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Nutrition in Critical Illness

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Introduction

The human body constantly strives to maintain homeostasis even when challenged by internal and external physical, biological, chemical, or psychological forces. Hospitalized patients are routinely exposed to factors that cause metabolic stress. These include semi-starvation, infection, trauma, surgery, and tissue ischemia. Malnutrition occurs in hospitalized patients mainly through starvation or metabolic stress.[1] These two pathways resulting in malnutrition exhibit very different metabolic alterations (Table 66.1). The development of malnutrition in critically ill patients can occur very rapidly secondary to the hormonal and nonhormonal mediators that result in the complex metabolic alterations.

Metabolic Response to Stress

The metabolic response to injury and sepsis has been well studied after the pioneering work of Kinney.[2] Stressed patients undergo several metabolic phases as a series of ebb and flow states reflecting a patient's response to the severity of the stress (Table 66.2). The earliest, or ebb, state is usually manifested by decreased oxygen consumption, fluid imbalances, inadequate tissue perfusion, and cellular shock. These changes decrease metabolic needs and provide a brief protective environment. The flow state is a hyperdynamic phase in which substrates are mobilized for energy production while increased cellular activity and hormonal stimulation is noted. Subsequently, most patients will enter a third phase of recovery, or anabolism, which is characterized by normalization of vital signs, increased diuresis, improved appetite, and positive nitrogen balance. There is an energy expenditure distinction for each phase, making the goals of nutrition therapy variable depending on the stage in question. As long as the patient is in a hyperdynamic catabolic state, optimal nutrition support can only at best approach zero nitrogen balance in attempts to minimize further protein wasting. Once the patient enters the anabolic phase, it is then realistic to anticipate a positive nitrogen balance and repletion of lean body mass through optimal

TABLE 66.1

Metabolic Comparisons between Starvation and Stress

	Starvation	Stress
Resting energy expenditure	↓	↑↑
Respiratory quotient	↓	↑
Primary fuels	Fat	Mixed
Glucagon	↑	↑
Insulin	↓	↑
Gluconeogenesis	↓	↑↑↑
Plasma glucose	↓	↑
Ketogenesis	↑↑	↓
Plasma lipids	↑	↑↑
Proteolysis	↑	↑↑↑
Hepatic protein synthesis	↑	↑↑
Urinary nitrogen loss	↑	↑↑↑

TABLE 66.2

Stress Phase Alterations

Phase	Hormonal/Nonhormonal	Metabolic	Clinical Outcomes
Ebb phase	↑ Glucagon ↑ Adrenocorticotropic hormone (ACTH)	Circulatory insufficiency (↑ Heart rate, vascular constriction) ↓ Digestive enzyme production ↓ Urine production	Hemodynamic instability
Flow phase	↑ Counterregulatory hormones (epinephrine, norepinephrine, glucagon, cortisol) ↑ Insulin ↑ Catecholamines ↑ Cytokines (TNF, IL-1,-2, and -6)	Hyperglycemia ↓ Protein synthesis ↑ amino acid efflux ↑ Gluconeogenesis ↑ Glycogenolysis ↑ Lipolysis ↑ Urea nitrogen excretion/ net (-) nitrogen balance	Fluid and electrolyte imbalances Mild metabolic acidosis ↑ Resting energy expenditure
Anabolic phase	↑ Insulin ↓ Counterregulatory hormones ↓ Cytokines	↑ Protein synthesis ↓ Urea nitrogen excretion/ net (+) nitrogen balance ↓ Gluconeogenesis ↓ Lipolysis	↓ Resting energy expenditure ↑ Lean body mass

nutrition intervention. Therefore, early nutrition intervention in critical illness, is primarily geared towards sustaining vital organ structure and immune function, ameliorating the catabolic effects of critical illness and promoting recovery without causing further metabolic derangements.

The high-risk patient usually remains in the catabolic phase for a prolonged period. In order to meet tissue demands for increased oxygen consumption following acute injury, there is an increase in oxygen delivery. This is accomplished by a systemic response that includes increases in heart rate, minute ventilation and myocardial contractility, and decreases in peripheral vascular resistance so that the cardiac index may exceed 4.5 L/min/m.[2,3] Other systemic responses include hypermetabolism yielding increased proteolysis and nitrogen loss, accelerated gluconeogenesis, hyperglycemia and increased glucose utilization, and retention of salt and water. When patients become critically ill, they rapidly shift from an anabolic state of storing protein, fat, and glycogen to a catabolic state by mobilizing these nutrients for energy utilization.[4] There is a direct correlation between the severity of the injury and the degree of substrate mobilization. The mobilization of protein,

fat, and glycogen is mediated through the release of cytokines such as tumor necrosis factor, interleukins-1,-2 and -6, and the counterregulatory hormones such as epinephrine, norepinephrine, glucagon, and cortisol.[5] These hormones are labeled counterregulatory because they counter the anabolic effects of insulin and other anabolic hormones. Circulating levels of insulin are elevated in most metabolically stressed patients, but the responsiveness of tissues to insulin, especially skeletal muscle, is severely blunted. This relative insulin resistance is believed to be due to the effects of the counterregulatory hormones. The hormonal milieu normalizes only after the injury or metabolic stress has resolved.

