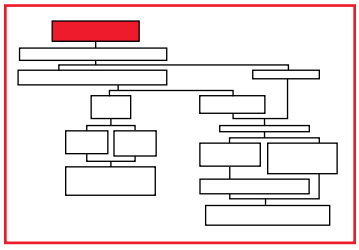
22 NUTRITIONAL SUPPORT

Rolando H. Rolandelli, M.D., Dipin Gupta, M.D., and Douglas W. Wilmore, M.D.

Nutritional Management of Hospitalized Patients

Evaluation of the Need for Nutritional Support



INDICATIONS FOR NUTRITIONAL INTERVENTION

Nutritional support is required in patients who fall into one of the following general categories:

1. The patient has been without nutrition for 10 days. In a well-nourished individual, body stores are generally adequate to provide nutrients during shorter periods of stress without compromising physiologic functions, altering resistance to infection, or impairing wound healing. Provision of nutrients becomes more important as body stores become eroded because of inadequate food intake and accelerated catabolism. In general, deficits occur in surgical patients after 7 to 10 days of partial starvation; nutritional intervention should be initiated before this time.
2. The duration of illness is anticipated to be longer than 10 days. In this context, nutritional support should be considered essential care. Thus, individuals with severe peritonitis or pancreatitis, major injury (injury severity score > 15), or extensive burns (> 20% total body surface area) are candidates for nutritional support because of the known duration of their illness. (The duration of illness in chronically malnourished patients also would be expected to exceed 10 days.)
3. The patient is malnourished (loss of > 10% of usual body weight over 3 months). In general, weight loss can be used as an index of nutritional deficiency, and recovery may be compromised in patients who lack adequate body nutrient stores because of an existing nutritional deficit [*see Figure 1*]. The patient should receive nutritional support when weight loss approaches or exceeds 15% of usual body weight:

$$\%\ \text{Weight loss} = \frac{\text{Usual weight} - \text{present weight}}{\text{Usual weight}} \times 100$$

Patients who do not meet one of these three general indications should be reassessed after 7 days to identify individuals in whom complications develop after hospital admission and who require nutritional support. Serum proteins with a short half-life, such as prealbumin, transferrin, or retinol-binding protein, are useful markers for assessing response to therapy.

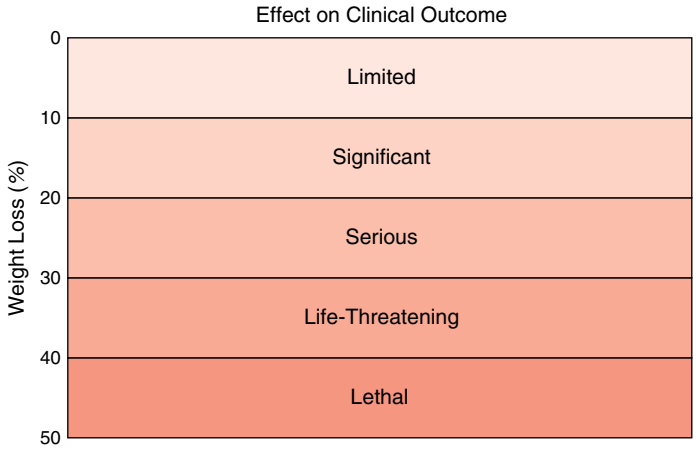
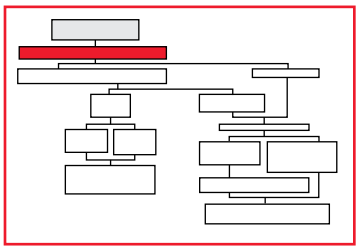


