Nutritional Support of the Stressed ICU Patient

Rosemary A. Kozar, MD, PhD; Frederick A. Moore, MD;
Margaret M. McQuiggan, MS, RD

Objectives:

- To discuss the rationale for nutritional support and nutrient requirements of ICU patients.
- To discuss the use of total parenteral nutrition in the ICU.
- To discuss the use of enteral nutrition in the ICU.

Key words: injury stress response, nutritional assessment, metabolic cart, nitrogen balance, total parenteral nutrition, enteral nutrition, immune-enhancing nutrition, catheter-related sepsis

Metabolic Response to Stress Versus Starvation

A variety of conditions that require ICU care lead to a stereotyped metabolism response which is called the "injury stress response". Traditionally, this has been viewed to be a CNS mediated endocrine response that increases circulating levels of the counter-regulatory hormones (catecholamines, corticosteroids, and glucagon). More recently, the systemic inflammatory response syndrome (SIRS) has been described and it is recognized that a variety of its mediators (*eg*, TNFα, IL-1, IL-2, IL-6) also play an important role in the injury stress response. Favorable modulation of the injury stress response is not currently feasible because the driving mechanisms are not understood. Our best options are to control the initiating insult and provide high-risk patients exogenous substrates that support the metabolic environment.

The injury stress response increases resting energy expenditure (REE). The increase in REE is dependent both upon the type and severity of the insult (REE can increase as much as 100% after burns, 50% with sepsis, 40% after trauma, 30% after major surgery). To meet this increased metabolic demand, endogenous substrates are mobilized. Glucose stores (*ie*, 2000-3000 kcal glycogen) are quickly depleted and gluconeogenesis (principally in liver, but also in kidney) produces glucose that is shunted to glucose dependent tissues (brain, erythrocytes, inflammatory cells, wound tissue). Adipose tissue is stimulated to release free fatty acids (FFA) and glycerol. The rate of lipolysis, however, exceeds lipid oxidation. As a result, plasma triglyceride levels increase and considerable reesterification occurs in the liver. This requires energy and creates futile cycles. The increase in protein catabolism is the most dramatic effect. Skeletal muscle protein, and later constitutive proteins such as albumin, prealbumin, and transferrin are broken down and the released amino acids become the substrate for acute phase protein synthesis (clotting factors, gammaglobulins, and C-reactive protein [CRP]), gluconeogenesis, and energy production. The injury stress response differs from chronic starvation in several important ways (Table 1).

With brief starvation (up to 72 h), glycogen stores are rapidly depleted and the body depends heavily on the breakdown of protein to provide amino acids as a primary energy source and as a source of new glucose for glucose-dependent tissues. These pathways provide about 85% of energy needs in this setting. In the absence of "stress," this process may be easily interrupted by providing exogenous substrate. After 72 h of starvation, adaptive changes favor the mobilization of fat and reduce the breakdown of protein to a low level (30% of energy requirements). Fat becomes the principal source of energy (70%). With longer starvation, protein is further protected by a fall in total energy requirements and reduced physical activity. As with brief starvation, the process is quickly and easily

Table 1. *Metabolic Response of Starved Versus Stressed Patients*

Metabolic Consequences	Starved	Stressed
Resting energy	↓	↑↑
Respiratory quotient	Low (0.7)	High (.85)
Primary fuel	Fat	Mixed
Proteolysis	↑	↑↑↑
Urinary nitrogen loss	↑	↑↑↑
Constitutive proteins	↓	↓↓↓
Acute phase proteins	–	↑↑↑
Gluconeogenesis	↑	↑↑↑
Ketone production	↑↑↑	↑

reversed by providing exogenous glucose alone (which returns the patient to the brief starvation pattern) or exogenous glucose and amino acids.

Nutritional support needs to be tailored to metabolic environment (Table 2). The stressed ICU patient compared to the starved patient requires more nonprotein calories (25 kcal/kg/day versus 20 kcal/kg/day) and more protein (1.3 g/kg/d vs. 1.0 gm/kg/d). As they become more stressed, they become more catabolic and less tolerant to glucose (see hyperglycemia section). As a result, the amount of protein administered is increased (from 1.3 to 2.0 g/kg/day). Thus the kilocalories to gram of nitrogen ratio is decreased from 120:1 to 100:1.

Rationale for Nutritional Support

Prevent Acute Protein Malnutrition

Persistent hypercatabolism dominates the metabolic response to critical illness (Figure 1). At first, the amino acids demands are met by skeletal muscle proteolysis. However, in a short period of time, crucial constitutive structural elements as well as circulating proteins are depleted. The resulting acute protein malnutrition is associated with cardiac, pulmonary, hepatic, gastrointestinal (GI), and immunologic dysfunction. In essence, subclinical multiple organ dysfunction evolves as the patient becomes progressively more immunosuppressed. Delayed infections then extend hypercatabolism with the progression to full-blown multiple organ failure (MOF). Based on this paradigm, a number of clinical studies have been performed in the 1980s to determine whether early nutritional support could improve the outcome of high risk patients. Unfortunately, many of these studies have failed to generate interpretable results. In large part, this is due to the heterogeneous nature of the patients included in the studies. Most of the positive trials have been generated from burn and trauma patients. These patients tend to be young and free of confounding comorbid disease. Additionally, the severity of the burn/trauma injury can be quantitated so that a high risk cohort of patients with persistent hypercatabolism can be identified for study enrollment. These studies have demonstrated early nutrition improves outcome (improved nitrogen balance and constitutive protein levels, improved immune function and decreased infections, decreased length of stay) and that the enteral route is preferred to the parenteral route. Whether these observations can be generalized to other ICU patient populations is not clear.

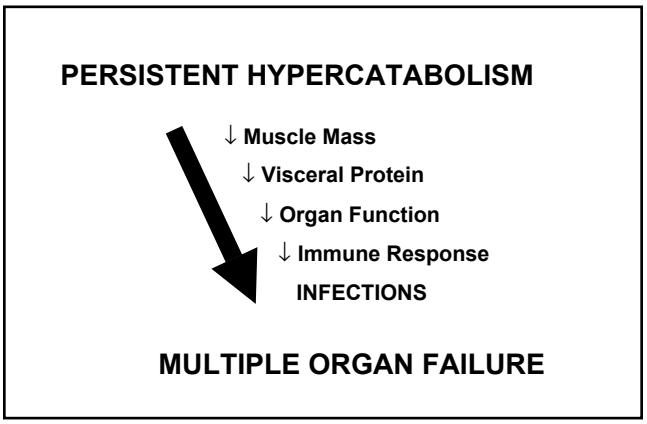

Figure 1. Role of persistent hypercatabolism.

Table 2. *Nutritional Support of Starved Versus Stressed Patients*

Nutritional Support	Starved	Moderate Stress	Severe Stress
Total Kcal (kcal/kg/day)	20*	25	30-35
Protein (g/kg/day)	1.0*	1.3-1.5	2.0
Fat	10% total kcal	10% total kcal	Up to 1 g/kg
Glucose	Remainder of kcal to meet goal	Remainder of kcal to meet goal	Remainder of kcal to meet goal but < 5 mg/kg/min
Total Kcal:Nitrogen**	150:1	120:1	100:1

* For initial support. Kcal are increased gradually for weight gain.
** 6.25 g of protein yields 1 g of nitrogen.

Modulate Immune Response

Despite tremendous advances in ICU care, nosocomial infections are a persistent problem. In large part, these late infections occur due to failure of local and systemic host defenses. While exact causes of late immunosuppression are not clear, it is now believed to occur in part as a result of dysfunctional regulation of inflammation (Figure 2). An initial insult (sepsis, trauma/burns, major operation) precipitates early systemic hyperinflammation (*ie*, SIRS), the amplitude and duration (generally 3-5 days) depends on the magnitude of the insult as well as some host factors. Severe SIRS can precipitate early MOF which typically presents as acute lung injury (ALI). As time proceeds, certain components of this early SIRS are endogenously down-regulated to prevent unnecessary, potentially auto-destructive inflammation. This is now referred to as the compensatory anti-inflammatory response syndrome (*ie*, CARS). The resulting delayed immunosuppression, however, sets the stage for secondary infection which can either worsen early MOF or trigger late MOF.

