferrin in plasma. Furthermore, the transferrin in plasma is only approximately 30% saturated with iron, so any increase in plasma iron will be quickly bound by transferrin, thus preventing any rise in plasma free iron.

Iron and Oxidation Injury

One reason why the body may be so concerned with binding iron is the ability of free iron to promote oxidation-induced cell injury (37,38). Iron in the reduced state (Fe-II) promotes the formation of hydroxyl radicals (see Figure 21.5), and hydroxyl radicals are considered the most reactive oxidants known in biochemistry. In this context, the ability to bind and sequester iron has been called the major antioxidant function of blood (38). This might explain why hypoferremia is a common occurrence in patients who have conditions associated with hypermetabolism (39) (because this would limit the destructive effects of hypermetabolism).

In light of this description of iron, a reduced serum iron level in a critically ill patient should not prompt iron replacement therapy unless there is evidence of total-body iron deficiency. This latter condition can be detected with a plasma ferritin level; that is, a plasma ferritin below 18 μg/L indicates probable iron deficiency, whereas a plasma ferritin above 100 μg/L means that iron deficiency is unlikely (40).

Selenium

Selenium is an endogenous antioxidant by virtue of its role as a co-factor for glutathione peroxidase, one of the important endogenous antioxidant enzymes (see Chapter 21). Selenium use is increased in acute illness, and plasma selenium levels can fall to subnormal levels within 1 week after the onset of acute illness (41,42). Since selenium supplementation is not routinely included in parenteral nutrition support regimens, prolonged parenteral nutrition is accompanied by selenium deficiency (43,44). The combination of increased selenium use and lack of daily selenium supplementation may make selenium deficiency common in patients in the ICU. Such a condition will promote oxidant cell injury.

The acute selenium status is best monitored by measuring plasma selenium levels. The normal range is 89-113 mg/L (45,46). The minimum daily requirement for selenium is 55 μg (46,47). This requirement is likely to be much higher in hypermetabolic patients in the ICU. The maximum daily dose of selenium that is considered safe is 200 μg, and this dose is probably more appropriate for ICU patients. If needed, selenium can be given intravenously as sodium selenite (200 μg IV daily) (44).

A FINAL WORD (OR TWO)

Before leaving this chapter, it is important to point out that there is a fundamental problem with promoting nutrient intake in critically ill patients. The problem is the fate of administered nutrients in the presence of a serious illness.

Nutrients Won't Correct Malnutrition in the ICU

The goal of nutrient intake in the malnourished patient is to correct the malnourished state. However, the malnutrition that accompanies critical illness is different from the malnutrition that accompanies starvation. Whereas the malnutrition from starvation is due to deficient body stores of essential nutrients, the malnutrition that accompanies serious illnesses is due to abnormal nutrient processing. As such, the intake of nutrients will not correct the malnutrition that is associated with serious illnesses until the underlying disease is controlled and the metabolic abnormalities abate. Therefore, the important factor in correcting the malnutrition in critically ill patients is successful treatment of the primary disease process (48), and not the intake of nutrients (48). In fact, in

the setting of abnormal nutrient processing, nutrient intake can be used to generate metabolic toxins. This is demonstrated below.

Nutrients as Toxins in the ICU

In healthy subjects, less than 5% of exogenously administered glucose is metabolized to form lactate. However, in acutely **ill** patients, up to 85% of an exogenous glucose load can be recovered as lactate (49). The graph in Figure 45.3 demonstrates the ability of exogenous glucose to generate lactic acid in acutely stressed patients undergoing major surgery (50). In this case, patients undergoing abdominal aneurysm surgery were given intraoperative fluid therapy with either Ringer's solutions or 5% dextrose solutions. In the patients who received the 5% dextrose solution (total amount of dextrose infused averaged 200 grams), the blood lactate increased by 3 mmol/L, whereas in the patients who received an equivalent volume of the glucose-free (Ringer's) solution, the blood lactate level

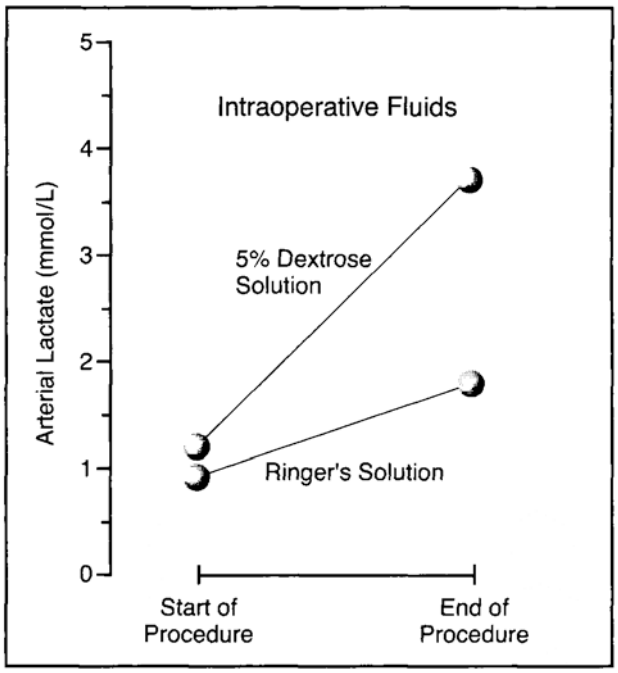

FIGURE 45.3 Effect of carbohydrate infusion on arterial lactate levels during abdominal aortic surgery. Each point represents the mean lactate level for 10 patients receiving Ringer's solution and 10 patients receiving 5% dextrose solution. Total volume infused is equivalent with both fluids. (Data from Degoute CS, Ray MJ, Manchon M, et al. Intraoperative glucose infusion and blood lactate: endocrine and metabolic relationships during abdominal aortic surgery. Anesthesiology 1989;71:355–361.)

increased only 1 mmol/L. Thus an organic nutrient (carbohydrate) can be used to generate a metabolic toxin (lactic acid) when nutrient processing is abnormal (during the stress of abdominal aneurysm surgery).
The study in Figure 45.3 illustrates that nutrient intake can have very different consequences in different subjects, and that *nutrients call become toxins* in the diseased host. Lucretius realized this more than 2000 years ago when he stated, "What is food to one man may be fierce poison to others." For this reason, one should not immediately jump on the bandwagon for aggressive nutritional support in critically ill patients.

REFERENCES

Chapter 46

ENTERAL TUBE FEEDING

One of the important features of the gastrointestinal (CD tract (as described in Chapter 4) is the role of the intestinal epithelium as a barrier to invasion by pathogenic microorganisms. As discussed in this chapter, the barrier function of the bowel mucosa is maintained by the intake and processing of bulk nutrients along the digestive tract. Therefore, providing nutrients via the enteral route not only provides nutritional support for the vital organs, but also supports host defenses against invasive infection (1-3). Several guidelines on the topic of enteral nutrition are included at the end of the chapter (4-6).

TROPHIC EFFECT OF ENTERAL NUTRIENTS
Complete bowel rest is accompanied by progressive atrophy and disruption of the intestinal mucosa (7). This effect becomes evident after just a few days and is not prevented by parenteral (intravenous) nutrition. The influence of luminal nutrients on the morphology of the intestinal mucosa is shown in Figure 46.1 (8,9). The photomicrograph at the top shows the normal appearance of the small bowel mucosa. Note the finger like projections (microvilli), which serve to increase the surface area for nutrient absorption. The photomicrograph at the bottom shows the mucosal changes after 1 week of a protein-deficient diet. Note the shortening of the microvillus on the left of the picture and the generalized disruption of the surface architecture. **This demonstrates that depletion of nutrients in the bowel lumen is accompanied by degenerative changes in the bowel mucosa.**
Observations like those in Figure 46.1 indicate that the bowel mucosa relies on nutrients in the bowel lumen to provide its nutritional needs. One of the nutrients that may play an important role in this process is the amino acid glutamine, which is considered the principal metabolic fuel for intestinal epithelial cells (10). The use of glutamine in enteral feedings is discussed later in this chapter.

FIGURE 46.1 Photomicrographs showing the normal appearance of the small bowel mucosa (*upper*), and the mucosal disruption after 1 week of a protein-deficient diet (*lower*). (Reprinted with permission from Deitch EA, Winterton J, Li M, et al. The gut as a portal of entry for bacteremia: role of protein malnutrition. Ann Surg 1987;205:681–692.)

Translocation

The process of translocation, where enteric pathogens move across the bowel mucosa and into the systemic circulation, is described in Chapter 4 (see Fig. 4.2). Translocation has been documented during periods of bowel rest in critically ill patients (7,11), and this has been attributed to mucosal disruption from lack of luminal nutrients. This means that enteral nutrition could help prevent translocation and subsequent sepsis by maintaining the functional integrity of the bowel mucosa. The potential for enteral nutrition to prevent sepsis of bowel origin is one of the major reasons why enteral nutrition has become favored over parenteral (intravenous) nutrition in critically ill patients.

PATIENT SELECTION

In the absence of contra indications, enteral tube feedings are indicated when oral nutrient intake has been inadequate for 1-3 days (5,12). In patients who are at risk of bacterial translocation across the bowel (e.g., burn victims), tube feedings should be started as soon as possible after the onset of inadequate nutrient intake (5).