During the hypermetabolic response of critical illness energy expenditure is increased, resulting in an increase in nutrient substrates in an attempt to meet these needs. This is exhibited by an elevated respiratory quotient (RQ) of 0.80 to 0.85 reflecting mixed fuel oxidation, as opposed to a non-stressed starved state where the RQ is in the range of 0.60 to 0.70, reflecting the oxidation of fat as the primary fuel source. Under the influence of the counterregulatory hormones, cytokines, and catecholamines, hepatic glucose production increases through glycogenolysis and gluconeogenesis.[4] The increased endogenous glucose production is poorly suppressed even with exogenous glucose or insulin administration. In stress metabolism, glycogen stores are depleted with 12 to 24 hours of a major catabolic insult, leaving only protein and adipose tissue as potential energy substrates. Gluconeogenic substrates include lactate, alanine, glutamine, glycine, serine, and glycerol. Accompanying the increased glucose production is an increase in flow to and uptake of glucose in the peripheral tissues. Hyperglycemia commonly results due to an increased glucagon/insulin ratio and insulin resistance in peripheral tissues.

Alterations in hormone levels also affect lipid metabolism. Elevations of epinephrine, growth hormone, glucagon, and beta-adrenergic stimulation induce lipolysis and increase glycerol and free fatty acid (FFA) levels which are then used as a fuel source.[5] Despite elevation in lipolysis, a proportionate increase in lipid oxidation is not observed. This is believed to be due to the elevated insulin levels. Therefore, even though lipid stores are abundant in most cases, they are poorly utilized.

With depleted glycogen stores and diminished ability to utilize fat stores, the body shifts to catabolizing and using lean body mass as a main energy source and substrate for gluconeogenesis. Although protein synthesis is higher relative to non-stress starvation, it is overall significantly reduced from the normal state due to the rate of protein catabolism. Increased nitrogen excretion is observed and is proportional to the severity of injury or infection. The major mediators of protein catabolism and the accelerated movement of amino acids from the skeletal muscle to the liver are the glucocorticoids.[4] Amino acids reaching the liver are used to produce glucose and acute-phase proteins such as fibrinogen, haptoglobin, C-reactive protein, ceruloplasmin, and alpha-2 macroglobulin.[5] Alanine is the primary amino acid used for gluconeogenesis, while glutamine supplies the necessary nitrogen to the kidneys for the synthesis of ammonia. Ammonia acts as a neutralizing substrate for the excess acid byproducts produced by the increased protein degradation that occurs during stress. The utilization of amino acids for an energy source results in increased ureagenesis and urinary nitrogen losses which may exceed 15 to 20 g/day.[2]

Nutritional Intervention in Critical Illness

The goals of nutrition intervention in critically ill patients are to minimize lean body tissue loss and support the body's immune system. Nutrient delivery is designed to maintain lean body mass without causing further metabolic complications. Achieving these goals

involves accurate and continued nutrition assessment, optimal and timely nutrient delivery, and continuous systematic monitoring of metabolic status.

Determination of Energy Requirements

Regardless of the metabolic state, energy requirements must be met in attempts to minimize the utilization of stored energy reserves. Although the protein-sparing effect of an adequate caloric intake is well recognized in the setting of adaptive starvation, it is equally clear in the setting of stress hypermetabolism that despite adequate caloric provision, protein catabolism continues despite delivery of adequate nutrients.[3]

Determination of energy requirements in the critically ill is often challenging. Critical illness and its treatment can profoundly alter metabolism and significantly increase or decrease energy expenditure.[6] Therefore, accurate determination of resting energy expenditure (REE) is necessary to ensure that energy needs are provided without over- or underfeeding. Overfeeding is associated with numerous metabolic complications. It is usually a result of excessive administration of carbohydrate or fat and can result in hepatic steatosis, hyperglycemia, and pulmonary compromise. Underfeeding leads to poor wound healing, impaired organ function, and altered immunologic status.

There are multiple methods for assessing energy requirements in the critically ill. Some methods actually measure energy expenditure, such as indirect calorimetry, and some predict caloric requirements with various equations, such as the Harris-Benedict Equation (Table 66.3). Each method of determination carries advantages as well as disadvantages. Indirect calorimetry currently remains the gold standard, and is the preferred method for assessment of energy requirements in critically ill patients. However, it is expensive to perform routinely, and many facilities do not have the equipment or trained personnel to conduct the studies. Also, indirect calorimetry can be inaccurate under a variety of circumstances that commonly affect critically ill patients, such as patients receiving greater than 70% FiO_2, or in those with malfunctioning chest tubes or endotracheal tubes in which the expired gas is not completely captured. Therefore, many clinicians rely upon predictive equations for determining energy needs. It is important to know the flaws of these equations to optimally interpret the results. The final estimate of energy needs assumes that the patients demonstrate a predictable metabolic response to their illness. The equations may overestimate the caloric needs of patients who are mechanically ventilated and sedated. Chemical neuromuscular paralysis, which is commonly used as an adjunct to the management of ventilated patients, can decrease the energy requirements of the critically ill patient by as much as 30%.[3] The calculated results are only as accurate as the variables used in the equation. Obesity and resuscitative water weight complicate the use of these equations and lead to a tendency for overfeeding.[7] However, when considering all forms and phases of critical illness, energy requirements can generally range from 20 to 40 kcal/kg lean body mass/day. Patients with extensive burns or head injury may fall at the higher end. In most cases, 20 to 30 kcal/kg per day is a reasonable initial estimate of energy requirements in critically ill adult patients (see Table 66.4). Most clinicians will use an ideal or estimated lean body mass for those individuals who are obese, to avoid overfeeding. For marasmic patients, it is important to use actual body weight to avoid overfeeding when calculating initial energy requirements.