While various strategies have been proposed and tested to modulate this dysfunctional inflammatory response, the most promising approach to date has been the delivery of specific nutrients (generally via the gut) that exert pharmacologic immune-enhancing effects above and beyond the prevention of acute protein malnutrition (see previous section and later immune enhancing formula section). Glutamine is acknowledged to be the preferred fuel of the enterocyte and is thought

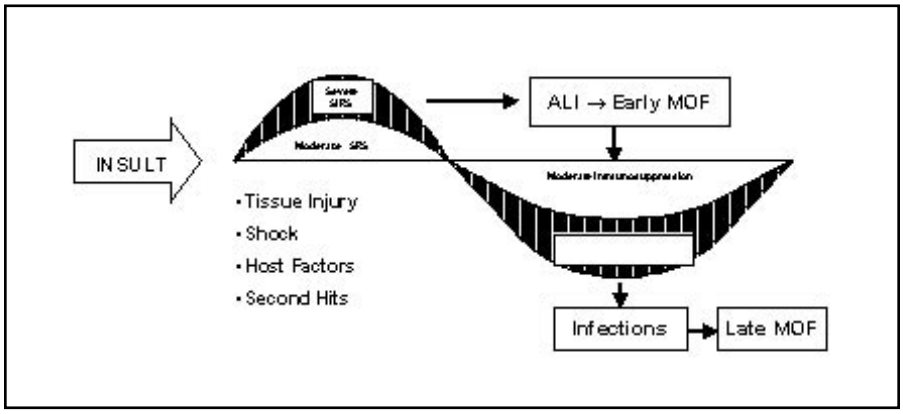

Figure 2. Dysfunctional regulation of inflammation. SIRS, systemic inflammatory response syndrome; ALI, acute lung injury; MOF, multiple organ failure.

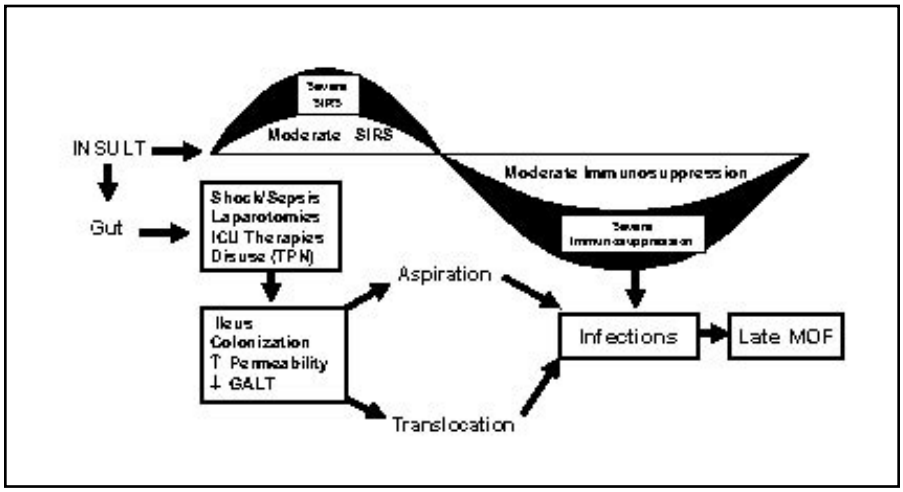

Figure 3. Role of gut in late infections. SIRS, systemic inflammatory response syndrome; MOF, multiple organ failure; GALT; gut-associated lymphoid tissue.

to stimulate lymphocyte and monocyte functions. Arginine promotes collagen synthesis required in wound healing and increases the number of total lymphocytes as well as the proportion of helper T cells. Additionally, arginine is the chief precursor of nitric oxide synthesis and has been shown to enhance delayed cutaneous hypersensitivity and lymphocyte blastogenesis. Traditional nutritional support includes a high proportion of plant-derived omega-6 polyunsaturated fatty acid (PUFA). However, diets with a low omega-6 PUFA and high fish-oil derived omega-3 PUFA content are known to suppress the synthesis of potent pro-inflammatory cytokines, *eg*, TNFα and IL-1β. Finally, exogenous nucleotides may be necessary in stressed states to maintain rapid cell proliferation and responsiveness.

Promote Gut Function

The dysfunctional gut is now believed to be the "reservoir for pathogens" that cause late MOF associated infections (Figure 3). The initial insult (via ischemia/ reperfusion, sepsis, inhibitory neuroendocrine reflexes) and emergency laparotomy (via anesthesia and bowel manipulation) cause an early ileus. Disuse (parenteral instead of enteral nutrition) and common intensive care unit therapies (*eg*, H_2-antagonists, narcotics, corticosteroids, broad-spectrum antibiotics) promote further gut dysfunction, characterized by progressive ileus, colonization of the upper gut, increased permeability, and decreased gut-associated lymphoid tissue (GALT) function. Consequently, the upper gut becomes a reservoir for pathogens, and local and systemic defense mechanisms that prevent the spread of these organisms become impaired; the primary route of dissemination (*ie*, aspiration vs. translocation) is not clear. Although there is good epidemiologic evidence for this sequence of events, prospective randomized controlled trials of gut-specific therapies (*eg*, selective gut decontamination, early enteral nutrition, and most recently immune-enhancing enteral formulas) that have consistently demonstrated a reduction in nosocomial infections (principally pneumonia) are the most convincing evidence. Thus, the provision of early enteral nutrition to promote more normal gut function is believed to prevent this cascade of events from occurring.

Nutritional Assessment

Medical History

Medical history should be reviewed to determine the presence of constitutional factors that signify increased risk of malnutrition, such as weight loss, anorexia, vomiting, diarrhea, and decreased or unusual intake. History of diabetes (especially with poor control), ASCVD, end-stage

Table 3. *Hepatically Synthesized Serum Proteins Shown to Correlate with Nutritional Status*

Protein	Clinical Significance	Half- Life	Limitations	Interpretation
Albumin (g/dL)	Relates to outcomes; relates to edema	20-21 days	Best case scenario for hepatic production – 12-25 g/24 h; dilutional effects; long half-life; used alone, sensitivity poor	Normal <3.5 Mild depletion 2.8-.5 Moderate 2.2-2.8 Severe < 2.2
Prealbumin (mg/dL)	Indicates nutritional deficits before albumin	2-4 days	Short half-life	Normal >18 Mild depletion 10-18 Moderate 5-10 Severe <5
Transferrin (mg/dL)	More sensitive than albumin; relatively useful parameter in liver disease compared with albumin; can calculate from TIBC	8-10 days	Poor marker of early repletion; sensitive to changes in body iron	Mild Depletion 150-200 Moderate 100-150 Severe <100
C-Reactive Protein (mg/dL)	Increases abruptly after injury. Earlier and reliable indicator of disease/injury severity.	48-72 h		Baseline Normal <3 Bacterial Infection 30-35 Viral Infection <20 Post-trauma 20-35

Data may also include measures of immune function (*eg*, total lymphocyte count, white blood cells × %lymphocytes).

renal disease (ESRD), CVA, Parkinson's, long-term steroid use, chronic obstructive pulmonary disease (COPD), cirrhosis, Crohn's disease, or gastric dysmotility may contribute to primary and secondary malnutrition.

Physical Examination

Physical examination focuses on an assessment of lean body mass (presence of muscle wasting), loss of subcutaneous fat, hydrational state, skin turgor, presence of decubiti, and the physical findings of micronutrient deficiencies (*eg*, dermatitis, glossitis, poor wound healing, hair changes).

Laboratory Data

Laboratory data should include constitutive protein concentrations and micronutrient concentrations (if clinical evaluation suggests possible deficiencies). Constitutive protein status is assessed by measuring serum concentrations of selected hepatically synthesized transport proteins that have been shown to correlate with nutritional status. Typically, these include albumin, transferrin, and prealbumin. Depletion of constitutive proteins may be categorized as mild, moderate, or severe (Table 3). Concurrent measurement of CRP, a sensitive indicator of acute phase response, reflects the degree of stress. The hepatic production of constitutive proteins is reprioritized once CRP significantly declines.

Anthropometric Measurements

Anthropometric measurements include height, weight, and limb circumference. They are relatively insensitive to acute changes in nutritional status and are difficult to measure in patients with edema; therefore, they are mostly useful in monitoring patients requiring long-term nutritional support, such as home TPN. Body weight is the most commonly used of these measures. Actual body weight should be interpreted in view of fluid status and relative to ideal weight for height or usual (*eg*, pre-illness or pre-weight loss) weight. Mid-arm muscle circumference correlates with somatic protein reserves, and triceps skin-fold thickness estimates the subcutaneous fat as compared to individuals of the same gender and age.

Nutrient Requirements

Estimating Kilocalorie Requirements

Harris Benedict Equation: This equation is a common method to estimate energy expenditure and thus determine caloric requirements. The Harris-Benedict equation was derived from a population-based analysis in 1919 using healthy, ambulatory subjects and is currently used to estimate basal energy expenditure (BEE) based on age, sex, height, and weight. The Harris-Benedict equations are as follows:

- Men: BEE = 66 + (13.7 × weight) + (5 × height) - (6.8 × age)
- Women: BEE = 665 + (9.6 × weight) + (1.9 × height) - (4.7 × age)

where weight is actual or in adjusted kg, height in cm, and age in years. The BEE represents energy requirements in the fasted, resting, non-stressed state. In the presence of metabolic stress, the BEE must be multiplied by an empirically derived stress factor to obtain an estimate of the caloric requirement. The numerical value for this empirically derived stress multiplication factor continues to be a source of controversy. In the past, BEE was multiplied by stress factors as high as 3 in major stress settings such as in burn patients, resulting in estimated energy requirements and caloric intake as high as 5000 kcal/day. Complications of overfeeding, such as hypercapnia, hyperglycemia, and hepatic steatosis, have resulted in revisions of these stress multiplication factors. Currently, the usual stress multiplication factors range from 1.2 to 1.6 times the BEE. The hypermetabolic injured and septic patients do not require 40 kcal/kg/day of nonprotein calories as was recommended in the past (Table 4).