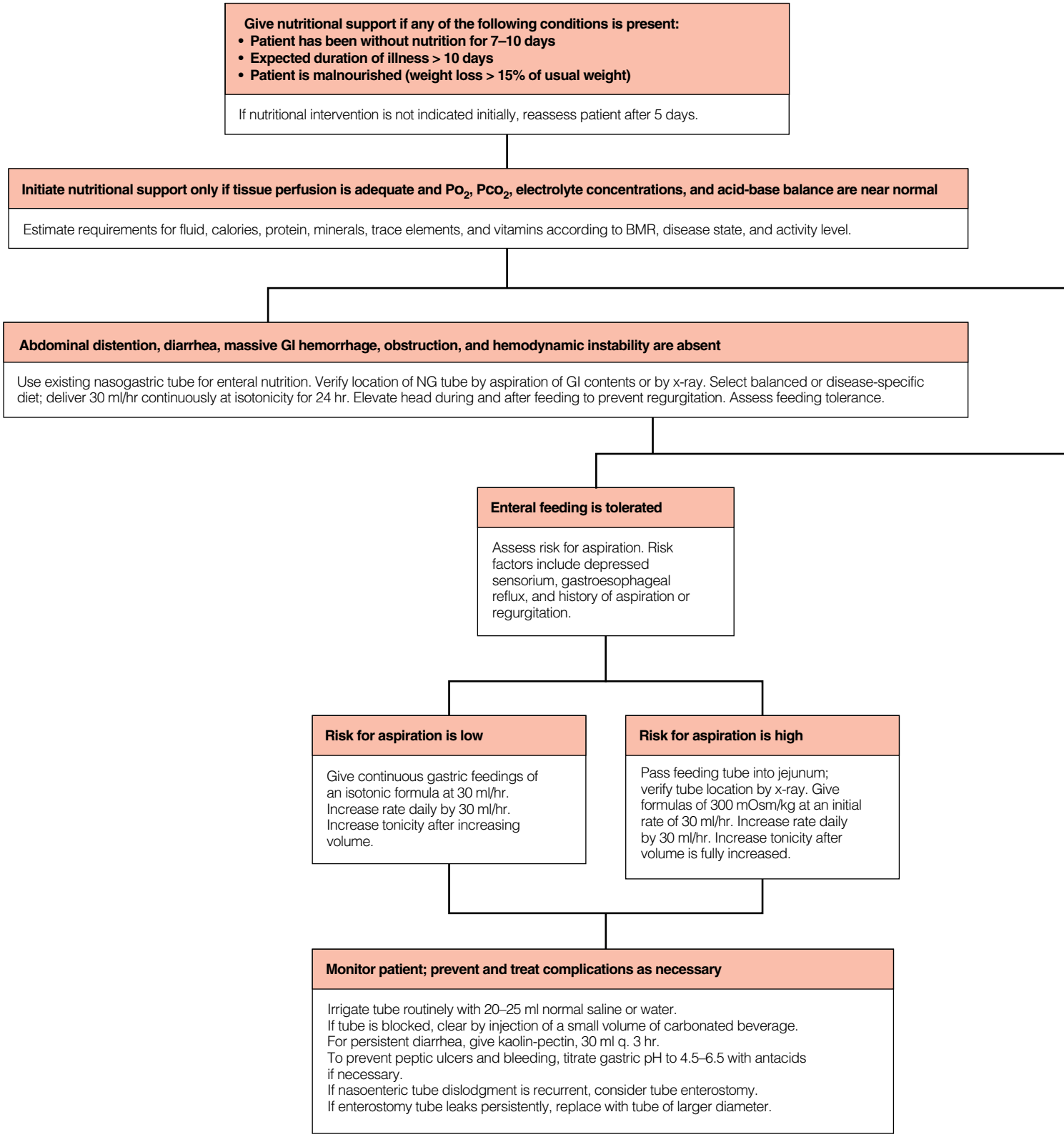
Figure 1 **The magnitude of weight loss is a rough predictor of its effect on clinical outcome.**

PRIORITY OF CARDIOPULMONARY FUNCTION



Intensive care unit patients are frequently candidates for nutritional support but often have complex medical and surgical problems that may take precedence. In decreasing order of importance, the priorities are to maintain airway patency, breathing, circulation, tissue oxygenation, acid-base neutrality, normal electrolyte concentrations, and adequate nutrition. The six functions that take priority over nutrition are usually impaired by acute and potentially life-threatening disorders that are often correctable over the short term. To optimize nutrient metabolism, circulation and tissue oxygenation must be adequate. In addition, hydrogen ion and electrolyte concentrations should be near normal in the extracellular fluid compartment, as reflected by blood or serum measurements.