Contraindications

Enteral feedings in any amount are contraindicated in patients with circulatory shock, intestinal ischemia, complete mechanical bowel obstruction, or ileus. Total enteral nutrition is not advised in patients with the following conditions: partial mechanical bowel obstruction, severe or unrelenting diarrhea, pancreatitis, or high-volume (more than 500 mL daily) enterocutaneous fistulas. Partial (low volume) enteral support is, however, possible in these conditions (13). In the case of pancreatitis, enteral feedings can be delivered into the jejunum (see "Jejunostomy Feedings").

FEEDING TUBES

Standard Salem sump nasogastric tubes (14 to 16 French) are no longer favored for enteral tube feedings because of patient discomfort. Although there has been concern about gastroesophageal reflux with these tubes, clinical studies do not support this concern (14). The feeding tubes that are currently favored are narrower (8 to 10 French) and more flexible than standard nasogastric tubes. Because these tubes are so flexible, a rigid stylet is also provided to facilitate insertion.

Insertion

Feeding tubes are inserted through the nares and advanced into the stomach or duodenum. The distance that the tube must be advanced to

reach the stomach can be estimated by measuring the distance from the tip of the nose to the earlobe and then to the xiphoid process (typically 50-60 cm) (4).
Proper placement in the stomach is sometimes possible to determine by measuring the pH (with litmus paper) of a specimen aspirated from the tip of the feeding tube (15). If the specimen has a pH less than 5, the tip of the tube is likely to be in the stomach (15).

Tracheal Intubation

The principal complication of feeding tube placement is accidental tracheal intubation in 1 % (16). Because feeding tubes are narrow, they readily pass through the larynx and around the inflated cuffs on tracheal tubes. Accidental intubation of the trachea is often asymptomatic (probably because of sedation, depressed consciousness, or an abnormal cough reflex), and in the absence of symptoms, tubes can be advanced into the distal airways. This is illustrated in Figure 46.2, which shows the tip of a small-bore feeding tube in the lower lobe of the right lung. If feeding tubes are advanced too far into the lungs, the rigid stylet makes it easy to puncture the visceral pleura and produce a pneumothorax (16,17).
Because of the risk of asymptomatic intubation of the lungs, a postinsertion chest x-ray is required to evaluate tube placement (unless pH testing confirms gastric placement). Auscultation of the upper abdomen

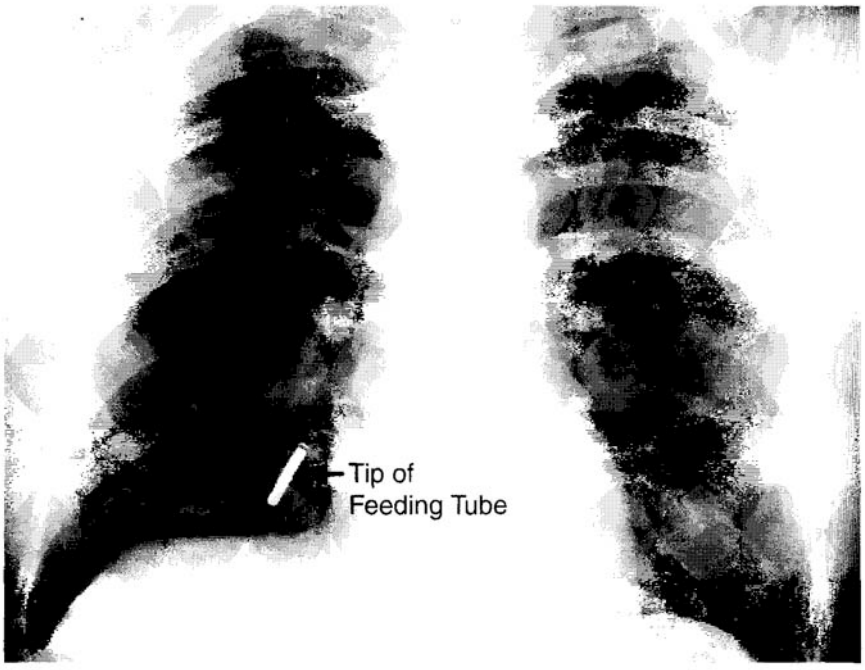

FIGURE 46.2 Routine chest x-ray following insertion of a small bore feeding tube. The tip of the tube is evident in the right lung.

while insufflating air through the tube is not a reliable method for excluding tube malposition in the lungs because sounds emanating from a tube in the lower airways can be transmitted into the upper abdomen (17,18).

Duodenal Placement

For those who prefer tube feedings placed in the duodenum instead of the stomach, gastric tubes must be advanced past the pylorus and into the duodenum (5,12). This can be accomplished by specialized bedside maneuvers or may require endoscopic or fluoroscopic guidance (4,16). Tube passage into the duodenum can be confirmed by radiographic localization.

Feeding Site

The proposed advantage of duodenal feedings is a reduced risk of reflux of feeding solution into the esophagus and subsequent pulmonary aspiration (19). However, clinical studies show that the risk of aspiration in duodenal feedings is the same as that in gastric feedings (5,20). Therefore, the time and effort devoted to advancing gastric tubes into the duodenum is not justified.

FEEDING FORMULAS

More than 115 liquid feeding formulas are available for enteral nutrition (21). The formulas that are most commonly used are described in Tables 46.1 through 46.5, see reference (22,23).
The following is a brief description of some of the features of enteral feeding formulas.

Caloric Density

The caloric density of feeding formulas is determined primarily by the carbohydrate content. Most formulas provide 1 to 2 kilocalories per liter of solution. The formulas that provide 1 to 1.5 kcallL (standard caloric density) are listed in Table 46.1, and the formulas that provide 1.5 to 2 kcallL (high caloric density) are listed in Table 46.2. The energy-rich formulas in Table 46.2 are well-suited for patients with excessive daily energy needs and for patients who are volume-restricted. The nutritional requirements of many ICU patients are met by providing 25-30 nonprotein kcal/kg, but individual requirements vary greatly and overfeeding (hyperalimentation) should be avoided (5).

Osmolality

The osmolality of liquid feeding formulas varies from 280 to 1100 mOsm/ kg H_20. The major determinant of osmolality is the carbohydrate content

TABLE 46.1 Characteristics of Selected Enteral Feeding Formulas

Formula	Caloric Density (kcal/mL)	Protein *(g/L)*	Osmolarity (mOsm/L)	Volume to Meet US RDA'
Ensure Plus	1.5	63	525	1000
Isacal	1.1	34	270	1890
Isocal HN	1.1	44	270	1180
Nutren	1.0	40	315	1500
Osmolite	1.1	37	300	1890
Osmolite HN	1.1	44	300	1320
Peptamen	1.0	40	270	150
Ultracal	1.1	37	500	1180
Vivonex TEN	1.0	38	630	2000
Vital HN	1.0	42	500	1500

"Indicates the volume needed to provide 100% of the recommended daily (RDAs) for vitamins and essential trace elements.

(because this is the most abundant nutrient in most feeding formulas). Because carbohydrates also determine caloric density, osmolality and caloric density are directly related. Formulas with the lowest caloric density (1 kcal/L) have the lowest osmolalities (approximately 300 mOsm/ kg H,O) and are usually isotonic to the body fluids. Formulas with the hIghest caloric density (2 kcal/L) have the highest osmolalities (1,000 mOsm/kg HP) and are markedly hypertonic to the body fluids.
Hypertonic formulas should be infused into the stomach to take advantage of the dilutional effects of the gastric secretions.

Protein
Liquid feeding formulas provide 35 to 40 grams of protein per liter. Although some formulas are designated as being protein-rich (these formulas often have the suffix HN to indicate "high nitrogen"), they provide only 20% more protein than the standard feeding formulas.

TABLE 46.2 Enteral Formulas with a High Caloric Density

Formula	Caloric Density (kcal/mL)	Osmolality (mOsm/Kg)	Volume to Meet US RDA
Nepro	2	665	1000
Novasource Renal	2	700	1000
TwoCal HN	2	725	950

Protein Complexity
Most enteral formulas provide intact proteins that are broken down into amino acids in the upper GI tract. Because small peptides are absorbed more rapidly than amino acids, some feeding formulas contain small peptides instead of intact protein to facilitate absorption. Peptide-based formulas such as Peptamen (Nestle) and Vital HN (Ross) can be used in patients with impaired intestinal absorption (e.g., from inflammatory bowel disease). These formulas also promote water reabsorption from the bowel, and thus they could prove beneficial in patients with severe or unrelenting diarrhea.

Lipids
The lipid emulsions used in feeding formulas are rich in long-chain triglycerides derived from vegetable oils. These lipids represent a concentrated source of calories, with an energy yield (9 kcal/ g) that is almost three times that of carbohydrates (3.4 kcal/ g). Because excessive fat ingestion is not well tolerated (i.e., it promotes diarrhea), the lipid content of most feeding formulas is limited to 30% of the total calories. Some formulas with an altered lipid composition are described in the following sections. These formulas are summarized in Table 46.3.

Lipid-Rich Formula
One liquid feeding formula with a high fat content is Pulmocare (Ross), which uses lipids to provide 55% of the total calories. This formula is intended for patients with respiratory failure. The proposed benefit is based on the low rate of CO) production relative to 0_7 consumption associated with lipid metabolism (see Table 45.1). Thus when lipids replace carbohydrates as the principal nutrient substrate, metabolic CO_2 production will decline and there will be less of a tendency for CO_2 retention in patients with compromised lung function (24).