Table 4. *Nutritional Goals for the Stressed ICU Patient*

Patient	Feeding Level (kcal/kg)	By Indirect Calorimetry
Normal weight patients	25-30 kcal/kg	REE** × 1.0
Underweight patients	35-40 kcal/kg	REE ×1.2
Obese patients	20-25* kcal/kg	REE × 0.85
Morbidly obese patients	10-20* kcal/kg	REE × 0.75

* Use adjusted weight

** Resting energy expenditure (REE) is the measure of energy expenditure in a fed state and is generally 5%-10% higher than basal energy expenditure.

Metabolic Gas Analysis: Metabolic gas analysis (also called metabolic cart or indirect calorimetry) can be used as an assessment tool in nutrition support of the mechanically ventilated ICU patient. A list of factors to control in order to obtain an adequate study as well as patient selection criteria appears at the end of this chapter in Appendix I. The study measures inspired and expired concentrations of oxygen (O_2), carbon dioxide (CO_2), and nitrogen (N_2) as well as expired minute ventilation (V_E). Table 5 depicts typical values.

As expected, inspired O_2 (F_{IO_2}) is greater than expired O_2 (F_{EO_2}) because O_2 is being absorbed; and, inspired CO_2 (F_{ICO_2}) is lower than expired CO_2 (F_{ECO_2}) because CO_2 is excreted. N_2 is neither absorbed nor excreted, therefore, the difference in F_{IN_2} and F_{EN_2} can be used to calculate inspired minute ventilation (V_I).

$$V_I = \frac{F_{EN_2} \times V_E}{F_{IN_2}}$$

O_2 consumption (V_{O_2}) can then be calculated as $V_{O_2} = (V_I \times F_{IO_2}) - (V_E \times F_{EO_2})$ and CO_2 production (V_{CO_2}) can be calculated as $V_{CO_2} = (V_E \times F_{ECO_2}) - (V_I \times F_{ICO_2})$.

From this information and a 24-h urine urea nitrogen (UUN) determination, resting energy expenditure (REE) can be calculated using the Weir equation:

$$REE = 3.9 \times V_{O_2} + 1.1 \times V_{CO_2} - 2.8 \times UUN$$

The second commonly derived variable is the respiratory quotient (RQ). This is an indicator of net substrate oxidation and, hence, provides insight into substrate utilization.

The RQ is calculated as follows:

$$RQ = V_{CO_2} / V_{O_2}$$

The RQ for fat oxidation = 0.7, protein oxidation = 0.85, glucose oxidation = 1.0, ethanol oxidation =.67, and lipogenesis = .87. Thus, any study with an RQ<.67 is out of physiologic range and is of limited usefulness clinically. An example of using indirect calorimetry to guide nutritional care follows.

Table 5. *Typical Metabolic Cart Measurement*

F_{IO_2}	39.29%
F_{EO_2}	35.70%
F_{ICO_2}	0.03%
F_{ECO_2}	3.32%
F_{IN_2}	60.67%
F_{EN_2}	60.98%

Case Example: A 68-year-old male with chronic COPD has been on the ventilator for 7 days after an emergency laparotomy for perforated sigmoid diverticulitis. He is being considered for extubation and has spontaneous ventilatory parameters measured which include a minute ventilation of 13 L/min, tidal volume of 300 mL, vital capacity of 750 mL and a negative inspiratory force of –30 cm H_2O. He is receiving total parenteral nutrition (TPN) and the question is how TPN might contribute to his high minute ventilation. There are two ways that TPN might increase CO_2 production and thus increase minute ventilation. The first way is by providing a high proportion of the nonprotein calories as glucose. Glucose oxidation has a higher RQ (1.0) than does fat oxidation (0.7). Therefore, a diet high in glucose will result in higher CO_2 production. This is most simply understood by reviewing the equations for glucose and fat oxidation.

Glucose Oxidation:

$$C_6H_2O_2 + 6\ O_2 \rightarrow 6\ CO_2 + 6\ H_2O$$

$$RQ = \frac{CO_2 \text{ produced}}{O_2 \text{ consumed}} = \frac{6\ CO_2}{6\ O_2} = 1.0$$

Lipid Oxidation:

$$2\ C_{54}H_{101}O_6 + 153\ O_2 \rightarrow 108\ CO_2 + 101\ H_2O$$

$$RQ = \frac{CO_2 \text{ Produced}}{O_2 \text{ Consumed}} = \frac{108\ CO_2}{153\ O_2} + 0.7$$

Thus, by providing a higher proportion of nonprotein calories as fat, CO_2 production may be decreased.

The second way that nutrition can contribute to excessive CO_2 production is by giving too many kilocalories. Excessive glucose is converted to fat.

Lipogenesis:

$$27\ C_6H_{12}O_2 + 6\ O_2 \rightarrow 2\ C_{55}H_{104}O_6 + 52\ CO_2 + 58\ H_2O$$

$$RQ = \frac{CO_2 \text{ Produced}}{O_2 \text{ Consumed}} = \frac{52\ CO_2}{6\ O_2} = 8.7$$

Of the two mechanisms proposed, the second is much more common. Please note, however, this problem with TPN has been overemphasized. In most critically ill patients, failure to wean is due to inadequate ventilatory endurance or unrecognized

hypermetabolism. What these patients need is time to resolve their inflammatory response. Additionally, during this waiting period adequate nutrition and partial ventilatory support should be given to strengthen their skeletal muscles and diaphragms. Historically, some clinicians, when faced with a difficult wean, reflexively cut nutrition and allow their patients to starve. Additionally, clinicians try to assess whether this is occurring by obtaining a metabolic cart study. However, when using the metabolic cart in critically ill ventilated patients, it is frequently necessary to place the patient in full ventilatory support to get accurate numbers. Then, the patient is put back on a mode of partial ventilatory support. Unfortunately, things have changed because the patient is now expending energy to breathe. This is particularly worrisome in the difficult to wean patient where the work of breathing can consume 10% to 15% of their oxygen. Consequently, metabolic cart studies offer confounding information. Pragmatically, when a patient has sufficient ventilatory strength but is requiring marginally high minute ventilation (13 L/min), cut nutrition in half the night before weaning ventilation. The next morning place the patient on a T-piece and if he fails, it is not due to overfeeding.

Estimating Protein Requirements: The following are general recommendations.

Recommended daily intake for healthy individuals	0.8 g/kg
Acute renal failure without dialysis	0.6 g/kg
Chronic renal insufficiency, advanced	0.6-0.8 g/kg
Hemodialysis	1.2-1.4 g/kg
Hepatic encephalopathy, acute	0.6 g/kg
Mild, moderate stress	1.3-1.5 g/kg
Severe stress	2.0 g/kg

Urinary urea nitrogen (UUN) is measured as an indicator of the protein catabolic rate (*ie*, stress) and is used to determine nitrogen balance. UUN represents 60% to 90% of the nitrogen excreted in the urine, and therefore, is a rough approximation of total urinary nitrogen (TUN). Although the latter is not widely available in clinical laboratories, it is the preferred test. As the stress level increases, the concomitant increase in protein catabolism results in an increase in urinary nitrogen. Quantitatively, this can be interpreted as in Table 6.

Nitrogen Balance: Nitrogen balance is the difference between nitrogen intake and nitrogen output. Nitrogen intake is determined from dietary intake per day (g nitrogen = g protein ÷ 6.25). Nitrogen output per day is determined by measuring UUN (g) in a 24-h urine collection and adding 4 g/day to approximate nonurea nitrogen loss in the urine plus other insensible N_2 losses in hair, skin, and feces (*ie*, grams of UUN + 4 g/day). Nitrogen balance is calculated as follows:

Nitrogen balance = (g/day protein intake/6.25) - (g/day UUN) - 4 g/day

Traditionally, a prime goal in nutritional support has been to place the patient in +3 to +5 nitrogen balance. Traditional nitrogen balance studies are useful in patients with creatinine clearance > 50 mL/min. Once renal function is further compromised, calculations of protein catabolic rate are necessary. These requires serial BUN ng/dL, serial weights, calculations of interdialytic time period and urinary losses of nitrogen.