Protein Requirements

Protein metabolism during metabolic stress is characterized by a net proteolysis. In addition to muscle proteolysis, increased ureagenesis, increased hepatic synthesis of acute

TABLE 66.3

Selected Methods for Estimating Energy Requirements

Harris-Benedict Equation — Estimates Basal Energy Expenditure (BEE)

Male: 13.75 (W) + 5 (H) – 6.76 (A) + 66.47
Female: 9.56 (W) + 1.85 (H) – 4.68 (A) + 655.1

W: weight in kilograms; H: height in centimeters; A: age in years
Note: to predict total energy expenditure (TEE) add an injury/activity factor of 1.2 to 1.8 depending on the severity and nature of illness

Ireton-Jones Energy Expenditure Equations (EEE)

Obesity
EEE = (606 × S) + (9 × W) – (12 × A) + (400 × V) + 1444

Spontaneously Breathing Patients
EEE (s) = 629 – 11 (A) + 25 (W) – 609 (O)

Ventilator Dependent Patients
EEE (v) = 1925 – 10 (A) + 5 (W) + 281 (S) + 292 (T) + 851 (B)

Where EEE = kcal/day, v = ventilator dependent, s= spontaneously breathing
A: age in years
W: body weight in kilograms
S: sex (male = 1, female = 0)
V: ventilator support (present = 1, absent = 0)
T: diagnosis of trauma (present = 1, absent = 0)
B: diagnosis of burn (present = 1, absent = 0)
O: obesity > 30% above IBW from 1959 Metropolitan Life Insurance tables (present = 1, absent = 0)

Curreri Burn Formula (EEE: Estimated Energy Expenditure)

EEE for 18-59 years old = (25 kcal × Wt) + (40 × % TBSA burn)
EEE for > 60 years old = BEE + (65 × % TBSA burn)
EEE = kcal/day; Wt: weight in kilograms; TBSA: total body surface area burn

TABLE 66.4

Energy and Substrate Recommendations

Kcalories	20-30 kcal/kg per day
Protein[a]	1.5-2.0 g/kg per day or 20-25% of total kcal
Carbohydrate[b]	≤ 4-5 mg/kg/min per day or 50-60% of total kcal
Fat[c]	15-30% of total kcal
Fluids	1 mL/kcal; maintain optimal urine output
Electrolytes	Maintain normal levels, especially Mg^{2+}, PO^{4-}, K^{+}
Vitamins/minerals	Recommended Daily Allowance; add vitamin K

[a] Adjust protein delivery for renal and hepatic dysfunction.
[b] Adjust glucose administration to maintain serum glucose levels ≤150 gm/dl.
[c] Adjust lipid delivery based on serum triglyceride levels.

phase proteins, increased urinary nitrogen losses, and the increased use of amino acids as oxidative substrate for energy production are also noted. Therefore, the protein needs of critically ill patients are significantly increased compared to those patients with simple starvation. Although the high catabolic rate is not reversed by provision of glucose and protein,[8] the protein synthetic rate is responsive to amino acid infusions, and nitrogen balance is attained through the support of protein synthesis.[9,10] Current recommendations

for stressed patients is for 20 to 25% of the total nutrient intake to be provided as protein. This equates to roughly 1.5 to 2.0 g/kg/day, providing the higher range to promote nitrogen equilibrium or at least minimize nitrogen deficit. Excess protein administration has not been shown to be beneficial, and in fact can cause azotemia.[11]

Carbohydrate Requirements

Glucose is the main fuel for the central nervous system (CNS), bone marrow, and injured tissue. A minimum of about 100 g per day is necessary to maintain CNS function. In the metabolically stressed adult, the maximum rate of glucose oxidation is 4 to 7 mg/kg/minute,[12] roughly equivalent to 400 to 700 g/day in a 70-kg person. Provision of glucose greater than this rate usually results in lipogenesis[13] and hyperglycemia. In the hypermetabolic patient, part of the oxidized glucose will be derived from endogenous amino acid substrates via gluconeogenesis. In the severely stressed patient, up to 2 mg/kg/min of glucose may be provided via gluconeogenesis and this endogenous production is poorly suppressed by exogenous glucose administration.[11] In fact, providing additional glucose in these situations can lead to severe hyperglycemia. Exogenous insulin delivery tends to be ineffective with increasing cellular glucose uptake in critically ill patients, since the rate of glucose oxidation is already maximized and because endogenous insulin concentrations are already elevated. Complications of excess glucose administration include hyperglycemia, hyperosmolar states, excess carbon dioxide production, and hepatic steatosis.[11,13] Therefore, it is recommended that glucose be provided at a rate ≤5 mg/kg/min or approximately 50 to 60% of total energy requirements in critically ill patients, and that they be monitored closely for metabolic complications as described above.

Lipid Requirements

Lipids become an important substrate in critically ill patients as they can facilitate protein sparing, decrease the risk of excess carbohydrate, limit volume delivery by their high caloric density, and provide essential fatty acids. Endogenous triglyceride breakdown continues in hypermetabolic patients despite increased plasma levels of glucose and insulin.[14] Daily fat can be provided without adverse effect, as critically ill patients efficiently metabolize exogenous lipids.[15] Fat may comprise 10 to 30% of total energy requirements, with a minimum of 2 to 4% as essential fatty acids to prevent deficiency. Hypermetabolic patients should be monitored for tolerance of lipid delivery, especially if high levels are provided, as it may cause metabolic complications.

These include hyperlipidemia, impaired immune function, and hypoxemia resulting from impaired diffusing capacity and ventilation/perfusion abnormalities. These complications are associated with intravenous infusions and are not only due to the quantity of lipids provided, but also result from the rate of delivery. The rate of infusion should not exceed 0.1 g/kg/hr. Complications may be minimized by infusing lipids continuously over 18 to 24 hours while monitoring serum triglyceride levels and liver function tests to assure tolerance.