TABLE 46.3 Feeding Formulas with an Altered Lipid Composition

Formula	Feature	Proposed Benefit
Immun-Aid (McGaw)	Contains omega-3 fatty acids, RNA, arginine, and glutamine.	Enhances immune function, limits inflammatory-mediated tissue injury.
Impact (Novartis)	Contains omega-3 fatty acids, RNA, arginine, and glutamine.	to
Oxepa (Ross)	Contains omega-3 fatty acids, arginine, antioxidants.	
Pulmocare (Ross)	High lipid content. Lipids provide 55% of the calories in the formula.	Limits nutrition-induced CO2 retention in respiratory failure.

Alternative Lipids

The two feeding formulas described in Table 46.3 contain dietary fat from sources other than vegetable oils. Polyunsaturated fatty acids from vegetable oils can serve as precursors for inflammatory mediators (eicosanoids) that are capable of producing widespread cell injury (1). The omega-3 fatty acids do not promote the production of harmful inflammatory mediators, and these might be preferred to the standard dietary fats to limit the risk of inflammatory-mediated tissue injury.

Several feeding formulas contain omega-3 fatty acids: Oxepa (Ross) (25), Impact (Novartis), and Immun-Aid (McGaw) (see Table 46.3). These formulas are intended for patients with systemic inflammation or acute respiratory distress syndrome who are at risk for inflammatory-mediated tissue injury 0, 26-28).

ADDITIVES

Glutamine

As mentioned earlier, glutamine is the principal fuel for the bowel mucosa **(O).** Therefore, daily supplementation with glutamine seems a reasonable measure for maintaining the functional integrity of the bowel mucosa. Although glutamine is not an essential amino acid (because it is produced in skeletal muscle), tissue glutamine stores decline precipitously in acute, hypercatabolic states. Therefore, glutamine can become an essential nutrient in the hypermetabolic, stressed patient (2,29).

Glutamine-Enriched Formulas

Because glutamine is a natural constituent of proteins, all feeding formulas that contain intact protein will also contain glutamine (30). However, little of this glutamine is in the free or unbound form. The formulas that contain glutamine as a free amino acid are listed in Table 46.4. With the exception of AlitraQ or Impact Glutamine, the glutamine content of enteral feeding formulas is low and may be insufficient to provide a benefit (31-33). In one study of glutamine administration in healthy adults (33), the average glutamine dosage (oral and intravenous) was 0.35 g/ kg/ day, or 24.5 g/ day for a 70-kg subject. Assuming a daily caloric intake of 2,000 kcal, the only feeding formulas in Table 46.4 that will provide a glutamine dosage of 0.35 g/kg/ day is AlitraQ or Impact Glutamine. In

TABLE 46.4 Glutamine-Enriched Feeding Formulas

Formula	Manufacturer	Glutamine *(gIL)*
AlitraQ	Ross	15.5
Impact Glutamine	Novartjs	15
Replete	Nestle	3.3
VivonexTEN	Novartjs	3.3

the setting of hypercatabolism, the glutamine provided by most enteral formulas will be even more inadequate. Therefore, although the use of glutamine-fortified enteral formulas seems reasonable, the amount of glutamine provided by most formulas may be inadequate.

Dietary Fiber

The term *fiber* refers to a group of plant products that are not degradable by human digestive enzymes. These products are classified by their fermentative properties.

FERMENTABLE FIBER (cellulose, pectin, gums) is degraded by intestinal bacteria to form short-chain fatty acids (e.g., acetate), which are used as an energy substrate by the large bowel mucosa. This type of fiber can slow gastric emptying and bind bile salts, and both of these actions can help alleviate diarrhea.

NONFERMENTABLE FIBER (lignins) is not degraded by intestinal bacteria, but it can create an osmotic force that adsorbs water from the bowel lumen. This type of fiber can therefore reduce the tendency for watery diarrhea. Thus fiber has several actions that can reduce the tendency for diarrhea during enteral feedings. Furthermore, fermentable fiber can serve as a source of metabolic support for the mucosa of the large bowel (34). This latter effect could play an important role in limiting the tendency for translocation across a disrupted large bowel mucosa. Several feeding formulas contain fiber, and they are shown in Table 46.5. The added fiber in all cases is soy polysaccharide, which is a fermentable fiber. Thus there is little difference between the fiber-enriched formulas, either in type or in content of fiber. Fiber-enhanced feedings can also be achieved by adding Metamucil (nonfermentable fiber) or Kaopectate (fermentable fiber) to the feeding regimen.

Performance

The effects of fiber-enriched feedings on the incidence of diarrhea have been inconsistent, with some studies showing a reduced incidence of diarrhea (35,36), and others showing no effect (37). However, relying on fiber to prevent diarrhea neglects the source of the diarrhea; the focus of prevention should be to eliminate or treat the process responsible for the diarrhea.

TABLE 46.5 Fiber-Enriched Enteral Feeding Formulas

Formula	Fiber (giL)	Formula	Fiber *(glL)*
Enrich	14.3	Isosource 1.5 Cal	8
Fibersource	10	Jevity	14.4
Fibersource	10	Nutren 1.0 Fiber	14
Glucerna	14.3	Ultracal	14.4

Miscellaneous

Branched Chain Amino Acids

The branched chain amino acids (BCAAs) isoleucine, leucine, and valine are available in feeding formulas intended for trauma victims and patients with hepatic encephalopathy. In trauma victims, the BCAAs can be used as a fuel source in skeletal muscle, thereby sparing the degradation of other muscle proteins to provide energy. In hepatic encephalopathy, the BCAAs can antagonize the uptake of aromatic amino acids (e.g., tryptophan) into the central nervous system, and this helps prevent the subsequent breakdown of the aromatic amino acids to form false neurotransmitters, which have been implicated in the pathogenesis of hepatic encephalopathy (38,39).

Examples of feeding formulas enriched with BCAAs for hepatic encephalopathy include NutriHep (Nestle) and Hepatic-Aid II (Hormel Health Labs). The benefits of these formulas are unproven.

Carnitine

Carnitine is necessary for the transport of fatty acids into mitochondria for fatty acid oxidation (40). Humans normally synthesize carnitine from lysine and methionine (essential amino acids) in sufficient amounts so that dietary intake is not required (40). Deficiency of carnitine (plasma concentration below 20 μmol/U can occur in prolonged states of hypercatabolism or during prolonged hemodialysis (40,41). The clinical consequences of carnitine deficiency include cardiomyopathy, skeletal muscle myopathy, and hypoglycemia.

The recommended daily dose of camitine is 20-30 mg/kg in adults (41,42). Enteral formulas that are supplemented with carnitine include Glucerna (Ross), Isocal HN (Novartis), Jevity (Ross), and Peptamen (Nestle).

FEEDING REGIMEN

Tube feedings are usually infused for 12 to 16 hours in each 24-hour period. Continuous infusion without a period of bowel rest is an unrelenting stress to the bowel mucosa and promotes malabsorption and diarrhea. Intermittent bolus feedings more closely approximate the normal condition, but the volumes required are often too large to be given safely.

Gastric Retention

Before gastric feedings are started, it is necessary to determine how much volume will be retained in the stomach over a 1-hour period because this will determine how fast the feedings can be administered. A volume of water that is equivalent to the desired hourly feeding volume should be infused over 1 hour. After the infusion is complete, the feeding tube should be clamped for 30 minutes. The tube should then be unclamped, and any residual volume should be aspirated from the stomach. If the

4 hour gastric residual volume is less than 200 mL, gastric feeding can proceed (4). If the residual volume is excessively high, duodenal or jejunal feedings may be more appropriate. When the gastric residual volume is measured, it is important not to administer the volume as a bolus because this will produce acute gastric distension and lead to overestimation of the residual volume.

Starter Regimens

The traditional approach to initiating tube feedings is to begin with dilute formulas and a slow infusion rate and gradually advance the formula concentration and infusion rate over the next few days until the desired nutrient intake is achieved. This presumably allows the atrophic bowel mucosa time to regenerate after a period of bowel rest. The drawback with starter regimens is the fact that nutrient intake is inadequate for the time required to advance to full nutritional support. In the malnourished patient, this added period of inadequate nutrition adds to the malnutrition.

Studies involving intragastric feedings show that full feedings can be delivered immediately without troublesome vomiting or diarrhea (43,44). This is presumably due to the ability of gastric secretions to dilute the feeding formula and reduce the osmotic load associated with the feedings. Therefore, starter regimens are unnecessary for gastric feedings. Because of the limited reservoir function of the small bowel, starter regimens are usually required for duodenal and jejunal feedings.

COMPLICATIONS

The complications associated with enteral feedings include occlusion of the feeding tube, reflux of gastric contents into the airways, and diarrhea.

Tube Occlusion

Narrow-bore feeding tubes can become occluded by accumulation of residue from the feeding formulas. One important mechanism is the precipitation of proteins in the feeding solution by acidic gastric juice that refluxes up the feeding tubes (45). Standard preventive measures include flushing the feeding tubes with 30 mL of water every 4 hours, and using a 10 mL water flush after medications are instilled (46).

Relieving the Obstruction

If there is still some flow through the tube, warm water should be injected into the tube and agitated with a syringe. This can relieve the obstruction in 30% of cases (47). If this is ineffective, pancreatic enzyme can be used as follows (47): Dissolve 1 tablet of Viokase and 1 tablet of sodium carbonate (324 mg) in 5 mL of water. Inject this mixture into the feeding tube and clamp for 5 minutes. Follow with a warm water flush.