If cardiopulmonary function is abnormal, nutrient administration may create additional problems. For example, in a patient with respiratory insufficiency, infusion of moderate quantities of carbohydrate could increase carbon dioxide tension (P_{CO_2}) and lower serum potassium concentration, thereby potentially initiating a life-threatening cardiac arrhythmia. The need for nutritional support in the ICU patient should always be evaluated with respect to other care problems; acute disorders of cardiorespiratory function, disturbed acid-base status, and altered electrolyte



Nutritional Management of Hospitalized Patients

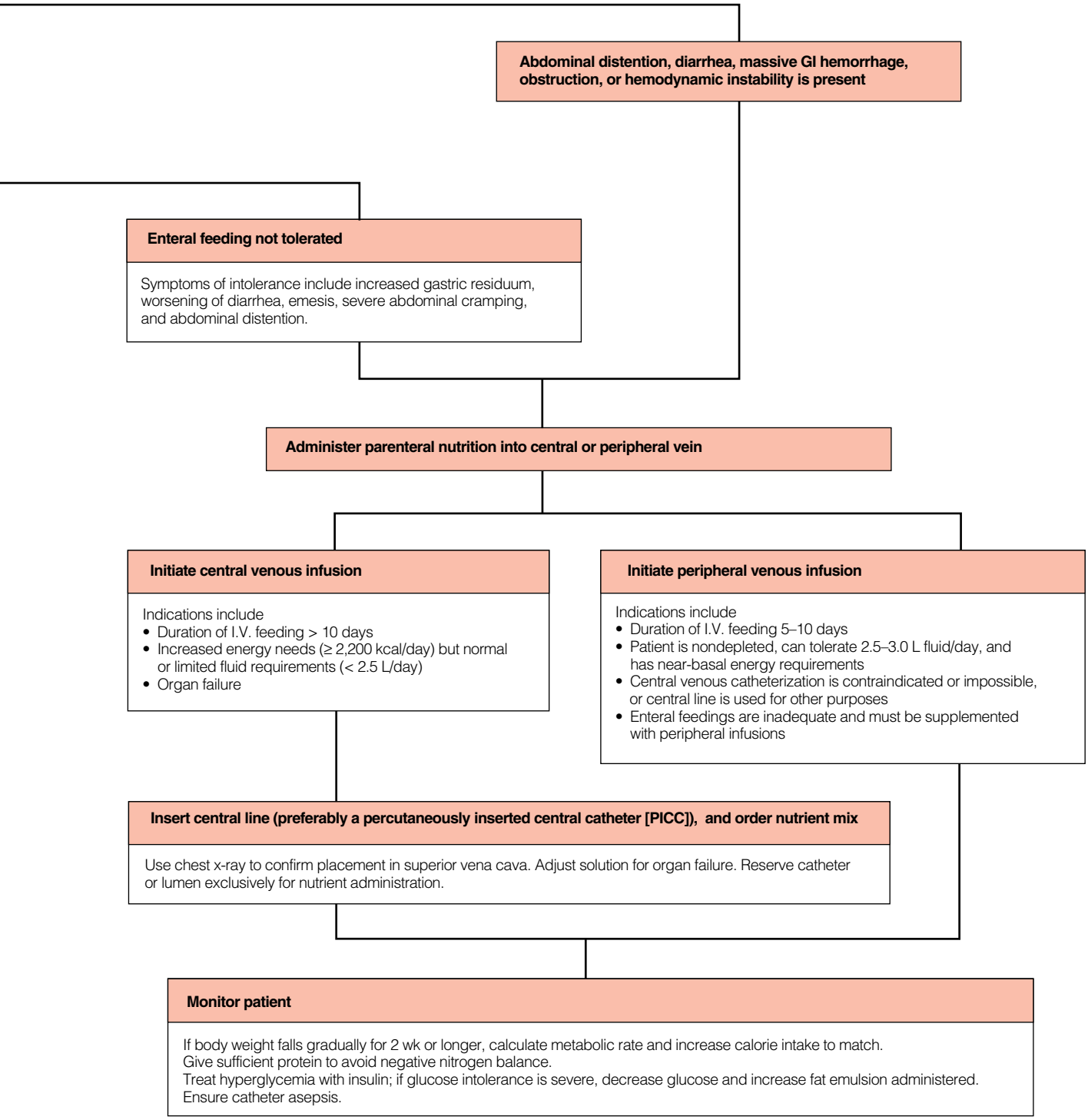


Table 1 Alterations in Metabolic Rate

Patient Condition	Basal Metabolic Rate
No postoperative complications Fistula without infection	Normal
Mild peritonitis Long-bone fracture or mild to moderate injury	25% above normal
Severe injury or infection in ICU patient Multiorgan failure	50% above normal
Burn of 40%–100% of TBS	100% above normal

concentrations should generally be corrected before nutritional support is initiated.