The current intravenous lipids available in the U.S. are composed of nearly 100% long-chain triglyceride (LCT) as omega-6 fatty acids, whereas enteral formulations contain mixtures of LCT and medium-chain triglycerides (MCT). In the past several years research has shown that high levels of omega-6 fatty acids provided in critically ill patients can be immunosuppressive.[16] Large and rapid infusions of LCTs favor the production of arachidonic acid and its proinflammatory metabolites such as prostaglandin E_2 (PGE_2), leukotrienes of the 4 series, and thromboxanes.[16-18] Also, LCTs are dependent upon carnitine for

TABLE 66.5

Electrolyte Recommendations for Critically Ill Patients

Electrolyte	Daily Needs (mEq/day)	Reasons for Increased Needs	Reasons for Decreased Needs
Sodium	70-100	Loop diuretics, cerebral salt wasting	Hypertension, fluid overload
Potassium	70-100	Refeeding syndrome, diuretic therapy, amphotericin wasting	Renal failure
Chloride	80-120	Prolonged gastric losses	Acid-base balance
Phosphorus	10-30 mmol/day	Refeeding syndrome	Renal failure
Magnesium	8-24	Refeeding syndrome, diruetic therapy, ↑ GI losses	—
Calcium	5-20	↑ Blood products	—

transfer from cytosol to the mitochondria to undergo beta-oxidation. It has been postulated that critically ill patients have a relative carnitine deficiency[19] due to an increased excretion, thus limiting the oxidation of LCT. MCTs, on the other hand, do not require carnitine for transport and are rapidly and efficiently oxidized to carbon dioxide and water within 24 hours. When MCT is delivered enterally, a significant portion is absorbed into the portal system, thereby bypassing the GI lymphatic LCT absorptive system. MCTs have been shown to be better tolerated in many situations, as they require minimal biliary and pancreatic secretion for absorption. The ideal ratio of LCT:MCT for critically ill patients is currently not known.

Fluid and Electrolytes

Critical illness disrupts normal fluid and electrolyte homeostasis. Sepsis, systemic inflammatory response syndrome (SIRS), gastrointestinal losses, delivery of medications, and acid-base disturbances contribute to the imbalances. Electrolyte deficiencies usually reflect shifts in concentrations between intravascular and extravascular as well as intracellular and extracellular spaces rather than total body depletion. Wound healing and anabolism have been shown to increase requirements of phosphorus, magnesium, and potassium. Altered electrolyte levels can impair organ function and are usually manifested by cardiac dysrhythmias, ileus, and impaired mentation. Fluid and electrolytes should be provided to maintain adequate urine output and normal serum electrolytes, with emphasis on the intracellular electrolytes, potassium, phosphorus, and magnesium. These are required for protein synthesis and the attainment of nitrogen balance. Once nutrition support is initiated, these electrolytes should be monitored closely, as they may deplete rapidly once adequate protein and kcalories have been provided and the patient shifts from catabolism to anabolism. Electrolytes can be safely provided in doses specified in Table 66.5.

Vitamins, Trace Elements, and Minerals

Currently there are no specific guidelines regarding vitamin and mineral requirements in the critically ill. It is presumed that needs are increased during stress and sepsis due to increased metabolic demands; however objective data to support supplementation is lacking. The antioxidant vitamins and minerals have received the most recent attention. Oxygen-free radicals and other reactive oxygen metabolites are believed to be generated during critical illness (trauma, surgery, reperfusion injury, acute respiratory distress syndrome, infection, burns). This response is most likely mediated by release of cytokines and initiation of an acute phase response and redistribution of hepatic protein synthesis.[20] Along

TABLE 66.6

Recommended Vitamin and Mineral Supplementation in the Critically Ill

	Enteral	Parenteral
Vitamin A	800-1000 μg RE	660 μg RE
Vitamin D	5-10 μg	5 μg
Vitamin E	8-10 mg TE	10 mg TE
Vitamin C	60-100 mg	100 mg
Vitamin K	70-140 μg	0.7-2.0 mg
Folate	200 μg	400 μg
Niacin	13-19 mg NE	40 mg NE
Riboflavin	1.2-1.6 mg	3.6 mg
Thiamine	1.0-1.5 mg	3 mg
Pyridoxine	1.8-2.2 mg	4 mg
Cyanocobalamin	2.0 μg	5.0 μg
Pantothenic acid	4.7 mg	15 mg
Biotin	30-100 μg	60 μg
Potassium	1875-5625 mg	60-100 mEq
Sodium	1100-3300 mg	60-100 mEq
Chloride	1700-5100 mg	—
Fluoride	1.5-4.0 mg	—
Calcium	800-1200 mg	600 mg
Phosphorus	800-1200 mg	600 mg
Magnesium	300-400 mg	10-20 mEq
Iron	10-15 mg	1-7 mg
Zinc*	12-15 mg	2.5-4.0* mg
Iodine	150 μg	70-140 μg
Copper	1.5-3 mg	300-500 μg
Manganese	2-5 mg	0.15-0.8 mg
Chromium	0.05-0.2 mg	10-20 μg
Selenium	0.05-0.2 mg	40-80 μg
Molybdenum	75-250 μg	100-200 μg

* Additional 2 mg in acute catabolic states.

with increased levels of free radicals, decreased levels of circulating vitamins C and E have been found after surgery, trauma, burns, sepsis, and long-term parenteral nutrition.[21-25]

Supplementation of large doses of antioxidants in critical illness has not consistently been shown to be beneficial. Current studies in progress are addressing supplementation at various levels and combinations. Apparently, providing more than therapeutic doses of single vitamins or minerals can be harmful by potentially upsetting the balance of metabolic pathways. Current recommendations are to provide the recommended dietary allowance for vitamins and minerals in the critically ill. Enteral formulations contain this recommended level when they are provided at specified volumes. If those volumes are not tolerated, patients should be supplemented intravenously.