This should relieve the obstruction in approximately 75% of cases (47). If the tube is completely occluded and it is impossible to introduce warm water or pancreatic enzyme, an attempt should be made to insert a flexible wire or a drum cartridge catheter to clear the obstruction.

Aspiration

Retrograde regurgitation of feeding formula is reported in as many as 80% of patients receiving gastric or duodenal feedings (48). As stated earlier, the risk of reflux in gastric feedings is the same as that in duodenal feedings (20,49). Elevating the head of the bed to 30 to 45 degrees can reduce-although not eliminate-the risk of reflux (48,50).

Glucose Reagent Strips

Aspiration of feeding formulas into the airways can be detected by testing tracheal aspirates with glucose oxidase reagent strips. The results are measured with an automated glucose meter. A glucose concentration greater than 20 mg/dL in tracheal aspirates is evidence of aspiration (51). Coloring the feeding formulas with food coloring and inspecting the color of the tracheal secretions is an insensitive method for detecting aspiration (51).

Diarrhea

Diarrhea occurs in approximately 30% of patients receiving enteral tube feedings (52). Although the hypertonicity of enteral feeding formulas can induce an osmotic diarrhea, in most cases of diarrhea associated with enteral feedings, the feeding formula is not responsible for the diarrhea (52,53). The cause of the diarrhea in many cases is a medicinal elixir that contains sorbitol (an osmotic agent) to improve palatability (52,54). Some of the sorbitol-containing liquid drug preparations are shown in Table 46.6 (54). Also shown is the daily dosage of sorbitol that would accompany each drug when given in the usual therapeutic dosages (54). In most cases, the daily dosage of sorbitol can be enough to induce an osmotic diarrhea. Therefore, a search for sorbitol-containing medicinal elixirs should be the first concern in the evaluation of diarrhea during enteral tube feedings.

Stool Osmolal Gap

Clostridium difficile enterocolitis is also a possible cause of diarrhea during enteral feedings. One method of differentiating the secretory diarrhea caused by C. *difficile* enterocolitis from the osmotic diarrhea caused by hypertonic feedings or medicinal elixirs is to calculate the stool osmolal gap as follows:

Osmolal gap = Measured stool osmolality - 2
x (Stool [Na - Stool [K +])

TABLE 46.6 Sorbitol-Containing Liquid Drug Preparations

Agent	Preparation	Usual Dosage	Daily Sorbitol Dose (g)
Acetaminophen	Tylenol Elixir	650 mg OID	16
Cimetidine	Tagamet Liquid	300 mg OID	10
Ferrous sulfate	Iberet Liquid	75 mgTID	22
Metoclopramide	Reglan Syrup	10 mg OID	20
Potassium chloride	Kolyum Powder	20 mEq BID	25
Theophylline	Theolar Liquid	200 mg OID	23
Trimethoprim-sulfamethoxazole	Septra Suspension	800/160 mg BID	18

From Cheng EY et al. Unsuspected source of diarrhea in an ICU patient. *Clin Care* 1992;3:33-36.

A stool osmolal gap greater than 160 mOsm/kg H?O suggests an osmotic diarrhea secondary to hypertonic tube feedings or medicinal elixirs, whereas a smaller (or negative) osmolal gap suggests a secretory diarrhea caused by C. *difficile* enterocolitis. (For more information on the diagnosis and treatment of C. *difficile* enterocolitis, see Chapter 42.)

JEJUNOSTOMY FEEDINGS

Although abdominal surgery usually is accompanied by 24 to 48 hours of gastric hypomotility, the motility of the small bowel is often unimpaired (55). Infusion of liquid feeding formulas into the jejunum takes advantage of the continued small bowel motility after abdominal surgery and allows immediate postoperative nutrition. Jejunal feedings can also be performed for nutritional support of patients with pancreatitis.

Needle Catheter Jejunostomy

A feeding jejunostomy can be performed as a "complementary" procedure during laparotomy. A needle catheter jejunostomy is shown in Figure 46.3 (56). A loop of jejunum 05 to 20 cm distal to the ligament of Treitz) is mobilized to the anterior abdominal wall, and a 16-gauge catheter is tunneled through the submucosa of the jejunum for a distance of 30 to 45 cm and then advanced into the bowel lumen. The jejunum is then secured to the peritoneum on the underside of the abdominal wall, and the catheter is secured to the skin.

Feeding Method

As mentioned, the small bowel does not have the reservoir capacity of the stomach, so starter regimens are recommended for jejunal feedings.

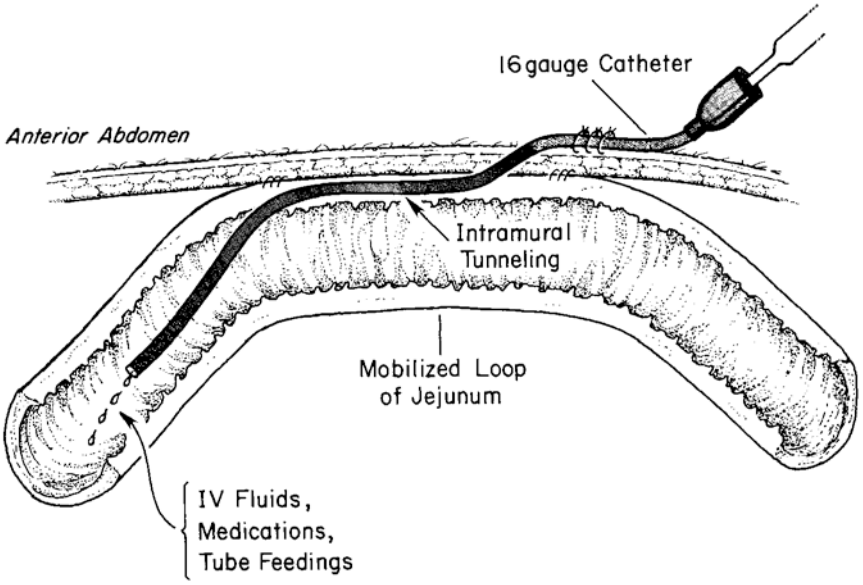

FIGURE 46.3 A needle catheter jejunostomy.

Feedings are usually initiated at a rate of 15 to 25 mL/hour, and the infusion rate is gradually increased over the next few days until full nutritional support is achieved (57). Catheters are flushed with 10 mL of isotonic saline every 6 hours to promote catheter patency.

Complications

The principal complications of needle catheter jejunostomies are diarrhea and occlusion of the narrow feeding catheters (57). Because of the latter complication, needle catheter jejunostomies are used only for temporary nutritional support (approximately 1 week). If more prolonged jejunal feedings are desired, a needle catheter jejunostomy can be converted to a standard jejunostomy (which uses a 12 French feeding tube) using a technique described in Reference 58.

A FINAL WORD

The most important role of enteral tube feedings in the ICU is not directly related to nutrition. This role is reviewed in the sequence of statements listed below.

The mucosal lining of the gastrointestinal (GO tract serves as a barrier to microbial invasion, and disruption of this barrier is an important source of systemic sepsis in critically ill patients.

The presence of bulk nutrients in the bowel lumen has a trophic effect on the bowel mucosa, and this maintains the structural and functional integrity of the mucosal barrier.
Prolonged bowel rest results in disruption of the bowel mucosa, and creates a risk for systemic sepsis.
Enteral tube feedings will maintain the integrity of the bowel mucosa, and prevent disruption of the mucosal barrier that occurs with prolonged bowel rest. This will reduce the risk of systemic sepsis.
Enteral nutrition is thus an infection control measure in the ICU, and this is the principal reason to favor enteral tube feedings over parenteral nutrition, and to avoid prolonged periods of bowel rest when possible.

REFERENCES

Chapter 47

PARENTERAL NUTRITION

When full nutritional support is not possible with enteral tube feedings, the intravenous delivery of nutrients can be used to supplement or replace enteral nutrition 0,2). This chapter introduces the basic features of intravenous nutritional support (3-6) and explains how to create a total parenteral nutrition (TPN) regimen to meet the needs of individual patients.

INTRAVENOUS NUTRIENT SOLUTIONS

Dextrose Solutions
As mentioned in Chapters 45 and 46, the standard nutritional support regimen uses carbohydrates to supply approximately 70% of the daily (nonprotein) calorie requirements. These are provided by dextrose (glucose) solutions, which are available in the strengths shown in Table 47.1. Because dextrose is not a potent metabolic fuel (see Table 45.1), the dextrose solutions must be concentrated to provide enough calories to satisfy daily requirements. As a result, the dextrose solutions used for TPN are hyperosmolar and should be infused through large central veins.