NUTRIENT REQUIREMENTS

Individual energy requirements are primarily related to body size, age, sex, and energy expenditure of activity (muscular work). In hospitalized patients who are generally inactive, the basal metabolic rate (BMR) accounts for the greatest amount of energy expenditure. The BMR in normal individuals is about 25 kcal/kg/day but can be calculated more precisely according to the Harris-Benedict formulas:

$$\text{Males: BMR (kcal/day)} = 66 + (13.7 \times \text{weight [kg]}) + (5 \times \text{height [cm]}) - (6.8 \times \text{age [yr]})$$

$$\text{Females: BMR (kcal/day)} = 665 + (9.6 \times \text{weight [kg]}) + (1.7 \times \text{height [cm]}) - (4.7 \times \text{age [yr]})$$

The BMR is influenced by the disease process. Hypermetabolism occurs in surgical patients with moderate to severe infection or injury, and the magnitude of the increase in the BMR depends on the extent of injury or infection. Patients generally fall into one of four categories according to their metabolic requirements [*see Table 1*].

Estimates that are based on normal basal metabolic requirements and adjusted only for disease state reflect the energy needs of patients requiring mechanical ventilation or those at bed rest. Further adjustments, however, are necessary for individuals who are out of bed and physically active. To meet the energy needs of such patients, who are in a nonbasal state, calculated requirements should be increased by an additional 15% to 20%. The metabolic response to stress and critical illness is complex and is mediated by interactions between the neuroendocrine system and circulating cytokines. This interaction produces a metabolic milieu in which the body cannot utilize supranormal amounts of nutritional substrates (i.e., hyperalimentation). In fact, administering excessive nutrients in an attempt at acute correction of nutrient deficits is often harmful, leading to an abnormal accumulation of hepatic glycogen, enhancing total energy expenditure, and causing increased urea production and elevation of the blood urea nitrogen (BUN).

Weight gain usually should not be a priority for ICU patients. Complications of nutrient delivery are minimized and nutrient metabolism generally optimized if only the energy necessary for weight maintenance is given. For most general surgical patients admitted to the ICU for non–trauma-related care, this amount is typically no more than 35 kcal/kg body weight/day. With resolution of the disease process, the hormonal environment is altered to favor anabolism. In addition, increases in spontaneous activity and in planned exercise stimulate rebuilding of lean body mass.

Protein

After energy requirements are determined, protein needs are calculated. For most patients, the protein requirement is 0.8 g/kg body weight/day (about 60 to 70 g/day). Critically ill patients, however, may need 1.5 to 2.0 g/kg/day (about 100 to 150 g/day). Most standard enteral and parenteral feeding mixtures provide this increased quantity of protein if enough formula is delivered to meet patients'

Table 2 Vitamin Requirements

Vitamin	Units	Recommended Dietary Allowance (RDA) for Daily Oral Intake	Daily Requirement of the Moderately Injured	Daily Requirement of the Severely Injured	Amount Provided by One Vitamin Pill	Daily Amount Provided by Standard Intravenous Preparations
Vitamin A (retinol)	IU	1,760 (females)–3,300 (males)	5,000	5,000	10,000	3,300 (retinal)
Vitamin D (ergocalciferol)	IU	200	400	400	400	200
Vitamin E (tocopherol)	mg TE	8–10	unknown	unknown	15	10 IU*
Vitamin K (phylloquinone)	µg	20–40†	20	20	0	0‡
Vitamin C (ascorbic acid)	mg	60	75	300	100	100
Thiamine (vitamin B_1)	mg	1.0–1.5	2	10	10	3.0
Riboflavin (vitamin B_2)	mg	1.2–1.7	2	10	10	3.6
Niacin	mg	13–19	20	100	100	40
Pyridoxine (vitamin B_6)	mg	2.0–2.2	2	40	5	4.0
Pantothenic acid	mg	4–7 (adults)†	18	40	20	15
Folic acid	mg	0.4	1.5	2.5	0	0.4
Vitamin B_{12}	µg	3.0	2	4	5	5
Biotin	µg	100–200†	unknown	unknown	0	60

*Equivalent to RDA. †Estimated to be safe and adequate dietary intakes. ‡Must be supplemented in peripheral venous solutions.