Total Parenteral Nutrition

Components of Total Parenteral Nutrition

Components of TPN include: (1) dextrose, (2) fatty acids, (3) amino acids, (4) electrolytes, (5) vitamins, (6) trace minerals, and (7) fluids. Dextrose monohydrate (caloric density 3.4 kcal/g) is the carbohydrate. Fat emulsions (caloric density 9 kcal/g) made from either soybean oil or a mixture of soybean oil and safflower oil provide fat calories and are the source of essential fatty acids (linoleic, linolenic, and arachidonic acids). Approximately 3% to 4% of total kcal are needed as linoleic and linolenic to prevent essential fatty acid deficiency; providing 10% of total kcal as lipid emulsion will deliver that amount. Propofol is packaged in a 10% fat emulsion (1.1 kcal/mL) and its fat kcal should

Table 6. *Clinical Condition and Concomitant Protein Catabolism as Indicated by Levels of Urinary Nitrogen Loss*

Clinical Condition	Urinary Nitrogen Loss (g/day)
Normal or Nonstressed, starvation	< 8
Low stress (*eg*, elective surgery)	8 – 12
Moderate stress (*eg*, major trauma)	13 – 18
High stress (*eg*, sepsis)	> 18

be subtracted from nutrition support regimens. Protein (caloric density 4 kcal/g) is provided as crystalline amino acids in 8.5%, 10% or 15% solutions. The more costly concentrated solution is reserved for patients requiring fluid restriction. Standard amino acid solutions contain a balance of essential and nonessential amino acids. The electrolyte cations, which include sodium, potassium, magnesium, phosphorus, and calcium, are admixed into the TPN solution using one of several anions. Acid-base status may be affected by the amount of chloride or acetate used in providing sodium and potassium. The concentrations of calcium and phosphorus are limited to avoid precipitation of a calcium phosphate salt. Multivitamin products that meet American Medical Association recommendations contain vitamins A, C, D, E and the B vitamins, including folate. Vitamin K has recently been included. A multitrace mineral product is added to provide copper, chromium, manganese, zinc, and selenium. Central TPN solutions are hyperosmolar and must be delivered through a large lumen vein. When central access is unavailable or undesirable, parenteral nutrition with a dilute solution (< 800 mOsm/L) may be delivered through a peripheral vein for 7 to 10 days.

ICU Indications for Total Parenteral Nutrition

Indications for TPN in the ICU include the following.

- Massive bowel resection if nutritional requirements cannot be met by oral or enteral feeding
- High-output fistula refractory to elemental diet
- Unable to meet > 60% of nutritional needs via enteral route by ICU day 6
- Malabsorption
- Persistent ileus or bowel obstruction
- Massive decubiti without diverting colostomy
- Diffuse peritonitis
- Intractable vomiting
- Intractable diarrhea
- GI ischemia
- Perceived high risk for nonocclusive bowel necrosis (shock resuscitation, α-agonists, persistent severe distention or cramping)
- Patients with pancreatitis who have demonstrated intolerance to enteral nutrition
- Patients with inflammatory bowel disease who have demonstrated intolerance to enteral nutrition
- Crohn's disease with fistulae

Preoperative Total Parenteral Nutrition

It is well documented that malnourished patients are at an increased risk for septic complications, problems with wound healing, longer hospital stays, and increased mortality. The unproved contention is that preoperative TPN can improve nutritional status and thereby reduce postoperative morbidity and mortality. Results of studies evaluating preoperative TPN and outcome are variable. Recent trials suggest that TPN may in fact promote postoperative septic complications. For the mild to moderately malnourished patients, the risks of preoperative TPN appear to outweigh the potential benefits. However, the small subgroup of patients who are severely malnourished appear to benefit from receiving 7 to 10 days of preoperative TPN. One trial (Otaki) reported decreased mortality and postoperative respiratory failure in marasmic, cardiopulmonary bypass patients provided 5 to 8 weeks of modest TPN (1000 kcal, 38 g protein). Perioperative nutrition support is recommended in patients undergoing liver resection for hepatocellular carcinoma associated with cirrhosis. Comparable outcome studies are needed employing enteral support. One of the confounding variables in the preoperative TPN trials is that many of the enrolled patients had cancer. Animal data show enhanced tumor growth with selected types of cancer when the animals are parenterally fed. Therefore, concern exists that preoperative TPN will simply promote tumor growth (*ie*, you are feeding the tumor rather than the patient). This concern is supported by the clinical observation that TPN does not improve the nutritional status of patients with large tumors. Additionally, immunocompromised patients with cancer are at increased risk for infectious complications due to TPN.

Specialized Total Parenteral Nutrition

These formulas have been modified to match the altered substrate utilization observed in stressed patients. Critical illness induces a hypercatabolic state (Figure 1). To blunt "autocannibalism" of endogenous protein stores, stress formula TPN provides increased amounts of exogenous amino acids. Specialty amino acid (AA) formulas which are designed to meet organ failure specific requirements include: (1) high branched-chain (HBC AA), (2) hepatic failure (low aromatic AA),

and (3) renal failure (high essential AA). The use of these specialty formulas remains controversial because of the extra expense. Additionally, studies comparing HBC AA solutions with standard AA formulas in stressed patients have shown improvements in nitrogen retention, constitutive protein levels, and immune function, but have failed to demonstrate reduced morbidity or mortality. The use of specific organ failure formulas (hepatic and renal) has not been shown to improve nutritional status or outcome compared with standard AA solutions. Given the absence of outcome data and the extraordinary expense, they are rarely used in contemporary practice.

Glucose intolerance is common in critically ill patients. Consequently, meeting caloric needs with carbohydrate calories is difficult and may further exacerbate the complications associated with poor blood glucose control. Providing a proportion of the nonprotein calories as lipid facilitates attaining the desired caloric intake without "stressing" carbohydrate metabolism and meets essential fatty acid requirements. On the other hand, lipid particles are taken up by the reticuloendothelial system (RES) in a dose-dependent fashion. When lipid is given in high doses (> 2.5 g/kg/day) or infused over a short period (<10 h), the RES may become saturated with lipid and, hence, unable to scavenge microbes and other particulate matter. This may result in an increased susceptibility to sepsis. Furthermore, the currently available lipid emulsions are composed of long-chain fatty acids. Of these, linoleic acid (representing 50%-65% by weight of the fatty acids) is the precursor for prostaglandin synthesis as well as other mediators of the inflammatory response and may be immunosuppressive. It has been proposed that an excessive intake of linoleic acid may inhibit the immune system, facilitate the inflammatory response, and compromise the patient's ability to fight infection. Currently, patients should not receive > 1 g/ kg/day of lipid.

Monitoring Total Parenteral Nutrition

This is done to (1) determine the efficacy of the TPN therapy; (2) determine changes in metabolic status (stress level); and (3) detect complications associated with TPN. Commonly-used measurements of efficacy in the acute care setting include weight, constitutive protein status (*eg*, albumin, transferrin, and prealbumin), nitrogen balance, blood glucose, and wound healing. However, it is important to remember that these levels are acutely decreased by the stress insult alone. Following a stress insult, the liver "reprioritizes" its protein synthesis (*ie* decreases normal constitutive protein synthesis so that it can increase acute phase protein synthesis) and this persists until the SIRS resolves. Metabolic status should be viewed first from the clinical perspective. Are there signs of SIRS with or without active infection? Is the patient hyperdynamic? What is the minute ventilation requirement? Metabolic status can be further assessed by laboratory variables that evaluate substrate tolerance (*eg*, blood glucose and serum triglyceride concentrations) as well as protein catabolic rate (24-h UUN). A metabolic gas study can document energy expenditure and respiratory quotient.

There are a variety of TPN-associated complications including: (1) nutritional (*eg*, overfeeding, underfeeding, specific nutrient deficiencies or toxicities); (2) metabolic (*eg*, hyperglycemia, electrolyte, fluid, and acid-base imbalances, liver function abnormalities); (3) infectious (*ie*, catheter-related sepsis); (4) mechanical (*eg*, hemothorax, pneumothorax, subclavian vein thrombosis); (5) gut atrophy; and (6) decreased immunocompetence.

Refeeding Syndrome

Refeeding syndrome can occur with rapid and excessive feeding of patients with severe malnutrition due to starvation, alcoholism, delayed enteral or parenteral nutritional support, anorexia nervosa, hyperemesis gravidarum, and massive weight loss after bariatric surgery. With refeeding, a shift in metabolism from fat to carbohydrate stimulates insulin release. This shift results in the cellular uptake of electrolytes, particularly phosphate, magnesium, potassium, and calcium. Serum levels of these ions can drop precipitously. Due to blunted basal insulin secretion, severe hyperglycemia may also arise. The refeeding syndrome can be associated with oral, enteral, or parenteral refeeding and symptoms include cardiac arrhythmias, confusion, respiratory failure, and even death. To prevent the development of refeeding, underlying electrolyte and volume deficits should be corrected. Additionally, thiamine should be administered prior to feeding being initiated. Caloric repletion should be instituted slowly. Recommendations include initiating feeds at a rate of 20 kcal/kg/day with

a gradual increase over the first week or TPN at approximately two-thirds of the required goal (decreased dextrose kcal). Vital signs, fluid balance and electrolytes should be closely monitored.

Hyperglycemia

Critical illness is accompanied by increased plasma counterregulatory hormone levels which have multiple effects on glucose homeostasis (Table 7). The end result is hyperglycemia with resistance to insulin.