Route of Nutrient Delivery

Parenteral vs. Enteral Nutrition

Despite nutrition intervention, critically ill patients undergo an obligatory loss of lean body tissue secondary to the hypercatabolic response of stress as previously described. If

TABLE 66.7

Indications for Parenteral Nutrition

Short bowel syndrome
Malabsorption
Intractable emesis or diarrhea
Severe pancreatitis
Bowel obstruction
Prolonged ileus
High output GI fistula
Unsuccessful enteral access

patients lose greater than 40% of their lean body mass, irreversible changes occur which make survival unlikely. This can occur as soon as 30 days after a serious metabolic insult if the patient is not nutritionally supported. Protein-calorie malnutrition, as a result of hypermetabolic stress, also leads to decreased immune function with subsequent increased infection risk. Impaired wound healing also becomes significant. Therefore, as stated previously, the primary goals of nutrition support in the critically ill are to preserve lean body mass, avoid metabolic complications, and preserve the body's immune function.

The ideal route of nutrition intervention in the critically ill has been well studied. Although total parenteral nutrition (TPN) has been lifesaving and has been successful in reversing malnutrition in many disease states (Table 66.7), several recent studies have found it to have potentially profound negative side effects. It has become more apparent that parenteral formulations currently available in the U.S. may in fact be systemically immunosuppressive, deliver imbalanced nutrient solutions, and alter nutrient uptake and utilization (Table 66.8).[26-28] TPN allows for more rapid achievement of nutrient requirements than enteral nutrition, but also allows for increased nitrogen excretion.[29] TPN has also been associated with a higher rate of hyperglycemia, adding to patient immunocompromise with decreased neutrophil chemotaxis, phagocytosis, oxidative burst, and superoxide production.[30,31] In animal models, TPN is associated with increasing the metabolic stress response, allowing atrophy of the gut mucosa, systemic immunocompromise, and altering gut flora when compared with enteral nutrition.[32-37] More recently, clinical research trials have suggested that TPN therapy may in fact be harmful. Prospective clinical trials

TABLE 66.8

Enteral vs. Parenteral Nutrition

Advantages	Disadvantages
Enteral	
Increased mucosal blood flow	Often difficult to access
Decreased septic morbidity	Aspiration risk
Preservation of gut flora and integrity	GI intolerance
Maintenance of GI hormone axis	Interruptions common
Balanced nutrient delivery	
Parenteral	
Ease of delivery	Overfeeding
Precise nutrient delivery	Exaggerated cytokine response
	Intestinal mucosal atrophy
	Decreased GALT and secretory IgA
	Decreased systemic immunity
	Increased cost

evaluating perioperative TPN have shown that subjects receiving TPN had greater postoperative infectious morbidity rates than those receiving no nutrition intervention.[38-40]

One of the more clinically relevant effects of enteral feeding is the incidence of septic complications.[41] This is most likely related to maintenance of the gut associated lymphoid tissue (GALT) and mucosal integrity. In review of the immunoglobulin-producing cells in the body, the bone marrow, spleen, and extra-GI tract lymph nodes together comprise about 2.5×10^{10} cells; the GI tract from mouth to anus comprises about 8.5×10^{10} immunoglobulin-producing cells. So, clearly 60% of the body's immunoglobulin-producing ability lies in the GI tract. When not utilizing the GI tract, a significant alteration in immune function can be expected. In review of the literature comparing parenteral to enteral nutrition, the gut has become recognized as a metabolically active, immunologically important, and bacteriologically decisive organ in critically ill patients.[42-44]

Low Flow States

Although research supports providing enteral nutrition in critically ill patients, it is often difficult to provide full energy requirements due to patient intolerance. Approximately 20% of the critically ill patient population is intolerant of enteral feeding. The etiology of this intolerance is often multifactorial. One clinically significant factor is low intestinal blood flow. Intestinal ischemia and reperfusion is an important determinant of the subsequent development of the posttraumatic proinflammatory state and multiple organ failure (MOF). Although the gut is able to increase its oxygen extraction up to tenfold in a normal state, it remains extremely vulnerable to ischemic injury during low flow states. Low flow not only exhibits negative effects on mucosal oxygenation and barrier maintenance,[45-47] but also has adverse effects on motility. It is now known that sepsis, endotoxemia, and low flow states have significant negative effects on GI tract motility, with the colon being the most affected, followed by the stomach and small intestine, respectively.[48] Low flow states also cause decreases in nutrient absorption, with protein absorption believed to be significantly altered; carbohydrate and lipid absorption are also altered, but to a lesser degree.[49]

A number of patient populations are at high risk for low flow states. These include those with sepsis, necrotizing enterocolitis, multiple trauma, intra-aortic balloon pump, coronary artery bypass pump, and those who undergo thoracoabdominal aortic aneurysm repair with cross-clamping of the mesenteric vessels.[50,51]