Amino Acid Solutions
Amino acid solutions are mixed together with the dextrose solutions to provide the daily protein requirements. A variety of amino acid solutions are available for specific clinical settings, as demonstrated in Table 47.2. The standard amino acid solutions contain approximately 50% essential amino acids (N = 9) and 50% nonessential (N = 10) and semiessential (N = 4) amino acids (7). The nitrogen in essential amino acids is partially recycled for the production of nonessential amino acids, so the metabolism of essential amino acids produces less of a rise in the blood urea nitrogen concentration than metabolism of nonessential amino acids. For this reason, amino acid solutions designed for use in renal failure are rich in essential amino acids (see Aminosyn RF in Table 47.2). Finally,

TABLE 47.1 Intravenous Dextrose Solutions

Strength	Concentration *(g/L)*	Energy Yield* (kcal/L)*	Osmolarity (mOsm/L)
5%	50	170	253
10%	100	340	505
20%	200	680	1010
50%	500	1700	2525
70%	700	2380	3530

<Based on an oxidative energy yield of 3.4 kcal/g for dextrose.

for reasons stated in Chapter 46, nutritional formulas for hypercatabolic conditions (e.g., trauma) and hepatic failure can be supplemented with branched chain amino acids (isoleucine, leucine, and valine), and two specialty amino acid solutions for each of these conditions are included in Table 47.2. **It** is important to emphasize that none of these specialized nutrient formulas have improved the outcomes in the disorders for which they are designed (8).

Glutamine

As mentioned in Chapter 46, glutamine is the principle metabolic fuel for intestinal epithelial cells, and glutamine-supplemented TPN may play an important role in maintaining the functional integrity of the bowel mucosa and preventing bacterial translocation (9,10). Although glutamine

TABLE 47.2 Standard and Specialty Amino Acid Solutions

Features	Aminosyn 7%, (Abbott)	Aminosyn-HBC 7%, (Abbott)	Aminosyn RF 5.2%, (Abbott)	HepatAmine 8%, (McGaw)
Indication	Standard TPN	Hypercatabolism	Renal Failure	Hepatic Failure
Concentration	70 g/L	70 g/L	52 g/L	80 g/L
Nitrogen Content (g/L)	11	11.2	7.7	12
Essential AAs (% Total)	48%	68%	89%	52%
Branched Chain AAs (% Total)	25%	51%	33%	36%
Osmolarity *(mOsm/L)*	700	665	475	785

Borgsdort LR, Cada OJ, Cirigliano M, et al. Drug Facts and Comparisons. 60th St. Louis. MO: Wolters Kluwer. 2006.

TABLE 47.3 Amino Acid Solutions with Glutamic Acid

Preparation	Manufacturer	Glutamate Content (mg/dL)
Aminosyn-PF 7%	Abbott	576
Aminosyn " 10%	Abbott	738
Aminosyn II 15%	Abbott	1107
Novamine 11.4%	Clintec	570
Novamine 15%	Clintec	749

Borgsdort LR, Cada OJ, Cirigliano M, et al. Drug Facts and Comparisons. 60th SI. Louis. MO: Wolters Kluwer. 2006.

is not an essential amino acid (because it is produced in skeletal muscle), glutamine levels in blood and tissues drop precipitously in acute, hyper-catabolic conditions (e.g., trauma), so glutamine may be a "conditionally essential" amino acid (9,11). The amino acids that contain glutamic acid are shown in Table 47.3. Glutamine is formed when glutamic acid combines with ammonia in the presence of the enzyme glutamine synthetase, so glutamic acid can be an exogenous source of glutamine.
Available evidence supports the role of glutamate-containing amino acid solutions in reducing infectious complications and mortality in ICU patients (10,12,13). For this reason, glutamine supplementation is recommended (4).

Lipid Emulsions
Intravenous lipid emulsions consist of submicron droplets (:50.45 mm) of cholesterol and phospholipids surrounding a core of long-chain triglycerides (2). The triglycerides are derived from vegetable oils (safflower or soybean oils) and are rich in linoleic acid, an essential polyunsaturated fatty acid that is not produced by the human body **(4)**. As shown in Table 47.4, lipid emulsions are available in 10% and 20% strengths (the percentage refers to grams of triglyceride per 100 mL of solution). The 10% emulsions provide approximately 1 kcal/mL, and the 20% emulsions provide 2 kcal/mL. Unlike the hypertonic dextrose solutions, lipid emulsions are roughly isotonic to plasma and can be infused through peripheral veins. The lipid emulsions are available in unit volumes of 50 to 500 mL and can be infused separately (at a maximum rate of 50 mL/hour) or added to the dextrose-amino acid mixtures. The triglycerides introduced into the bloodstream are not cleared for 8 to 10 hours, and lipid infusions often produce a transient, lipemic-appearing (whitish) plasma.

Lipid Restriction
Lipids are used to provide up to 30% of the daily (nonprotein) calorie requirements. However, because dietary lipids are oxidation-prone and can promote oxidant-induced cell injury (15), restricting the use of lipids

TABLE 47.4 Intravenous Lipid Emulsions for Clinical Use

	Intralipid* (Clintec)		Liposyn 11* (Hospira)		Liposyn III' (Hospira)	
Feature	10%	20%	10%	20%	10%	20%
Calories (kcal/mL)	1.1	2	1.1	2	1.1	2
% Calories as EFA (Linoleic acid)t	50%	50%	66%	66%	55%	55%
Cholesterol (mg/dL)	250-300	250-300	13-22	13-22	19-21	19-21
Osmolarity (mOsm/L)	260	260	276	258	284	292
Unit volumes	50	50	100	200	100	200
(mL)	100	100	200	500	200	500
	250	250	500		500	
	500	500				

*'ntralipid and Liposyn III are derived from soybean

~Liposyn II is derived from soybean oil (50%) and safflower oil

tThe essential fatly acid (EFA) in lipid emulsions is linoleic acid. To deficiency, approximately 4% of the total daily calories should be provided by (Barr LH, Dunn GO, Brennan MF. Essential fatty acid deficiency during total nutrition. Ann Surg 1981 ;193:304-311.).

Adapted from: Borgsdort LR, Cad a OJ, Cirigliano M, et al. Drug Facts and 60th ed. 51. Louis. MO: Wolters Kluwer.

in critically ill patients (who often have high oxidation rates) seems wise. Although lipid infusion is necessary to prevent essential fatty acid deficiency (cardiomyopathy, skeletal muscle myopathy), this can be accomplished with minimal amounts of lipid (see footnote in Table 47.4).

ADDITIVES

Commercially available mixtures of electrolytes, vitamins, and trace elements are added directly to the dextrose-amino acid mixtures.

Electrolytes

Most electrolyte mixtures contain sodium, chloride, potassium, and magnesium; they also may contain calcium and phosphorous. The daily requirement for potassium or any specific electrolyte can be specified in the TPN orders. If no electrolyte requirements are specified, the electrolytes are added to replace normal daily electrolyte losses.

TABLE 47.5 Trace Element Preparations and Daily Requirements

Trace Element	Daily Parenteral* Requirement	MTE-5* concentrated	MTE-6* concentrated
Chromium	10-15 μg	10 μg	10 μg
Copper	300-500 μg	1 mg	1 mg
Iodine	150 μg	–	75 μg
Iron[t]	2.5-8 mg	–	–
Manganese	60-100 μg	500 μg	500 μg
Selenium	20-60 μg	60 μg	60 μg
Zinc	2.5-5 mg	5 mg	5 mg

"Adapted from: Mirtallo J, Canada T, Johnson 0, et al. Safe practices for tion. J Parenter Enteral Nutr
tBorgsdort LR, Cada DJ, Cirigliano M, et al. Drug Facts and Comparisons. St. Louis, MO: Wolters Kluwer, 2006.
tIron is not a routine component of premixed element

Vitamins

Aqueous multivitamin preparations are added to the dextrose-amino acid mixtures. One unit vial of a standard multivitamin preparation will provide the normal daily requirements for most vitamins (see Table 45.4) (6). Enhanced vitamin requirements in hypermetabolic patients in the ICU may not be satisfied. Furthermore, some vitamins are degraded before they are delivered. Some examples are riboflavin and pyridoxine (which are degraded by light) and thiamine (which is degraded by sulfites used as preservatives for amino acid solutions) (17).

Trace Elements

A variety of trace element additives are available, and two commercial mixtures are shown in Table 47.5. Most trace element mixtures contain chromium, copper, manganese, and zinc, but they do not contain iron and iodine. Some mixtures contain selenium, and others do not. Considering the importance of selenium in endogenous antioxidant protection (see Chapter 21), it seems wise to select a trace element additive that contains selenium. Routine administration of iron is not recommended in critically ill patients because of the pro-oxidant actions of iron (see Chapter 21, Fig. 21.5).

CREATING A TPN REGIMEN

The following stepwise approach shows how to create a TPN regimen for an individual patient. The patient in this example is a 70-kg adult who is not nutritionally depleted and has no volume restrictions.

Step 1
The first step is to estimate the daily protein and calorie requirements as described in Chapter 45. For this example, the daily calorie requirement will be 25 kcal/kg, and the daily protein requirement will be 1.4 g/kg. Therefore, for the 70-kg patient, the protein and calorie requirements are as follows:

Calorie requirement = 25 (kcal/kg) X 70 (kg) = 1750 kcal/ day
Protein requirement = 1.4 *(g/*day) X 70 (kg) = 98 *g/*day (47.1)

Step 2
The next step is to take a standard mixture of 10% amino acids (500 mL) and 50% dextrose (500 mL) and determine the volume of this mixture that is needed to deliver the estimated daily protein requirement. Although the dextrose-amino acid mixture is referred to as A10-D50 the final mixture actually represents 5% amino acids (50 grams of protein per liter) and 25% dextrose (250 grams dextrose per liter). Therefore, the volume of the A10-D50 mixture needed to provide the daily protein requirement is as follows:

Volume of A10-D50 = 98 *(g/day) / 50* (g/L) = 1.9 L /day (47.2)

If this mixture is infused continuously over 24 hours, the infusion rate will be 1900 mL/24 hours = 81 mL/hour (or 81 microdrops/minute).