Other factors that contribute to this "stress diabetes" include obesity, SIRS (TNFα, IL-1, IL-2, and IL-6), advanced age, exogenous steroid or catecholamines, increased free fatty acids and nutritional support (parenteral route greater than enteral route). The absorption of excess dextrose kcal in peritoneal dialysate (70%-100% absorption), and in post-dialytic continuous venovenous hemodialysis (CVVHD) replacement solutions should be considered in calculating nutrition regimens.

The resulting hyperglycemia can adversely affect outcome through several mechanisms including (1) glycosuria and inappropriate diuresis, (2) exacerbation of cerebral edema, and (3) increased risk of infection (by impairing neutrophil and immunoglobulin function). A recent prospective randomized trial demonstrated a significant reduction in morbidity and mortality among critically ill patients in a surgical ICU when blood glucose level was maintained at or below 110 mg/dL.

Table 7. *Counterregulatory Effects of Hormones on Glucose Homeostasis*

Hormone	Perturbs	Effect
Catecholamines	Glycogenlysis	↑
	Gluconeogenesis	↑
	Lipolysis	↑
	Insulin release	↓
Glucagon	Glycogenolysis	↑
	Gluconeogenesis	↑
	Ketogenesis	↑
Glucocorticoids	Gluconeogenesis	↑
	Catecholamine response	↑
	Insulin resistance	↑

Catheter-Related Sepsis

The pathogenesis of catheter-related sepsis (CRS) is straightforward. The in-dwelling catheter becomes contaminated and over time, the bacteria or yeast proliferate resulting in heavy local colonization, which then seeds the blood, resulting in bacteremia and signs of systemic sepsis. The catheter may have been contaminated (1) at the time of insertion, (2) later due to local skin colonization with bacteria or yeast which then tracked down the external surface of the catheter, and (3) by hub contamination during manipulation which then tracked down the inside of the catheter. Other less frequent sources of contamination include infusion of contaminated solutions or hematogenous seeding from a distal site of infection.

Preventative measures can be broken down into three categories: (1) catheter insertion, (2) catheter care, and (3) catheter removal. Important components of catheter insertion include skin preparation (chlorhexidine is more efficacious than alcohol or povidone iodine) and the use of maximal sterile barriers. Although it is commonly believed that multiple-lumen catheters have a higher rate of CRS compared to single-lumen catheters, randomized studies (which use rigorous central venous catheter protocols) show equal rates of CRS. Recent randomized trials indicate that CRS can be reduced by use of antibiotic- or antiseptic-bonded catheters. However, these catheters are considerably more expensive and run the risk of resistant organisms emerging, especially staphylococci. These catheters should be used in select patients whose catheters are going to be in place for a prolonged period (*eg*, 5-7 days). Other catheter care guidance includes the following: (1) dressing/tubing should be changed every 48 to 72 h; (2) antibiotic ointment is of questionable benefit and may promote fungal catheter colonization and antibiotic resistance; and (3) dressing may be gauze or a transparent, semipermeable polyurethane dressing. Finally, a recent meta-analysis of 12 randomized trials of catheter-replacement strategies concluded that the data do not support either scheduled, routine exchange of catheters over a guide wire or scheduled, routine replacement of at a new site. Scheduled changes over a guide wire were actually associated with a trend toward increased catheter-related blood stream infections. Removing the catheter at set intervals effectively reduces CRS, but must be

weighed against the increased risk of mechanical complications associated with a new stick. The use of a "virgin port" for the administration of TPN has been a standard of care but supportive data are limited.

Enteral Nutrition

Enteral Route Is Preferred to the Parenteral Route

The optimal route of substrate delivery is an ongoing debate and, like most good debates, it continues to evolve. TPN became widely available by the late 1970s. However, the enteral route was favored because it was safer and cheaper. By the mid-1980s, as a result of nutritional support teams, TPN had become reasonably safe and convenient because central venous catheters were being widely utilized in ICUs. An inappropriate fear of GI intolerance discouraged the use of enteral nutrition and by default TPN became the preferred route in ICUs. By the late 1980s, however, clinical trials had convincingly demonstrated that enteral nutrition is well tolerated when delivered into the small bowel (see next section). Moreover, basic research observations offered compelling physiologic benefits for enteral feeding. Substrates (*ie*, nitrogen and glucose) delivered by the enteral route are better utilized than those administered parenterally. In addition, total enteral nutrition (TEN), compared with current TPN, prevents GI mucosal atrophy, may attenuate the stress response to injury, maintains immunocompetence, and preserves normal gut flora. Finally, prospective, randomized, controlled trials (PRCTs) have consistently shown that early TEN, when compared to TPN, is associated with reduced septic morbidity. Thus, today the enteral route is preferred and considerable research efforts are being directed at elucidating the mechanisms responsible for the improved outcomes (principally septic morbidity) associated with enteral nutrition and at modifying TPN so that it can achieve the same outcomes in patients who cannot tolerate enteral diets.

The role of enteral feeding in reducing septic morbidity remains to be elucidated. Multiple factors are likely involved. First, lack of enteral nutrition or lack of specific nutrients (*eg*, glutamine, SCFA, fiber) may promote bacterial translocation. While bacterial translocation has been a popular endpoint in laboratory models, clinical studies have not clearly demonstrated that bacterial translocation is a common pathogenic event in critically ill patients. Second, excessive administration of glucose or lipids with TPN may worsen immunosuppression. This has been demonstrated in laboratory models, and three recent prospective randomized controlled trials of perioperative TPN have demonstrated that the TPN-fed patients, compared to controls who received no nutritional supplementation, have higher postoperative septic morbidity. Third, specific nutrients (*eg*, glutamine, arginine, omega-3 fatty acids, and nucleotides) enhance immune effector cell function independent of preventing SIRS-induced acute protein malnutrition (see immune-enhancing formulas). Fourth, stimulation of the enteric nervous system by enteral feeding enhances both local GALT and systemic mucosal-associated lymphoid tissue (MALT) function, which decreases the risk of nosocomial pneumonia.

Indications for Enteral Nutrition

In general, enteral nutrition should be considered for any critically ill patient who will be unable to meet their nutritional needs orally for a period of 5 to 10 days. Additionally, early enteral nutrition should be considered the following groups of patients:

Chronically malnourished patients anticipated to be NPO > 5 days and:

- Admission albumin < 2.5 g/dL
- Recent weight loss > 10%
- Less than 80% ideal body weight (IBW)

Patients with limited physiologic reserve anticipated to be NPO > 5 days and significant comorbid disease:

- Lung disease: Chronic obstructive pulmonary disease requiring bronchodilators or steroids
- Liver disease: Admission bilirubin > 2.5 mg%, history of hepatic encephalopathy, or established cirrhosis
- Kidney disease: Chronic renal disease requiring dialysis or renal transplant
- Active malignancy
- Immune dysfunction: AIDS or current chemotherapy, or prednisone
- Age over 70 years

Disease- or injury-specific patients:

- Hyperemesis gravidarum patients unable to achieve appropriate weight gain despite the use of noninvasive therapies
- Anorexia nervosa patients with severe malnutrition (> 30% recent weight loss or < 65% IBW) who are unable or unwilling to ingest adequate nutrient.
- Moderate or severely malnourished patients undergoing major GI surgery should receive specialized nutrition support preoperatively for 7 to 14 days if the operation can be safely postponed.
- Trauma patients with major head injuries, torso trauma, orthopedic trauma, chest trauma
- Patients with acute lung injury secondary to smoke inhalation, near-drowning
- Patients with major upper GI surgery that precludes oral intake for > 5 days (*eg*, esophagectomy, combined pancreatic-duodenal injury)
- Burn patients with 2nd or 3rd degree burns > 20% total body surface area (TBSA)
- Patients with major wounds, decubiti, necrotizing fasciitis

Achieving Enteral Access

The first decision to be made is whether the patient should be fed into the stomach or small bowel. The risk of aspiration (as summarized below), GI anatomy and function, and disease process all play a role in this decision. Access can generally be divided into the following three groups: (1) those placed via the "push" technique (nasogastric and nasojejunal tubes); (2) those placed endoscopically (endoscopic nasojejunal tube or percutaneous endoscopic gastric [PEG]/jejunal tube [PEJ]); or (3) surgically placed tubes (open gastrostomy or jejunostomy tube, needle-catheter jejunostomy, or laparoscopic jejunostomy). In general, an attempt at a "push" tube should be initially made. If this fails, then a feeding tube can be placed under endoscopic or fluoroscopic guidance. If the patient requires a laparotomy, a surgically placed tube should be placed; if the need for long-term feeding has been established and the patient does not require surgery, a PEG/PEJ should be considered. Our protocol for obtaining jejunal access is shown in Figure 4.