Gut perfusion can be indirectly assessed using tonometric techniques to measure the gastric intramucosal pH (pHi).[52] Trauma patients with a pHi <7.32 and otherwise adequate central hemodynamics and oxygen transport 24 hours after ICU admission showed a higher rate of MOF and mortality compared to a group of patients with adequate central and intestinal perfusion.[53] Several other investigators have attempted to improve the pH in critically ill patients by improving global perfusion, but they were not successful in decreasing mortality or MOF.[54,55] A drawback to this approach has been the inability to selectively improve gut perfusion in the setting of otherwise adequate systemic perfusion. The question remains whether enteral nutrient delivery during low flow states increases potential gut ischemia or whether increased blood flow associated with enteral feeding protects the mucosa. Several investigators using animal models have found that enteral nutrient delivery at low rates will enhance visceral blood flow during low flow states.[56-60]

After trauma or major metabolic insult, ileus commonly results, lasting 24 to 48 hours in the stomach and about 48 to 72 hours in the large intestine. In the small intestine, gut motility returns to near normal 12 to 24 hours after the insult. Several hemodynamic factors can affect the duration of ileus, such as elevated intracranial pressure and significant hyperglycemia. Generally, if small bowel access is available, critically ill patients may be fed enterally as soon as eight hours after insult. Three recent studies have

attempted to address the question of how much nutrient delivered into the GI tract is required to yield the immune benefits.[61-63] From these studies it can be estimated that only 15 to 30% of caloric requirements delivered enterally is needed to provide the immune benefits. In other words, full measured or estimated nutrient requirements are not required to be delivered enterally in order to obtain the immunologic and mucosal protective effects. In fact, attempting to obtain 100% of nutrient requirements in critically ill patients often results in intolerance of early enteral feeding. Therefore, a clinically rational approach to enteral feeding in critically ill populations is to initiate and maintain feedings at a low rate (10 to 20 ml/h) until tolerance is demonstrated. Signs of intolerance include abdominal distention and pain, hypermotility, significant ileus, pneumatosis intestinalis, significant increase in nasogastric tube output, and uncontrollable diarrhea. Enteral feeding should only be advanced according to patient tolerance, and decreased or discontinued if any of the above symptoms are present. Most critically ill patients will tolerate full enteral feeds within five to seven days, but if goal tube feedings are not tolerated after five to seven days of injury, then it is appropriate to start parenteral nutrition to either provide the balance of the nutrient requirements or provide full nutrition support as clinically indicated.

Nutrition Support in Trauma and Burns

Trauma and burn patients exhibit similar metabolic alterations as described earlier in critical illness, except that the metabolic alterations often occur to a much greater extent. Few traumatic injuries result in a hypermetabolic state comparable to that of a major burn. As the skin functions to maintain body temperature and fluid balance, loss of this protective barrier leads to excessive fluid, electrolyte, heat, and protein losses.[64] Thermal injury induces hypermetabolism of varying intensity and duration depending on the extent and depth of the body surface affected, the presence of infection, and the efficacy of early treatment.[65] Energy requirements peak at approximately postburn day 12, and typically slowly normalize as the percentage of open wound decreases with reepithelialization or skin grafting.[64] Although still debated, there is no single agent that is entirely responsible for the dramatic rise in metabolic needs observed during the flow phase of burn injury.[66] Rather, the etiology of hypermetabolism appears to be multifactorial (Table 66.9). As

TABLE 66.9

Factors Known to Affect Metabolic Rate in Burn Patients

Activity	Other trauma or injuries
Age	Pain
Ambient temperature and humidity	Physical Therapy
Anxiety	Preexisting medical conditions
Body surface area	Sepsis
Convalescence	Sleep deprivation
Dressing changes	Surgery
Drugs and anesthesia	Treatments rendered
Evaporative heat loss	Type and severity of injury
Gender	
Hormonal and non-hormonal influences	
Lean body mass	
Metabolic cost of various nutrients when digested and absorbed	

Adapted from Mayes T, Gottschlich M. In: *Contemporary Nutrition Support Practice* W.B. Saunders, Philadelphia, 1998: pg 590-607.

TABLE 66.10

Select Nutrients and Their Immune Effect During Critical Illness

Nutrient	Immune Effect
Carbohydrate	↓ (if provision results in blood glucose levels > 200 mg/dL)
Protein	
Glutamine	↑
Arginine	↑
Fat	
n-6 fatty acids	↓ (in large amounts)
n-3 fatty acids	↑
Micronutrients	
Vitamin A	↑ (in burns)
Vitamin C	↑ (in burns)
Vitamin E	??
Zinc	↑ (in burns)
Selenium	↑

previously discussed with critical illness, the goal of acute management in trauma and burns is to stabilize these system-wide effects. Optimal nutrition intervention is an important component in improving immunocompetence, attenuating the hypermetabolic response, and minimizing losses in lean body mass. As in critical illness, enteral feeding is preferred to parenteral. A few select nutrients have been shown to have an impact on the immune system in critical illness (Table 66.10).

Estimating Nutrient Requirements

Energy

Burn patients require individualized nutrition plans to provide optimal energy and protein to accelerate muscle and protein synthesis and minimize proteolysis.[67] There are numerous predictive equations to estimate energy needs in burn patients (Table 66.3).