Step 3
Using the total daily volume of the dextrose-amino acid mixture determined in Step 2, the next step is to determine the total calories that will be provided by the dextrose in the mixture. Using an energy yield of 3.4 kcal / g for dextrose, the total dextrose calories can be determined as follows:

Amount of dextrose = 250 (g/L) X 1.9 (L/day) = 475 g/day
Dextrose calories = 475 *(g/*day) X 3.4 (kcal/g) = 1615 kcal/day

Because the estimated requirement for calories is 1750 kcal/ day, the dextrose will provide all but 135 kcal/ day. These remaining calories can be provided by an intravenous lipid emulsion.

Step 4
If a 10% lipid emulsion (1 kcal/mL) is used to provide 135 kcal/day, the daily volume of the lipid emulsion will be 135 m*L/*day. Because the lipid emulsion is available in unit volumes of 50 mL, the volume can be

adjusted to 150 mL /day to avoid wastage. Thus volume can be infused at half the maximum recommended rate (50 mL/hour) to minimize the tendency to develop lipemic serum during the infusion.

Step 5
The daily TPN orders for the previous example can then be written as follows:

Provide standard TPN with A10-D50 to run at 80 mL / hour.

Add standard electrolytes, multivitamins, and trace elements.

Give 10% Intralipid: 150 mL to infuse over 6 hours.

TPN orders are rewritten each day. Specific electrolyte, vitamin, and trace element requirements are added to the daily orders as needed.
The example just presented applies to the separate administration of dextrose-amino acid mixtures and lipid emulsions. Another practice that is gaining popularity is to add the nutrient solutions and additives together to form a total nutrient admixture (TNA). Although this simplifies nutrient administration and reduces cost, there are lingering concerns regarding compatibility (e.g., multivitamin preparations may not be compatible with lipid emulsions).

COMPLICATIONS
A multitude of complications are associated with parenteral nutrition (6,18,19). Some of the more prominent ones are mentioned in the following paragraphs.

CATHETER-RELATED COMPLICATIONS
Because the dextrose and amino acid solutions are hyperosmolar (Tables 47.1 and 47.2), TPN is administered through a large central vein, preferably the superior vena cava. The complications associated with central venous catheters are described in Chapters 6 and 7. A misdirected catheter, like the one shown in Figure 47.1, should not be used for the administration of TPN because of the increased risk of venous thrombosis (20). Misdirected catheters can be repositioned over a guidewire as described next.

Catheter Repositioning
When a catheter has been misdirected up into the neck, the patient should be placed in a semirecumbent or upright position if possible and the catheter should be withdrawn until only a few centimeters of the catheter tip remains inserted. A flexible guidewire is then inserted through the catheter and advanced 10 cm. The catheter is removed over the guidewire,

and a new catheter is inserted and advanced 15 cm. The guidewire is removed and a Doppler probe (the one used by nurses to detect pedal pulses) is placed over the internal jugular vein in the neck. A bolus of saline is then injected through the catheter. If the catheter has been rethreaded up into the neck, the bolus injection will produce an audible noise from the Doppler probe. If this occurs, a new catheter will need to be inserted into the internal jugular vein on the same side. If no sound is detected, a repeat chest x-ray study should be obtained to determine whether the catheter has been repositioned in the superior vena cava.

CARBOHYDRATE INFUSIONS

Hyperglycemia

Glucose intolerance is one of the most common complications of TPN. Even though this problem can be reduced by providing fewer nonprotein calories as glucose (and more as lipids), persistent hyperglycemia usually requires the addition of insulin to the TPN solutions. It is important to emphasize that insulin adsorbs to all plastics and glass used in intravenous infusion sets. The amount lost to adsorption varies with the amount of insulin added, but an average loss of 20 to 30% should be expected (21). Albumin has been used to reduce insulin binding to intravenous infusion sets (21), but this is a costly and unreliable measure.

Instead, the insulin dosage is adjusted to achieve the desired glycemic control. When TPN is discontinued, the insulin requirement will be less than that needed during TPN.

Hypophosphatemia
The effects of TPN on the serum phosphate level is shown in Figure 35.2. This effect is due to enhanced uptake of phosphate into cells associated with glucose entry into cells. The phosphate is then used to form thiamine pyrophosphate, an important cofactor in carbohydrate metabolism.

Fatty Liver
When glucose calories exceed the daily calorie requirements, there is lipogenesis in the liver and this can progress to fatty infiltration of the liver and elevated levels of transaminase enzymes in the blood 09,22). It is unclear whether this process has any pathologic consequences or whether it merely serves as a marker of excess carbohydrate calories.

Hypercapnia
Excess carbohydrates promote CO_2 retention in patients with respiratory insufficiency. Although this has been attributed to the high respiratory quotient associated with carbohydrate metabolism (see Table 45.1), this may be a reflection of overfeeding in general and not specific overfeeding with carbohydrates (23).

LIPID INFUSIONS
One of the major (and often overlooked) toxicities associated with lipid infusions is an increased risk of oxidation-induced cell injury 05). Lipid formulations used in TPN are rich in oxidizable lipids, and infusion of such lipids can promote organ injury similar to that seen in critically ill patients. For example, infusion of oleic acid, a fatty acid that is abundant in lipid emulsions used in TPN, is the standard method for producing the acute respiratory distress syndrome (ARDS) in animals (Am Rev Respir Dis 1994;149:245-260), and this might explain why lipid infusions in TPN formulations are associated with impaired oxygenation and prolonged respiratory failure (24,25). The possible role of lipid infusions in promoting oxidant-induced organ injury deserves more attention.

GASTROINTESTINAL COMPLICATIONS
Two indirect complications of TPN are related to the absence of bulk nutrients in the bowel.

Mucosal Atrophy
The absence of bulk nutrients in the bowel produces atrophy and disruption of the bowel mucosa. This is described in Chapter 46 and is illustrated in Figure 46.1. These changes can predispose to translocation of enteric pathogens across the bowel mucosa and subsequent septicemia. Because TPN is usually accompanied by bowel rest, one of the indirect complications of TPN is bacterial translocation and sepsis of bowel origin (9,10). As mentioned earlier, glutamine-supplemented TPN may help reduce the risk of this complication.

Acalculous Cholecystitis
The absence oflipids in the proximal small bowel prevents cholecystokinin-mediated contraction of the gallbladder and the bile stasis that results may promote acalculous cholecystitis (8). This disorder is described in Chapter 42.

PERIPHERAL PARENTERAL NUTRITION
Parenteral nutrition can occasionally be delivered via peripheral veins for short periods. The goal of peripheral parenteral nutrition (PPN) is to provide just enough nonprotein calories to spare the breakdown of proteins to provide energy (i.e., protein-sparing nutritional support). PPN does not create enough of a positive nitrogen balance to build up protein stores, and thus it is not intended for patients who are protein depleted or for patients who are hypercatabolic and at risk of becoming protein depleted.
The osmolality of peripheral vein infusates should be kept below 900 mOsm/L and the pH within the range of 7.2-7.4 to slow the rate of osmotic damage to vessels (26,27). Therefore, PPN must be delivered with dilute amino acid and dextrose solutions. Because lipid emulsions are isotonic to plasma, lipids can be used to provide a significant proportion of the nonprotein calories in PPN.

Method
A common admixture used in PPN is a mixture of 3% amino acids and 20% dextrose. This mixture produces a final concentration of 1.5% amino acids 05 grams of protein per liter) and 10% dextrose 000 grams of dextrose per liter), with an osmolarity of approximately 500 *mOsm/L.* The dextrose will provide 340 kcal/L, so 2.5 L of the mixture will provide 850 kcal. If 250 mL of 20% Intralipid is added to the regimen (adding 500 kcal), the total nonprotein calories will increase to 1350 kcall day. This should be close to the nonprotein calorie requirement of an average-size adult at rest (25 kcal/kgl day). In hypermetabolic patients, large volumes of PPN are required to satisfy daily energy requirements.
In summary, peripheral intravenous nutrition can be used as a temporary measure to prevent or limit protein breakdown in patients who

are not already protein depleted and are expected to begin oral feedings within a few days. Postoperative patients seem best suited for this form of nutritional support.

A FINAL WORD

The final word on parenteral nutrition is .. *avoid* .. (whenever possible). For an explanation, see the FINAL WORD section of the last chapter.

REFERENCES

Chapter 48

ADRENAL AND THYROID DYSFUNCTION

Endocrine disorders that involve the adrenal and thyroid glands are noted for their ability to act as catalysts for serious, life-threatening conditions while escaping notice themselves. This chapter explains how to unmask an underlying or occult disorder of adrenal or thyroid function and how to treat each disorder appropriately.

ADRENAL INSUFFICIENCY

The adrenal gland plays a major role in the adaptive response to stress. The adrenal cortex releases glucocorticoids and mineralocorticoids that promote glucose availability and maintain extracellular volume, while the adrenal medulla releases catecholamines that support the circulation. Attenuation or loss of this adrenal response leads to hemodynamic instability, volume depletion, and defective energy metabolism. The important feature of adrenal insufficiency is its ability to remain silent until the adrenal gland is called on to respond to a physiologic stress. When this occurs, adrenal insufficiency becomes an occult catalyst that speeds the progression of acute, life-threatening conditions.