Table 3 Trace Mineral Requirements

Mineral	Recommended Dietary Allowance (RDA) for Daily Oral Intake (mg)	Suggested Daily Intravenous Intake (mg)	Daily Amount Provided by a Commercially Available Mixture (mg)
Zinc	15	2.5–5.0*	5.0
Copper	2–3†	0.5–1.5	1.0
Manganese	2.5–5.0†	0.15–0.8	0.5
Chromium	0.05–0.2†	0.01–0.015	0.1
Iron	10 (males)–18 (females)	3	—

*Burn patients require an additional 2 mg. †Estimated to be safe and adequate dietary intakes.

increased caloric requirements. The nitrogen-to-calorie ratio for most feeding formulas prepared for surgical patients is 1:150 (i.e., 1 g of nitrogen for every 150 kcal).

The contraindications to this increased quantity of protein are renal failure before dialysis (BUN > 40 mg/dl) and hepatic encephalopathy. Patients with systemic inflammatory response syndrome (SIRS) often require increased quantities of dietary protein [*see 8:13 Multiple Organ Dysfunction Syndrome*]. Nutritional support reduces net nitrogen losses in such patients, but positive or even neutral nitrogen balance is generally not achieved because of the disturbance in metabolism and reduced intake of dietary protein.

Vitamins and Minerals

The requirements for vitamins, minerals, and trace elements are usually met when adequate volumes of balanced nutrient formulas are provided [*see Tables 2 and 3*]. The requirements for most of the major minerals (sodium, potassium, chloride, phosphorus, magnesium, and zinc) are satisfied by monitoring serum concentrations of these elements and adjusting intake to maintain levels within the normal range. Some minerals and electrolytes are restricted in patients with renal failure. Although serum concentrations may not directly reflect total body deficits, sufficient quantities of these nutrients are available to support normal cellular functions if adequate blood concentrations are maintained. Most premixed enteral formulas provide adequate quantities of these substances if caloric needs are met. Vitamins and trace elements must be added to parenteral solutions.

Pharmacologic recommendations for stress in surgical patients The doses of vitamins given are often not the recommended dietary allowance (RDA) but rather some multiple thereof; for example, stressed patients usually receive three to 10 times the normal RDA.

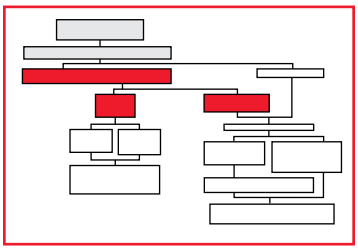
Table 4 Safety Levels of Vitamins[2]

Safety Level	Vitamin
At least 50 to 100 times RDA	Vitamin B_1 Vitamin B_2 Niacin Vitamin C Vitamin E Biotin Folic acid Pantothenic acid
10 times RDA	Vitamin A Vitamin B_6 Vitamin D Vitamin K

The prescription of vitamins and minerals for therapeutic use should be based on the patient's nutritional history as well as on estimated requirements for the current disease state. These considerations are particularly important for fat-soluble vitamins, which are stored in body fat and thus may become toxic at high levels. Current recommendations stipulate that therapeutic dosages of vitamins should not exceed 10 times the RDA[1]; however, it has been suggested that some vitamins may be safe if given at dosages 50 to 100 times the RDA [*see Table 4*].[2] Vitamins and minerals are sometimes given in large dosages to exert antioxidant effects. Vitamins A, C, and E and the minerals zinc and selenium can attenuate the tissue-damaging effects of free radicals. One randomized, prospective trial, primarily involving trauma patients, demonstrated a significant reduction in organ failure with the administration of vitamins C (1,000 mg) and E (1,000 IU).[3] Many physicians are giving these vitamins and minerals as supplements to injured and infected patients[4]; supplementation with glutamine should also be considered [*see* Discussion, *below*].

Electronic Ordering to Optimize Nutritional Support

In hospital settings, nutritional care is often standardized to optimize formula composition and delivery. A useful electronic approach to nutritional prescription is available on the Internet (http://epen.kumc.edu).



Enteral Nutrition

Enteral nutrition is the provision of liquid-formula diets by mouth or tube into the GI tract. It is the preferred method of feeding critically ill patients; however, it cannot be used safely in patients who are hemodynamically unstable or who have abdominal distention, intestinal obstruction, or massive GI bleeding [*see Table 5*]. For those who are able to receive enteral nutrition, either a balanced or a modified diet is selected on the basis of diagnosis and nutritional requirements. An isotonic (approximately 300 mOsm/kg) diet is given continuously for a trial period of 24 hours. If the patient tolerates this regimen but is at increased risk for aspiration, feeding is delivered into the jejunum rather than into the stomach. A standard protocol is helpful in reducing complications.