Several studies have reviewed the accuracy of predictive equations in determining energy requirements in burn patients.[68-70] The consensus appears to be that predictive equations tend to overestimate energy expenditure, and the preferred method of determining energy requirements is by using indirect calorimetry. If indirect calorimetry is not available in the clinical situation, it is suggested that REE can be estimated as 50 to 60% above the Harris-Benedict equation for burns >20% of total body surface area.[71]

Protein

Trauma and sepsis initiate a cascade of events that leads to accelerated protein degradation, decreased rates of synthesis of selected proteins, and increased amino acid catabolism and nitrogen loss. Clinical consequences of these metabolic alterations may increase morbidity and mortality of patients, causing serious organ dysfunction and impaired host defenses. Therefore, trauma and burn patients require increased amounts of protein in attempts to minimize endogenous proteolysis as well as support the large losses from wound exudate. In a landmark study, Alexander et al. found that providing 23% of energy as protein in

burned patients resulted in fewer systemic infections and a lower mortality rate when compared to providing 16.5% of energy as protein.[72] Results of another study recommended that burn patients receive 1.5 to 3.0 g/kg/d protein with a nonprotein kcalorie to gram nitrogen ratio of 100:1.[73] More recent studies have questioned these high amounts of protein, as they may cause excessive urea production[74] and protein depletion that is related to altered muscle amino acid transport[67] and/or activation of the ubiquitin-proteasome pathway.[75] Overall recommendations are to provide 1.5 to 2.0, rarely up to 3.0, g protein per kilogram body weight per day in attempts to minimize protein losses. Providing these higher levels of protein requires continuous monitoring of fluid status, blood urea nitrogen, and serum creatinine because of the high renal solute load.

In addition to the quantity of protein provided, the protein quality is also significant. The use of high-biologic value protein, such as whey or casein rather than soy, is preferred for burn patients. Whey protein has been further endorsed over casein due to its beneficial effects on burned children, improvement in tube feeding tolerance, enhanced solubility at low gastric pH, greater digestibility, and improved nitrogen retention.[66] Pharmacologic doses of the single amino acids, arginine and glutamine, have also been explored as to their benefit in critical illness and burns.

Glutamine

Glutamine is known to be a major fuel source for rapidly dividing cells such as enterocytes, reticulocytes, and lymphocytes. In normal metabolic states, glutamine is a non-essential amino acid. However during times of metabolic stress, glutamine is implicated as being conditionally essential as it has been shown to be needed for maintenance of gut metabolism, structure, and function.[76-78] Despite the accelerated skeletal muscle release of amino acids, blood glutamine levels are not increased after burns.[79] In fact, decreased plasma glutamine levels have been reported after severe burns, multiple trauma, or multiple organ failure.[65]

A number of studies have shown beneficial effects with supplemental glutamine, its precursors (ornithine α-ketoglutarate and α-ketoglutarate),[80] or glutamine dipeptides (alanine-glutamine, glycine-glutamine).[81] These studies deliver glutamine in pharmacologic doses of 25 to 35% of the dietary protein.[82] Supplemental glutamine has been shown to have multiple benefits to include increased nitrogen retention and muscle mass,[83] maintenance of the GI mucosa,[84] permeability,[85] preserved immune function,[86] reduced infections,[87] as well as preserved organ glutathione levels (Table 66.11).[88] These protective effects of glutamine supplementation could have significant effects on morbidity and mortality in trauma and burn patients. Safety and cost effectiveness of glutamine supplementation in trauma and burns continues to be researched.

TABLE 66.11

Benefits of Human Glutamine Supplementation

↑ Nitrogen balance
Enhanced gut barrier function
↓ Systemic infections
↓ Ventilator days
↓ Hospital stay
↓ Hospital expense
↓ Sepsis, bacteremia
↑ Survival
Maintenance of tissue glutathione levels

Arginine

Arginine, like glutamine, has gained recent attention in critical care nutrition, and like glutamine is considered a conditionally essential amino acid. Arginine is the specific precursor for nitric oxide production as well as a potent secretagogue for anabolic hormones such as insulin, prolactin, and growth hormone. Under normal circumstances, arginine is considered a non-essential amino acid since it is adequately synthesized endogenously via the urea cycle. However, research suggests that during times of metabolic stress, optimal amounts of arginine are not synthesized to promote tissue regeneration or positive nitrogen balance.[66]

Studies in animal and humans have investigated the effects of supplemental arginine in various injury models. Positive outcomes from supplementation include improved nitrogen balance,[89,90] wound healing,[91-94] immune function,[91-96] and increased anabolic hormones, insulin, and growth hormone.[97] The outcomes are of special interest in the post-trauma and burn patient during the flow phase, when enhancement of these processes would yield the greatest advantage.

However, despite these positive effects, caution with excessive arginine supplementation is warranted in burn patients due to its potential effects on nitric oxide production. The possibility that increased nitric oxide production from arginine supplementation may affect septic patients has not been addressed. Recently it has been shown that marked deregulation of arteriolar tone in patients with endotoxemia septic shock and increased permeability to bacteria in critically ill patients are induced by nitric oxide.[98] Although arginine supplementation for non-septic burn and trauma patients in amounts sufficient to normalize serum and intracellular levels (~2% of kcalories) appears safe and beneficial, the effects of arginine supplementation on nitric oxide production in septic burn patients should be carefully evaluated.[65]

Lipid

Lipid is an important component of a trauma or burn patient's diet for many reasons, as it is an isoosmotic concentrated energy source at 9 kcalories per gram. Carbohydrate and protein provide half as many kcalories as fat and can significantly contribute to the osmolality of the enteral or parenteral formulations. Dietary lipid is also a carrier for fat-soluble vitamins as well as a provider of essential fatty acids, linoleic, and linolenic acids. These essential fatty acids should comprise a minimum of 4% of kcalories in the diet to prevent deficiencies. This often equates to ~10% of total kcalories as fat, since most sources do not solely contain essential fatty acid.