Adrenal insufficiency can be a primary (inability of the adrenal gland to elaborate cortisol) or secondary disorder (inability of the hypothalamic-pituitary axis to release ACTH). The description that follows pertains to primary adrenal insufficiency, and how it behaves in the critically **ill** patient (1-4).

Plasma Cortisol

In healthy subjects, 90% of the cortisol in plasma is bound to corticosteroid-binding globulin and albumin, and only 10% is in the free or biologically active form (1,5). The evaluation of adrenal function is based on a

radioimmunoassay that measures total cortisol in plasma (bound and unbound fractions). Unfortunately, this can be misleading in acutely **ill** patients because the cortisol transport proteins are often decreased in these patients (5). For example, one study of septic patients revealed that total cortisol levels are diminished in 40% of patients, while free cortisol levels are consistently elevated (5). The inability to measure free cortisol levels in plasma is a major problem that must be considered in interpreting tests of adrenal function in critically **ill** patients.

Predisposing Conditions
Several conditions that are common in ICU patients can predispose to primary adrenal insufficiency. These include major surgery, circulatory failure, septic shock, severe coagulopathy, and human immunodeficiency virus (HIV) infections 0,2). In some of these conditions, the adrenal insufficiency is caused by pathologic destruction of the adrenal gland (e.g., coagulopathy with adrenal hemorrhage), while in others, there is diminished adrenal responsiveness (e.g., septic shock). In addition, some of the drugs that are used in critically **ill** patients can decrease cortisol levels by either inhibiting synthesis (e.g., etomidate and ketoconazole) or accelerating metabolism (e.g., phenytoin or rifampin) 0,2).

Incidence
In surveys of randomly-selected ICU patients, the incidence of adrenal insufficiency is approximately 30% (2). In patients with septic shock, the incidence is higher at 50-60% (2,4). In many of these cases, adrenal insufficiency was not evident clinically but was uncovered by biochemical evidence of abnormal adrenal responsiveness (2,4). In ICU patients with laboratory evidence of adrenal insufficiency, the mortality rate is as much as twice that of patients with normal adrenal responsiveness (6-8).

Clinical Manifestations
In critically ill patients, the most prominent manifestation of adrenal insufficiency is hypotension that is refractory to vasopressors (1,2,7,8). Other features of adrenal insufficiency, such as electrolyte abnormalities (hyponatremia, hyperkalemia), weakness, and hyperpigmentation, are either uncommon or not specific enough to suggest the diagnosis in ICU patients.

Hemodynamics
In mild or chronic cases of adrenal insufficiency, the hemodynamic changes are often a reflection of hypovolemia (low filling pressures, low cardiac output, high systemic vascular resistance). In acute adrenal failure, the hemodynamic changes are similar to those of hyperdynamic shock (high cardiac output, low systemic vascular resistance) (1,9). Because many cases of adrenal insufficiency are uncovered in patients with septic shock, where the hemodynamic changes are similar to those of acute adrenal failure (i.e., hyperdynamic shock), it is often impossible to identify adrenal failure based on hemodynamic profiles in critically **ill** patients.

Clinical Suspicion
Adrenal insufficiency should be suspected in any patient in the ICU who develops an unstable or reduced blood pressure of unclear etiology, or has hypotension that is refractory to fluid resuscitation and vasopressors.

EVALUATION OF ADRENAL FUNCTION
The diagnostic test of choice for primary adrenal insufficiency in ICU patients is the rapid adrenocorticotropic hormone (ACTH) stimulation test 0). This test evaluates the acute adrenal response to a bolus injection of synthetic ACTH (cosyntropin).

Rapid ACTH Stimulation Test
The rapid ACTH stimulation test can be performed at any time of the day or night because it is not influenced by diurnal variations in cortisol secretion (which are often absent in critically **ill** patients anyway) (2). An initial blood sample is obtained for a plasma cortisol level, and synthetic ACTH (250 μg) is injected intravenously. A post-ACTH plasma cortisol level is then obtained at 30 and 60 minutes after the ACTH injection.

Interpretation
The interpretation of the ACTH stimulation test is outlined in Table 48.1 (1). Both the baseline cortisol level and the increment in cortisol at 30 or 60 minutes (whichever is greater) are used to evaluate adrenal function. A baseline cortisol level that is above 34 μg/ dL (940 nmol/U is evidence of normal or adequate adrenal function, while a baseline cortisol level that is below 15 μg/dL (415 nmol/L) is evidence of adrenal insufficiency. When the baseline cortisol level is between 15 and 34 μg/ dL (415 and 940 nmol/ L), the increment in plasma cortisol is used in the

TABLE 48.1 Interpretation of the Rapid ACTH Stimulation Test in Critically 1/1 Patients

Plasma Cortisol in μg/dL·			Probability of
Baseline	Increment		Adrenal Insufficiency
<15		→	Very High
15-34		<9	High
15-34		>9	Low
>34		→	Very Low

·To convert *μg/dL* to nmol/L, multiply by 27.6.

tConsider corticosteroid replacement

From Cooper MS, Stewart PM. Corticosteroid insufficiency in critically ill Med 2003:348:727-734.

interpretation: an increment that is greater than 9 μg/ dL (250 nmol/L) is evidence of normal or adequate adrenal function, while an increment that is less than 9 μg/ dL (250 nmol/U is evidence of adrenal insufficiency.

Steroid Therapy
In patients with suspected adrenal insufficiency who have severe or refractory hypotension, steroids can be started immediately, before the ACTH stimulation test is performed. Steroid administration can proceed as follows:

Dexamethasone (Decadron) will not interfere with plasma cortisol assay (2) and can be given before or during the ACTH stimulation test. The initial dose should be 2 mg (as an IV bolus), which is equivalent to 270 mg of hydrocortisone (cortisol) (2).

After the ACTH stimulation test is completed, empiric therapy can begin with hydrocortisone (Solu-Cortef). The dose is 50 mg IV every 6 hours until the test results are available.

If the ACTH stimulation test is normal, the hydrocortisone can be abruptly discontinued, without a taper. If the test reveals primary adrenal insufficiency, the hydrocortisone should be continued at 50 mg IV every 6 hours until the patient is no longer in a stressed condition (1). When this occurs, the daily dose of hydrocortisone should be reduced to 20 mg (which is equivalent to the amount of cortisol secreted daily by the adrenal glands).

Limitations in Adrenal Function Testing
The evaluation of adrenal function is limited in critically ill patients for the following reasons:

There is no standard definition of adrenal insufficiency in ICU patients 0,2,6).

Cortisol transport proteins in blood are diminished in acutely ill patients, and this invalidates the assessment of adrenal function based on total plasma cortisol (rather than free plasma cortisol) levels.

Cytokines released during inflammation can blunt end-organ responsiveness to cortisol, which means that blood cortisol levels will underestimate the severity of abnormal adrenal responsiveness in patients with systemic inflammation.

The appropriate dose of ACTH to use for the rapid ACTH stimulation test is unclear. The standard dose (250 μg) is 100 times the maximal pituitary output of ACTH, and the excessive adrenal stimulation from this dose could mask a case of adrenal insufficiency that occurs during physiologic conditions of adrenal stimulation (2,6). A small dose of ACTH (1 μg) may be more appropriate for matching the level of adrenal stimulation that occurs during clinical illness (2,6).

In cases of vasopressor-dependent septic shock, the ACTH stimulation test does not predict which patients will benefit from corticosteroid supplemenation.

Because of these limitations, a clinical suspicion of adrenal insufficiency might be sufficient enough to begin an empiric trial of steroids (e.g., hydrocortisone, 50 mg IV every 6 hours), and then assess the clinical response.

EVALUATION OF THYROID FUNCTION

Laboratory tests of thyroid function can be abnormal in 70% of hospitalized patients and in up to 90% of critically ill patients (11). In most cases, the abnormality represents an adaptive response to non-thyroidal (systemic) illness and is not a sign of pathologic thyroid disease 01,12). This section describes the laboratory evaluation of thyroid function and explains how to determine if a laboratory abnormality represents a true disorder of thyroid function 01-13).

Thyroxine (T4) and Triiodothyronine (T3)

Thyroxine (T_4) is the principal hormone secreted by the thyroid gland, but the active form is triiodothyronine (T_3), which is formed by deiodination of thyroxine in extrathyroidal tissues. Both T3 and T4 are extensively (>99%) bound to plasma proteins, especially thyroxine-binding globulin. Approximately 0.2% of the total T3 is in the unbound or physiologically active form. Because of the minor representation of unbound T3 and T4 in plasma, and the potential for plasma protein concentrations to vary in ICU patients, only measurements of free T3 and T4 should be performed in ICU patients.

Thyroid-Stimulating Hormone (TSH)

For patients who have an abnormal level of free T3 or T4 in plasma, the thyroid-stimulating hormone (TSH) level in plasma can help to identify those with primary thyroid disorders (hyperthyroidism hypothyroidism), secondary thyroid disorders (hypothalamic-pituitary dysfunction), and non-thyroidal illness. The negative feedback exerted by the thyroid hormones on TSH secretion allows the TSH to distinguish primary from secondary thyroid disorders. For example, in patients with an abnormally low level of free T4 in plasma, an elevated TSH level is evidence for primary hypothyroidism, while a reduced TSH level is evidence for hypothyroidism secondary to hypothalamic-pituitary dysfunction.