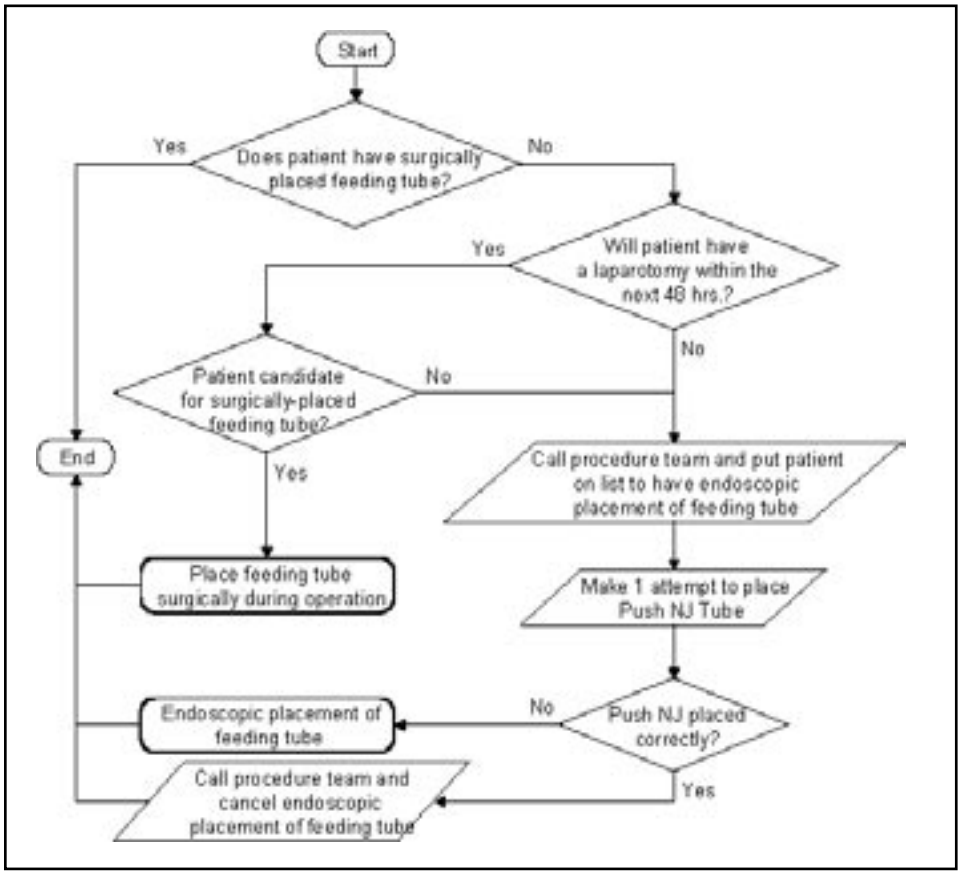

Figure 4. Algorithm to obtain jejunal access. From Kozar RA, McQuiggan MM, Moore FA. Nutritional support of trauma patients. In: Shikora SA, Martindale RG, Schwaitzberg SD, eds. Nutritional considerations in the intensive care unit: science, rationale, and practice. Dubuque, IA: Kendall/Hunt Publishing Co, 2002; 229-244.

Gastric Feeding in Critical Illness

Consider patients for gastric feeding if they are *not* at high-risk for aspiration (Table 8), have a functioning GI tract, and have no evidence of delayed gastric emptying as defined by history or radiologic examination. Additionally, patients should not be septic as this may delay gastric emptying for up to 48 h. Since even mild hyperglycemia affects gastric emptying, one must be able to control blood glucose < 140 mg/dL. Nasogastric (NG) output should be < 500 mL/12 h at the initiation of NG feedings.

Gastric feeding can be used in patients with 0-1 major risk factors for aspiration with special precaution (Table 9).

Feeding Protocol

Special consideration needs to be given to positioning the patient at ≥ 30° head up. This is a major factor for prevention of aspiration. Feedings should be held 4 h prior to undergoing an anesthetic for an operative procedure, but may be restarted immediately postoperatively at the previous rate. Feedings are held 4 h prior to endotracheal extubation.

Optimal management of gastric residual volumes has not been well established. This has limited success of this route by preventing achievement of caloric goals. Because salivary and gastric secretions proximal to the pylorus normally approach 200 mL/h, there is no need to respond to values less than this. Feedings should be discontinued at 500 mL and a postpyloric feeding started. An example of an algorithm for managing gastric

Table 8. *Risk Factors for Aspiration*

Major Risk Factors	Example
Endotracheal intubation	Risk of aspiration increases in the first 48 h after endotracheal extubation
Decreased level of consciousness	CHI with a GCS <12, dementia, ETOH withdrawal, sedatives/ analgesics (morphine, meperidine and barbiturates increase aspiration rate by decreasing LES pressure)
Neuromuscular disease and structural of the aerodigestive tract	DM gastroparesis, Parkinson's disease, scleroderma, GERD, abnormalities ESRD with visceral neuropathy
Recent CVA	
Major intra-abdominal injury or major upper gastrointestinal surgery	< 5 days postoperatively
Documented previous episode of aspiration	
Persistently high gastric residual volumes (GRV)	GRV > 500 mL
Need for prolonged supine position or need for prone position	
Vomiting	

CHI, closed-head injury; ETOH, alcohol; LES, lower esophageal sphincter; DM, diabetes mellitus; GERD, gastroesophageal reflux disease; ESRD , end-stage renal disease.

Table 9. *Candidate Selection for Nasogastric (NG) Feedings*

Risk Factors	Feeding Type	Care and Precautions
No major risk factors	NG	HOB 30 degrees Good oral care per protocol Regular assessment of tolerance and tube placement
One major risk factor	NG	All of the above Maintain tight glycemic control Correct electrolyte abnormalities Minimize narcotics
≥2 risk factors, documented aspiration	Nasojejunal	Feeding tube post Ligament of Treitz

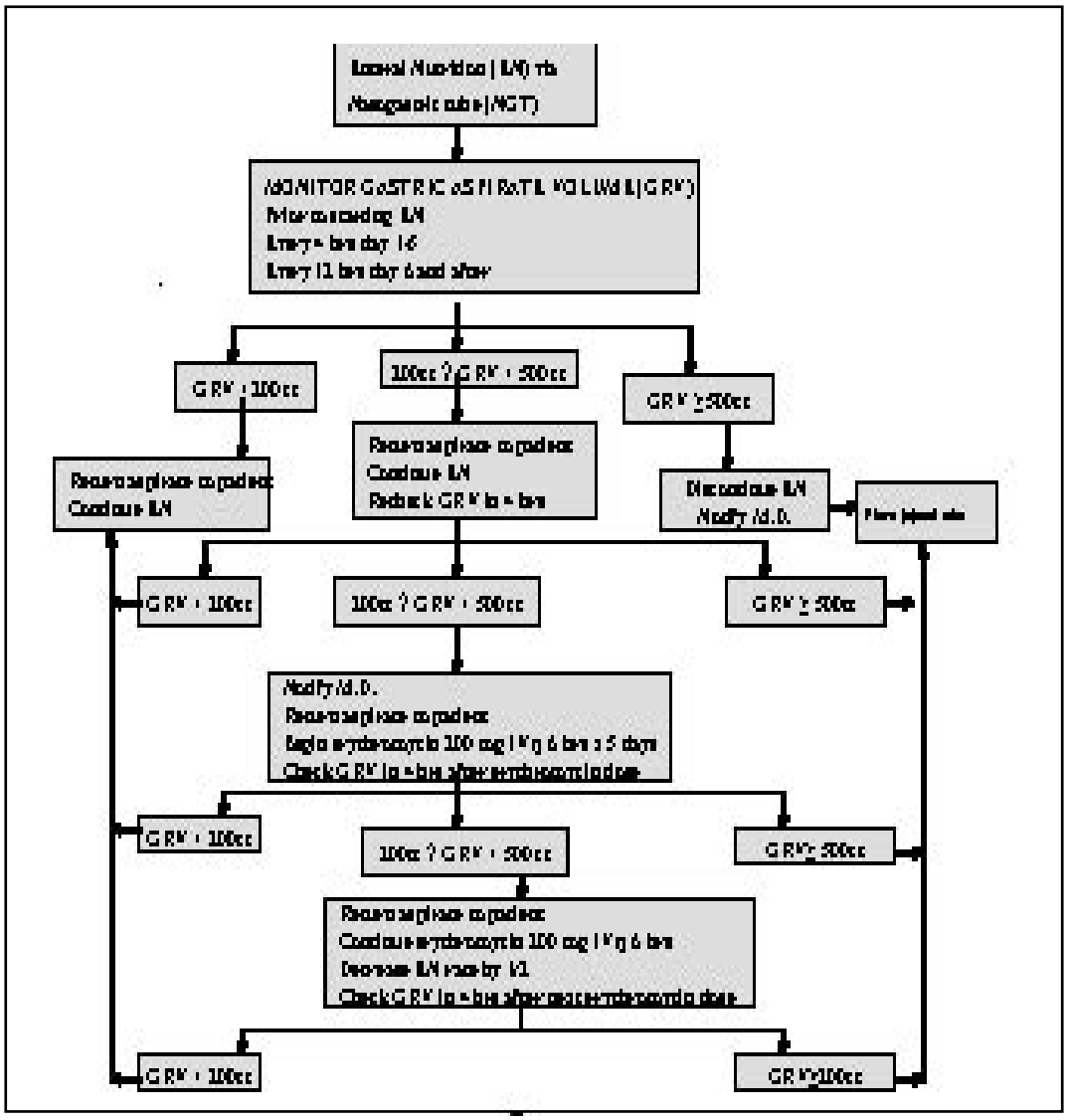

Figure 5. Adapted from Mentec et al. Crit Care Med 2001; 29:1955-1961.