SAFE USE OF THE GI TRACT FOR FEEDING

Enteral nutrition should be prescribed only if safety and a low complication rate can be ensured. To determine whether enteral

Table 5 Indications for Enteral Nutrition (Partial Listing)

Considered Routine Care in the Following:
Protein-calorie malnutrition with inadequate oral intake of nutrients for the previous 5–7 days
Normal nutritional status but < 50% of required oral intake of nutrients for the previous 7–10 days
Severe dysphagia
Major full-thickness burns
Low-output enterocutaneous fistulas
Major trauma
Usually Helpful in the Following:
Radiation therapy
Mild chemotherapy
Liver failure and severe renal dysfunction
Massive small bowel resection (> 50%) in combination with administration of total parenteral nutrition
Of Limited or Undetermined Value in the Following:
Intensive chemotherapy
Immediate postoperative period or poststress period
Acute enteritis
> 90% resection of small bowel
Contraindicated in the Following:
Complete mechanical intestinal obstruction
Abdominal distention
Ileus or intestinal hypomotility
Severe diarrhea
Severe GI bleeding
High-output external fistulas
Severe, acute pancreatitis
Shock
Case of aggressive nutritional support not desired by the patient or legal guardian and respect of such wish being in accordance with hospital policy and existing law
Prognosis not warranting aggressive nutritional support

nutrition is feasible, a clinical assessment of intestinal function is performed. If GI output—defined as the volume of effluent from a nasogastric tube, an ostomy, or a rectal tube—is less than 600 ml/24 hr, enteral nutrition is likely to be well tolerated. Examples of conditions in critically ill patients that produce excessively high (> 600 ml/24 hr) GI outputs and therefore preclude the use of enteral nutrition are gastroparesis, intestinal obstruction, paralytic ileus, high-output enteric fistulas, antibiotic-induced colitis, severe idiopathic diarrhea, and the initial phase of short bowel syndrome. Selected patients with enteric losses exceeding 600 ml/24 hr may receive enteral nutrition, however, if carefully monitored by an experienced team.

Massive GI bleeding may also cause increased GI output. Conditions that produce bleeding of this magnitude include peptic ulcer disease, esophageal varices, diverticulosis, and angiodysplasia of the colon. Mild bleeding (e.g., that produced by stress gastritis) may actually resolve with the delivery of enteral nutrition into the stomach because the liquid diet buffers gastric acid.[5] Enteral nutrition does not exacerbate mild lower intestinal bleeding.

Although commonly used at the bedside as indicators of intestinal function, bowel sounds and passage of flatus are nonspecific and are unrelated to the eventual tolerance of enteral nutrition.

In the absence of excessively high GI output, abdominal distention, and massive GI bleeding, a trial of enteral nutrition is warranted to determine if the GI tract can be used safely for feeding.

SELECTION OF DIET

Before delivery of enteral nutrition, the appropriate diet must be selected on the basis of the patient's nutrient requirements [*see* Indications for Nutritional Intervention, *above*]. Most liquid-formula diets consist of either a balanced or a modified formula.

Balanced diets contain carbohydrates, proteins, and fats in complex (polymeric) forms in proportions similar to those of a regular Western diet. Frequently, however, the fat content is reduced to 10% to 15% of total calories, and the carbohydrate content is increased. Carbohydrates are present as oligosaccharides, polysaccharides, or maltodextrins; fats consist of medium-chain triglycerides (MCTs) or long-chain triglycerides (LCTs). The nitrogen source is a natural protein, which may be either intact or partially hydrolyzed. In general, balanced diets are isotonic, lactose free, and available in ready-to-use, liquid form. Flavored balanced diets can be used for oral supplementation as well as for enteral tube feeding.

Selection of a balanced diet is based on nutrient and fluid requirements. The caloric density of balanced diets can be 1.0, 1.5, or 2.0 kcal/ml; the largest number of commercially available diets provide 1.0 kcal/ml. Nonprotein caloric content is derived from either carbohydrates or lipids. Balanced diets formulated with carbohydrates as the main caloric source have higher osmolarity than isocaloric diets containing lipids. These carbohydrate-based diets are well tolerated when administered directly into the stomach and may be helpful for patients with steatorrhea. Fat-based balanced diets may be more appropriate for patients with diarrhea caused by diet hyperosmolarity, especially when feedings are infused directly into the small intestine. However, fat malabsorption is common in critically ill patients when the fat content of the diet exceeds 30% of total calories.