Non- Thyroidal Illness

The TSH level can also help to identify patients with non-thyroidal illness. For example, in patients with a low level of free T4 in plasma, a normal TSH level is evidence of non-thyroidal illness. The TSH level is

TABLE 48.2 Common Patterns of Thyroid Function Tests in Critically Ill Patients

Condition	FreeT_4	Free T3	TSH
Non-thyroidal illness:			
Early systemic illness	NL	decrease	NL
Early critical illness	decrease	decrease	NL
Chronic critical illness (>2 days)	decrease	decrease	decrease or NL
Thyroid disease:			
Primary hypothyroidism	decrease	decrease	increase
Primary hyperthyroidism	increase	increase	decrease

Adapted from: Dayan CM. Interpretation of thyroid function tests. Lancet 2001 624. Peeters RP, Debaveye Y, Fliers E, et al. Changes within the thyroid axis illness. Crit Care Clin 2006;22:41-55.

normal in a majority of patients with non-thyroidal illness, but it can be reduced in 30% and elevated in 10% of these patients (11). TSH secretion can be depressed by sepsis, corticosteroids, diphenylhydantoin, and dopamine infusions (14), and these factors must be considered when interpreting plasma TSH levels.

Patterns of Thyroid Function Abnormalities

The changes in free T4 free T3 and TSH levels in both thyroid disease and non-thyroidal illness are shown in Table 48.2.

Non- Thyroidal Illness

Thyroid function abnormalities secondary to systemic illness (e.g., trauma or infection) occur in 70% of hospitalized patients (11,12,15). Within a few hours following the onset of illness, free T3 is decreased in proportion to illness severity (11). With increasing illness severity, both free T3 and free T4 levels are depressed (this pattern occurs in 30 to 50% of ICU patients), and this pattern is associated with an increase in mortality (11,12). After several days of critical illness, there is a further decline in free T_3 levels, and TSH levels may be decreased (11,12). As explained earlier, TSH levels are normal in a majority of patients with non-thyroidal illness.

Thyroid Disorders

Primary thyroid disorders are characterized by changes in both free T3 and free T4 levels (increased in hyperthyroidism and decreased in hypothyroidism) with reciprocal changes in the plasma TSH level. Hypothyroidism due to hypothalamic-pituitary dysfunction is characterized by a reduced TSH level, as explained earlier. The salient features of thyroid disorders in critically ill patients are presented next (13).

TABLE 48.3 Manifestations of Thyroid Dysfunction

Hyperthyroidism	Hypothyroidism
Cardiovascular:	Effusions:
Sinus tachycardia	Pericardial effusion
Atrial fibrillation	Pleural effusion
Neurologic:	Miscellaneous:
Agitation	Hyponatremia
Lethargy (elderly)	Skeletal muscle myopathy
Fine tremors	Elevated creatinine
Thyroid Storm:	Myxedema Coma:
Fever	Hypothermia
Hyperdynamic shock	Dermal infiltration
Depressed consciousness	Depressed consciousness

HYPERTHYROIDISM

Most cases of hyperthyroidism are due to primary thyroid disorders (e.g., Grave's disease, autoimmune thyroiditis). Chronic therapy with amiodarone, an iodine-containing antiarrhythmic agent, can also cause hyperthyroidism 06,17).

Clinical Manifestations

Some of the common or characteristic manifestations of hyperthyroidism are listed in Table 48.3. It is important to note that elderly patients with hyperthyroidism may be lethargic rather than agitated (apathetic thyrotoxicosis). The combination of lethargy and unexplained atrial fibrillation is characteristic of apathetic thyrotoxicosis in the elderly (18).

Thyroid Storm

An uncommon but severe form of hyperthyroidism known as *thyroid storm* can be precipitated by acute illness or surgery. This condition, characterized by fever, severe agitation, and high-output heart failure, can progress to hypotension and coma 09,20) and is uniformly fatal if overlooked and left untreated.

Diagnosis

As shown in Table 48.2, hyperthyroidism will be accompanied by an elevated free Tq and free T3 level, and a reduced TSH level. Because hyperthyroidism is almost always caused by primary thyroid disease, the TSH is not necessary in hyperthyroidism.

Management

Beta Receptor Antagonists
Immediate management of troublesome tachyarrhythmias can be achieved by administering intravenous propanolol (1 mg every 5 minutes until the desired effect is achieved). Oral maintenance therapy (20 to 120 mg every 6 hours) can be used until antithyroid drug therapy is effective.

Antithyroid Drugs
The two drugs used to suppress thyroxine production are methimazole and propylthiouracil (PTU). Both drugs are given orally. Methimazole is preferred to PTU because it causes a more rapid decline in serum thyroxine levels and has a lower incidence of serious side effects (agranulocytosis) (21). The initial dose of methimazole is 10 to 30 mg once a day, and the initial dose of PTU is 75 to 100 mg three times daily 09,21). The dose of both drugs is reduced by 50% after 4 to 6 weeks of therapy.

Iodide
In severe cases of hyperthyroidism, iodide (which blocks thyroxine release from the thyroid gland) can be added to therapy with PTU. Iodide can be given orally as Lugol's solution (4 drops every 12 hours) or intravenously as sodium iodide (500 to 1,000 mg every 12 hours). If the patient has an iodide allergy, lithium (300 mg orally every 8 hours) can be used as a substitute (20).

Special Concerns in Thyroid Storm
In addition to the above measures, the management of thyroid storm often requires aggressive volume resuscitation to replace fluid losses from vomiting, diarrhea, and heightened insensible fluid loss. Thyroid storm can accelerate glucocorticoid metabolism and create a relative adrenal insufficiency. Therefore, in cases of thyroid storm associated with severe or refractory hypotension, hydrocortisone (300 mg IV as a loading dose, followed by 100 mg IV every 8 hours) may help correct the hypotension. Successful management of thyroid storm also requires treatment of the precipitating event (20,22).

HYPOTHYROIDISM
Hypothyroidism is uncommon in hospitalized patients. When present, most cases represent primary hypothyroidism (23).

Clinical Manifestations
Some of the more common or characteristic manifestations of hypo-thyroidism are listed in Table 48.3. The most common cardiovascular manifestation is pericardial effusion (24), which develops in approximately 30% of cases, and is the most common cause of an enlarged

cardiac silhouette in patients with hypothyroidism (24). These effusions usually accumulate slowly and do not cause cardiac compromise. Pleural effusions are also common in hypothyroidism. The pleural and pericardial effusions are due to an increase in capillary permeability and are exudative in quality.
Hypothyroidism can also be associated with hyponatremia and a skeletal muscle myopathy, with elevations in muscle enzymes (creatine phosphokinase, aldolase, lactate dehydrogenase). Enhanced release of creatinine from skeletal muscles can also raise the serum creatinine in the absence of renal dysfunction (25).

Myxedema Coma
Advanced cases of hypothyroidism are accompanied by hypothermia and depressed consciousness. Although this condition is called myxedema coma, frank coma is uncommon (26). The edematous appearance in myxedema is due to intradermal accumulation of proteins (26) and does not represent accumulation of interstitial edema fluid.

Diagnosis
As shown in Table 48.2, the hypothyroid patient will have a decrease in free T3 and free T4 levels, and in primary hypothyroidism, the TSH level is elevated. A normal total serum T4 level will virtually exclude the diagnosis of hypothyroidism.

Thyroid ReplacementTherapy
The treatment for mild to moderate hypothyroidism is levothyroxine, which is given orally in a single daily dose of 50 to 200 μg (27). The initial dose is usually 50 μg/ day, and this is increased in 50 μg/ day increments every 3 to 4 weeks. The optimal replacement dose of levothyroxine is determined by monitoring the serum TSH level. The optimal dose is the lowest dose of levothyroxine that returns the TSH to within the normal range (0.5 to 3.5 mU /L). In 90% of cases, this occurs with a levothyroxine dose of 100 to 200 μg/ day (27).
Oral thyroxine therapy can also be effective in severe hypothyroidism, but intravenous therapy is often recommended (at least initially) because of the risk of impaired gastrointestinal motility in severe hypothyroidism. One recommended regimen includes an initial intravenous thyroxine dose of 250 μg, followed on the next day by a dose of 100 μg, and followed thereafter by a daily dose of 50 μg (26).

T3 Replacement Therapy
Because the conversion of T4 to T3 (the active form of thyroid hormone) can be depressed in critically ill patients (26), oral therapy with T, can be used to supplement thyroxine replacement therapy. In patients with depressed consciousness, oral T3 can be given in a dose of 25 μg every 12 hours until the patient awakens (28). However, the benefits of T3 supplementation are unproven.

A FINAL WORD

Adrenal insufficiency is considered to be common in critically ill patients, but it is difficult to determine how common it is because the rapid ACTH stimulation test is fraught with problems (e.g, which dose of ACTH to use, measuring total cortisol instead of free cortisol, etc). Patients with septic shock, severe coagulopathies, and HIV infection seem to be particularly prone to adrenal insufficiency. When a patient with any of these conditions develops unexplained hypotension or hypotension that is difficult to control with fluids and pressors, adrenal insufficency deserves consideration. You can give steroids first and then do the rapid ACTH stimulation test (don't use hydrocortisone if you are planning to do the test), or just give steroids (hydrocortisone) and see what happens. A response to hydrocortisone should be readily apparent if adrenal insufficency is a problem.

REFERENCES