Table 10. *ICU Enteral Formulary*

Classification	Example*	General characteristics
Immune-enhancing	Impact, Immun-Aid, Crucial, Alitraq, Perative	A polymeric formula containing one or more immune-enhancing nutrients
Polymeric high protein	Replete, Promote®	A polymeric formula offering higher levels of protein for the critically ill patient
Elemental	FAA, Optimental, Vivonex Plus®	Contains short-chain proteins, dipeptides, amino acids, dextrose and (possibly) limited fat
Renal	Novasource Renal, Nepro®	Polymeric, concentrated formula with reduced electrolytes for renal failure
Fiber-containing	Jevity, Promote with Fiber, Replete with Fiber	Polymeric formula with additional insoluble and/or soluble fiber to modulate bowel function
Modular Component	ProMod, Polycose, Corn oil, MCT oil	Single macronutrient added to other formulas to customize nutrient load

*List does not contain all commercially available formulas.
ProMod, Perative, Promote, Alitraq, Optimental, Nepro, Jevity, Promote with fiber and Polycose—Ross Laboratories, Columbus, OH; Immun-Aid—McGaw, Irvine, CA; Vivonex Plus, Impact, Vivonex Plus, Novasource Renal—Novartis, Minneapolis, MN; Replete, FAA, Replete with fiber, and Crucial—Nestle, Deerfield, IL.

residual volume is shown below in Figure 5. The use of erythromycin has been shown to increase tolerance to gastric feeds.

Formula Selection

Many of the early clinical trials were done with elemental formulas that were low in fat. It was assumed these would be better tolerated. However, in more recent studies, other types of formulas appear to be equally well tolerated. The numerous available formulas may be categorized into polymeric formulas (which contain nutrients in high molecular weight forms and require normal digestive and absorptive ability), predigested or elemental formulas (which contain one or more partially digested macronutrients or combinations of nutrients and can be absorbed in patients with compromised GI tracts), and modular formulas (which are composed of individual nutrients or combinations of nutrients but are nutritionally incomplete and intended for use as supplements or in combination with other products). Unfortunately, with the exception of the immune-enhancing formulas (see next section), very little comparative data exist to guide clinicians in selecting the most appropriate formula for their ICU patients. Table 10 depicts a typical ICU enteral formulary. Generally, a limited selection can meet the specific needs of particular patient populations.

Typically formulas contain 1 kcal/mL and 37 to 62 g protein/1000 kcal and are 85% water. Concentrated formulas are 2 kcal/mL, approximately 36 g protein/1000 kcal and are 70% water. The RDI for vitamins and minerals is delivered in 1000 to 1800 kcal of formula. Criteria for usage of specialized formulas should be evidence-based.

Immune-Enhancing Diet: Recent basic and clinical research suggests that the beneficial effects of enteral nutrition can be amplified by supplementing specific nutrients that exert pharmacologic immune-enhancing effects beyond the prevention of acute protein malnutrition. Such nutrients include glutamine, arginine, omega-3 PUFA, and nucleotides. At present, at least three immune-enhancing enteral formulas (*ie*, enriched with various combinations of the above nutrients) are commercially available and have been tested in prospective randomized controlled trials. In this era of evidence-based medicine, these data are becoming increasingly difficult to dismiss. To date, there are at least 18 published PRCTs where an immune-enhancing diet (IED) is compared with a standard enteral diet (SED) or no diet and where the patient outcome was a predetermined end point (Table 11). Of the 18 PRCTs, 11 trials demonstrated improved outcome, four trials were highly suggestive of improved outcome, and three trials did not demonstrate any clinical outcome advantage.

There have also been three meta-analyses that have demonstrated improved patient outcome. The indications in critically ill patients, though, remain controversial.

The following groups of patients receive IEDs in our surgical ICU.

- Major chest trauma requiring mechanical ventilation
- Major abdominal trauma
- Major orthopedic trauma
- Moderate or severely malnourished patients undergoing elective upper GI or hepatobiliary surgery; severely malnourished patients undergoing lower GI surgery. Results may be enhanced by preoperative IED feeding for 5 to 7 days.

The following patients may benefit from IEDs:

- Aortic reconstruction with COPD and expected prolonged need for mechanical ventilator
- Malnourished patients undergoing head and neck surgery
- Severe head injury (GCS<8)
- Burns >30% TBSA
- Ventilator-dependent, nonseptic, medical or surgical ICU patients at risk for subsequent infectious morbidity.

Polymeric High-Protein Formula: These formulas should be used in patients who do not meet the criteria for EIDs, but have normal digestive and absorptive capacity of the GI tract, and are believed to have increased nitrogen requirements.

Elemental Formulas: These should be used in patients who have:

- Proven intolerance to the first formula used
- As initial formula after prolonged bowel rest
- Pancreatitis (controversial)
- Short gut with demonstrated intolerance to polymeric feedings
- High-output distal colonic or ileal fistula
- Persistent, severe diarrhea > 48 h while on polymeric formula
- Moderate distention > 24 h

Renal Failure Formula: This formula should be used in patients with renal failure requiring intermittent dialysis or acute renal failure without dialysis. Patients on continuous venovenous hemodialysis (CVVHD) do *not* require renal formula.

Nonocclusive Bowel Necrosis

With wider application of enteral nutrition in ICU patients, this entity has emerged as a devastating complication. The incidence among patient populations described is < 0.3%, however

Table 11. *Assessment of Patient Outcome in 18 Prospective Randomized Controlled Trials Comparing Immune-Enhancing Diets (IED) versus Standard Enteral Diets (SED) or No Diet*

First Author/ Year (Journal)	Patient Type (Number)	IED vs SED	Results with IED	Improved Outcome
Gottschlich/1990 (JPEN)	Burns (n=50)	Noncommercial Study Formula vs Osmolite + Promote or Traumacal	↓WI ↓LOS	Yes
Daly/1992 (Surgery)	Cancer (n=77)	Impact vs Noncommercial Control Diet	↓WC ↓Inf	Yes
Brown/1994 (Pharmacotherapy)	Trauma (n=37)	Noncommercial Study Formula vs Osmolite HN + Promod	↓Inf	Yes
Moore/1994 (J Trauma)	Trauma (n=98)	Immun-Aid vs Vivonex TEN	↓IAA ↓MOF	Yes
Bower/1995 (Crit Care Med)	Mixed ICU (n=296)	Impact vs Osmolite HN	↓Inf ↓LOS	? Yes Subsets
Daly/1995 (Ann Surg)	Cancer (n=60)	Impact vs Traumacal	↓WC, ↓Inf ↓LOS	Yes
Kudsk/1996 (Ann Surg)	Trauma (n=35)	Immun-Aid vs Promote + Casec	↓ABT, ↓Inf ↓LOS	Yes
Senkel/1997 (Crit Care Med)	Cancer (n=154)	Impact vs Noncommercial Control Diet	↓Late Inf	Yes
Mendez/1997 (J Trauma)	Trauma (n=43)	Noncommercial Study Formula vs Osmolite HN + Promod	↑ARDS	No
Saffle/1997 (J Trauma)	Burns (n=50)	Impact vs Replete	------	No
Heslin/1997 (Ann Surg)	Cancer (n=154)	Impact vs No Diet	------	No
Braga/1998 (Crit Care Med)	Cancer (n=154)	Impact vs Noncommercial Control Diet	↓Inf ↓LOS	? Yes Subsets
Atkinson /1998 (Crit Care Med)	Mixed ICU (n=369)	Impact vs Nonncommercial Control Diet	↓Vent Days ↓LOS	? Yes Subsets
Weimann /1998 (Nutrition)	Trauma (n=32)	Impact vs Noncommercial Control Diet	↓SIRS ↓MOF	? Yes Definitions
Senkel/1999 (Arch Surg)	Cancer (n=154)	Impact vs Noncommercial Control Diet	↓Late Inf	Yes
Braga/1999 (Arch Surg)	Cancer (n=206)	Impact vs Noncommercial Control Diet	↓Inf	Yes
Snyderman/1999 (Laryngoscope)	Cancer (n=129)	Impact vs Replete	↓Inf	Yes
Galban/2000 (JPEN)	Septic ICU (n=181)	Impact vs Precitene Hiperproteico	↓Late Inf	Yes

WI, wound infection; WC, wound complication; LOS, length of stay; Inf, infections; IAA intra-abdominal abscess; MOF, multiple organ failure; ABT, antibiotics; SIRS, systemic inflammatory response syndrome.
Osmolite, Ross Laboratories, Columbus, OH; Promote, Ross Laboratories, Columbus, OH; Traumacal, Mead Johnson, Evansville, IN; Impact, Novartis, Minneapolis, MN; ProMod, Ross Laboratories, Columbus, OH; Immun-Aid, McGaw, Irvine. CA; Vivonex TEN, Novartis, Minneapolis, MN; Casec, Mead Johnson, Evansville, IN; Replete, Nestle, Deerfield, IL.

the mortality exceeds 50%. The pathogenesis is not understood. While gut hypoperfusion due to incomplete resuscitation is commonly stated to be the prelude, most cases of nonocclusive bowel necrosis occur in a delayed fashion in ICU patients with a complicated course (pneumonia, sepsis, renal failure) that requires progressively higher acuity care (*eg*, nonconventional modes of ventilation, vasopressors, dialysis). GI signs and symptoms tend to occur late and as a result clinical monitoring fails to detect this entity early in its course. The clinical presentation resembles bacterial sepsis.