Even though lipids are required in critical illness, excess lipid can be detrimental. Excessive lipid administration has been associated with hyperlipidemia, fatty liver immune suppression, and impaired clotting ability.[99] All of the long-chain fatty acids share the same enzyme systems, as they are elongated and desaturated with each pathway competitive, based upon substrate availability. Dietary fatty acids modulate the phospholipid cell membrane composition and the type and quantities of eicosanoids produced (Figure 66.1). Prostaglandins of the 3 series (PGE3) and series 5 leukotrienes have proven to be anti-inflammatory and immune-enhancing agents.[100,101] Also, PGE3 is a potent vasodilator.[102] These concepts have received considerable attention for the potential of n-3 fatty acids ability to enhance immune function and reduce acute and chronic inflammation.

In most standard enteral formulations, the fat source is predominantly n-6 fatty acids, with a portion coming from medium-chain triglycerides. Formulations supplemented with fish oil, a rich source of n-3 fatty acids (eicosapentenoic [EPA] and docosahexanoic acids [DHA]), and canola oil (alpha-linolenic acid) are now available. Clinical trials utilizing

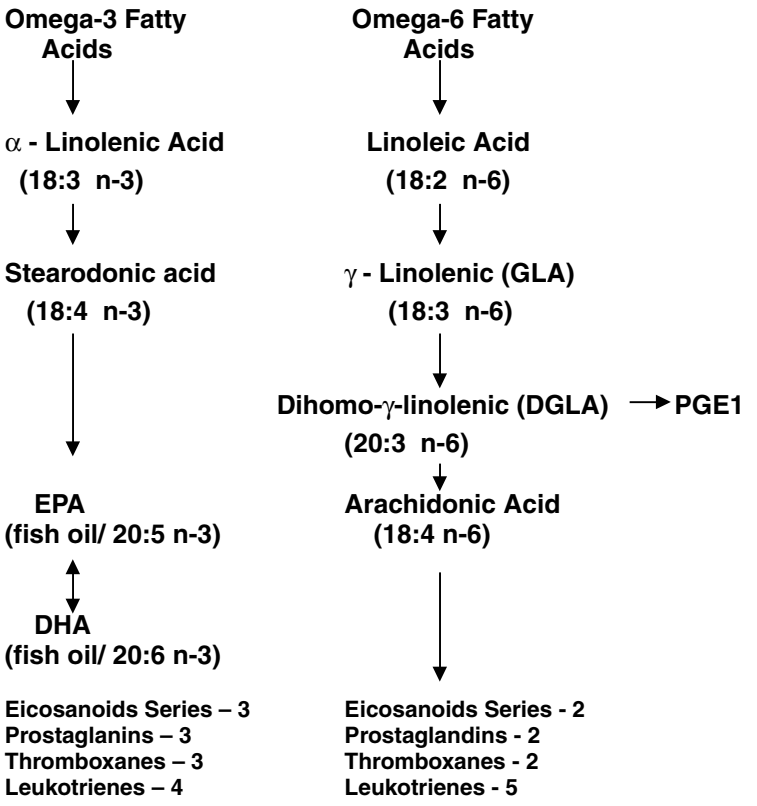

FIGURE 66.1
Metabolism of dietary long-chain fatty acids. EPA — eicosapentenoic acid, DHA — docosahexanoic acid.

these formulations have shown positive benefits in patients with psoriasis,[103] rheumatoid arthritis,[104] burns,[105,106] sepsis,[107,108] and trauma.[109] These benefits are thought to be due to alterations in eicosanoid and leukotriene production, with decreased arachidonic acid metabolites (e.g, PGE2), as well as increased production of the less biologically active trienoic prostaglandins and pentaenoic leukotrienes.[110]

For burn and multiple trauma patients, the recommended amount of total fat delivery is 12 to 15% of total kcalories, with at least 4% coming from essential fatty acids.[65] Provision of formulations with n-3 fatty acids, especially EPA and DHA, is of particular interest for the potential anti-inflammatory and immune-enhancing benefits as described above. Many enteral formulations do not contain these exact proportions of fat and typically have greater amounts, often leading to modular modification. Current parenteral formulations available in the U.S. (Jan. 2000) contain nearly 100% n-6 fatty acids and should not comprise ≥15 to 25% of the total kcalories as fat when delivered to the burn or severely traumatized patient.

Micronutrients

Micronutrients function as coenzymes and cofactors in metabolic pathways at the cellular level. With the increased energy and protein demands associated with traumatic and burn injury, one would expect increased need for vitamins and minerals. In addition, increased nutrient losses from open wounds and altered metabolism, absorption, and excretion, would also be anticipated to have requirements beyond the Recommended Dietary Allow-

TABLE 66.12

Nutrient Recommendations for Burn Patients[a]

Protein	20-25% of total kcalories
Fat	10-15% of total kcalories
Carbohydrate	60-70% of total kcalories (5 mg/kg/min per day)
Vitamins and minerals	Multivitamin and mineral *AND* *Vitamin C*: 500 mg twice daily *Vitamin A*: 5000 IU per 1000 kcalories of enteral nutrition *Zinc*: 220 mg of zinc sulfate (or other compound to provide 45 mg elemental zinc/d)

[a] Patients >40 pounds.

Adapted from Mayes T, Gottschlich M. In: *Contemporary Nutrition Support Practice* W.B. Saunders, Philadelphia, 1998: pg 590-607.

ances. Various vitamins and minerals have also been found to aid with wound healing, immune function, and other biologic functions. Unfortunately, few data are available to support exact requirements during these hypermetabolic states. However, a few studies[111,112] support recommendations in burn patients for vitamin A, vitamin C, and zinc (Table 66.12).

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