Controversies

Anabolic Compounds

The four major classes of anabolic compounds include recombinant human growth hormone (rhGH), insulin-like growth factor (IGF-1), anabolic steroids, and high-dose insulin. These drugs have been tested most extensively in burn patients where it has been observed that despite aggressive nutritional support, persistent metabolic stress and immobilization leads to major muscle wasting which is a major obstacle in rehabilitation. One PRCT in trauma patients given 20 mg oxandrolone daily starting early in the ICU stay demonstrated no nutritional or clinical outcome benefit. RhGH is the most tested compound and has powerful anabolic effects on most body cells, either directly or by stimulating IGF-1 secretion. Relatively small trials have demonstrated accelerated donor site healing, improved muscle protein synthesis, decreased length of hospital stay, and improved mortality. A recent large multicenter trial, however, observed an increased mortality in critically ill patients who received rhGH. While there is no explanation for this increased mortality, this report has tempered enthusiasm for using rhGH in nonburned ICU patients.

Pancreatitis

Acute pancreatitis induces severe hypercatabolism. Without exogenous nutritional support, acute protein malnutrition can occur. TPN has been a standard of care to provide nutrients while "resting" the pancreas. However, recent studies have indicated that enteral feeding into the jejunum in patients with acute pancreatitis is feasible. When compared with TPN, jejunal feeding does not cause increased pancreatic stimulation and is associated with reduced septic complications. Studies comparing elemental vs. polymeric or IED formulas are needed.

Obese Patients

Approximately 60% of the US population is overweight or obese. Obesity is associated with a number of comorbid conditions that place patients at increased risk for ICU admission. Controversies concerning nutritional support of the obese patient include the following: (1) the definition of obesity, (2) what body weight (ideal, actual, or adjusted) to use when estimating energy needs, and (3) the amount of nonprotein calories and protein to administer. Obesity begins when an individual exceeds 120% IBW which can be obtained with height/weight tables. Energy needs should be calculated using adjusted body weight which is calculated by determining the obese patient's actual weight (ABW) and the IBW. Then, 25% of the difference between these numbers is added to the IBW.

$$0.25\ (ABW - IBW) + IBW = \text{Adjusted Body Weight}$$

This takes into account the increased lean body mass seen in obese patients. The adjusted body weight is then used in the Harris-Benedict equation (or other equations) to predict energy needs. Obese patients experience a similar metabolic response to critical illness. However, they tend to have more resistance to insulin and hyperlipidemia. "Letting them live off their excess fat" is an inappropriate strategy and if pursued will result in unnecessary and potentially harmful loss of lean body mass. Obese patients should be started on nutritional support as early as their nonobese counterparts. While controversial, data are emerging that support the concept of "hypocaloric" feeding where the obese patient is provided high protein (2 g/kg IBW/day), but low nonprotein calories (15 kcal/kg/day).

Specialized Formulas for the Critically Ill Patient with Diabetes Mellitus

Formulas with reduced carbohydrate and increased fat loads are available for use in patients with diabetes and are marketed as being superior in maintaining glycemic control. These products have not undergone PRCTs to demonstrate superior

outcome in ICU patients. The use of standard high-protein formulas in an isocaloric or hypocaloric load, combined with appropriate insulin therapy may be the most effective treatment for insulin resistance in the stressed, Type 2 diabetic patient. The level of glycemic control associated with enhanced outcome is best achieved with insulin, as opposed to carbohydrate restriction. Furthermore, gastric feedings with high-fat formulas in the diabetic patient with gastroparesis may be associated with delayed gastric emptying and increased risk of aspiration.

Specialized Formulas for the Patient with ARDS

One industry-funded PRCT demonstrated superior outcome (reduced days on the ventilator, reduced LOS in ICU, decreased incidence of organ failure) in patients with ARDS when provided a high-omega-3 fatty acid enteral product vs. a high-omega-6 "pulmonary" formula. However, the control diet was not the standard of care and may worsen ARDS. High omega-6 fatty acids increase inflammation and production of lipid mediators that worsen ventilation/perfusion mismatch in the lung, and thus worsen oxygenation in ARDS. Duplication of the results and comparison to standard, moderate-fat polymeric formulas are needed. Currently the American Society of Enteral and Parenteral Nutrition (ASPEN) practice guidelines for pulmonary disease state "that provision of a modified enteral formulation containing omega 3 fatty acids may be beneficial in the patient with early ARDS".

Arginine-Containing Formulas in the Septic Patient

Arginine is provided in pharmacologic doses in IEDs such as Altraq, Crucial, Immunaid, Impact and Perative. The other key ingredients include glutamine, omega-3 fatty acids, and nucleotides. Arginine is thought to be a semi-essential amino acid in critically ill patients. It is a metabolic fuel for lymphocytes and fibroblasts. It is also a secretagogue for a variety of hormones (most notably growth hormone). PRCTs have shown that supplemental arginine improves wound healing and immune responsiveness in high-risk surgical patients. As previously discussed, a number of PRCTs have shown that IEDs reduce infections and decrease hospital LOS. However, trials that have enrolled less homogenous ICU patients have had a difficult time demonstrating improved outcome and subset analysis suggest that IEDs may be harmful in septic ICU patients. Reviewing the potential immunomodulating effects of the key ingredients in IEDs has led some authorities to hypothesize that arginine supplementation is harmful in the septic patient. Septic patients have increased levels of inducible nitric oxide synthetase (iNOS). Arginine is a substrate for iNOS and in its presence, arginine combines with molecular oxygen to produce citrulline and nitric oxide (NO). The resulting NO could have numerous adverse effects in sepsis including vasodilation, cardiac dysfunction and direct cytotoxic injury by generating potent reactive oxygen species. Unfortunately, there is very little data to support or refute this hypothesis.

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Large multicenter prospective randomized trial demonstrated the preoperative TPN, compared to no nutritional supplementation, was associated with increased infectious morbidity. This has been confirmed by two more recent PRCTs. The only patients who appear to benefit from preoperative TPN were severely malnourished. Severe malnutrition represented only a small subset of the enrolled patients.

Additional Selected Reading

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APPENDIX I: Indirect Calorimetry

Patient selection

The following clinical scenarios may merit an indirect calorimetry study:

a. Whenever a knowledge of caloric balance is a critical part of management
b. Patients in whom *overfeeding* would be especially detrimental
   Diabetics
   Obese
   COPD with CO_2 retention (increased pCO_2, increased serum CO_2)
   Pancreatitis
c. Patients in whom *underfeeding* would be especially detrimental
   Renal failure
   Hepatic failure
   Massive soft tissue defects, decubiti, necrotizing fasciitis
   Limited nutritional reserve (<90% IBW)
d. Patients whose physical or clinical factors promote energy expenditure deviant from the norm
   Obesity
   Hypothermia
   Pharmacologic coma/sedation
   Severe CHI
   Chronic starvation
   Hypothyroidism
   Spinal cord injury with loss of motor function
   Anasarca
e. Patients who don't respond as predicted to calculated regimens

Controlling clinical factors to assure reliable results

a. No vent changes past hour
b. Feeding regimen is noted on report and regimen is stable for >2 hours prior to the study.
c. Patient is quiet, there are no interruptions, seizures, procedures, or severe pain. Analgesics and sedatives may be used to facilitate study.
d. Vent settings
   FIO_2 <50-60%
   PEEP<10
e. ICP<18 mm Hg
f. Performed at least 2 hours after hemodialysis
g. No leaking chest tubes, bronchopleural fistulae, incompetent ETT cuffs
h. Test Endpoint:
   Steady state x 5 min (deviations in VO_2<10%, VCO_2<10%,RQ<5%)
   Measurement in physiologic range:
   RQ (0.67-1.25)
   VO_2 (1.7-3.4 ml/min/kg)
   VCO_2 (1.4-3.1 ml/min/kg)
i. No severe metabolic acidosis
j. No therapeutic hyperventilation/hypoventilation
k. No volume diffusive respirator
l. No supplemental O_2 (if patient off the ventilator)

Notes

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