In modified formulas (also known as elemental or chemically defined diets), the proportions and types of nutrients differ from those of a regular Western diet. Such diets may be characterized according to the conditions for which they are formulated: stress, immunomodulation, and hepatic, renal, respiratory, or GI dysfunction [*see Table 6*]. Modified diets contain crystalline amino acids or short peptides in compositions that differ from the reference composition of proteins of high biologic value (e.g., egg albumin). The fat-to-carbohydrate ratio of modified diets varies depending on the purpose of the modification. The source of carbohydrate is either dextrose or oligosaccharides; fats are usually in the form of MCTs, essential fatty acids, or both. Because they are not palatable, modified diets are rarely used as oral supplements.

Diets for patients with GI dysfunction have modified nitrogen and fat composition. Transport of dietary nitrogen across the intestinal mucosa is enhanced when nitrogen is provided in the form of short peptides rather than free amino acids. It is also well documented that small bowel mucosa utilizes glutamine as the preferred fuel [*see* Discussion, *below*]. Consequently, some modified diets contain nitrogen in the form of short peptides, whereas others contain extra glutamine. MCTs are more easily absorbed and metabolized than LCTs are; accordingly, diets modified for improved absorption contain a higher proportion of MCT oil. These diets may be efficacious when used during the transition phase after a period of prolonged bowel rest or when the intestine is inflamed. Controlled trials are necessary to verify their clinical efficacy. Stress formulas are indicated for hypercatabolic patients whose nitrogen balance continues to be negative despite increased intake of a balanced diet; these diets usually contain more nitrogen and frequently have an altered amino acid composition. Little evidence supports the use of diets that provide branched-chain amino acids (BCAAs) in concentrations higher than 20% to 25% of total amino acid content for stressed patients.

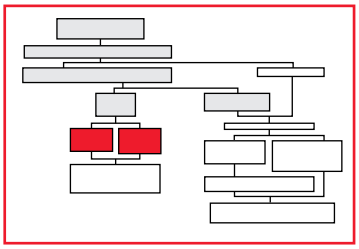
The fat sources used for enteral diets are primarily omega-6 fatty acids [*see 8:26 Molecular and Cellular Mediators of the Inflammatory Response*]. Supplementation with omega-3 fatty acids results in the synthesis of eicosanoids that enhance the immune response. Enteral diets may also include other substances believed to have immunomodulatory effects [*see* Discussion, *below*].

ASSESSMENT OF FEEDING TOLERANCE

The selected formula is started at isotonicity and delivered continuously at 30 ml/hr for 24 hours. During this initial trial, the formula is delivered via a previously inserted Salem sump or rubber nasogastric (Levin) tube. If a nasogastric tube is not already in place, a soft tube made of either silicone rubber or polyurethane is inserted (see below).

Feeding tolerance is assessed for the first 24 hours. Poor tolerance is indicated by vomiting and severe abdominal cramps, a gastric residuum greater than 50% of the volume administered during the previous 4-hour feeding period, increased abdominal distention (particularly in patients who are comatose or undergoing mechanical ventilation), and worsening diarrhea. If any of these conditions is present, parenteral nutrition is recommended. If there is no evidence of feeding intolerance, the patient is assessed for the aspiration risk.

ASSESSMENT OF RISK OF ASPIRATION



Aspiration is a major complication in patients receiving enteral nutrition. The propensity to aspirate enteral feedings is often related to the patient's primary disease and neurologic status as well as to the site of GI access and the method of delivery.

Important factors in assessing risk of aspiration include depressed sensorium, increased gastroesophageal reflux, and history of previously documented episodes of aspiration. Depressed sensorium in the critical care setting is secondary to organic lesions of the central nervous system, metabolic encephalopathies, or medications. Head trauma, hypoxemia, hepatic and septic encephalopathies, and the use of H_2 receptor blockers are common causes of depressed sensorium in critically ill patients. Increased gastroesophageal reflux may be present in individuals with reduced lower esophageal sphincter (LES) pressure and increased intragastric pressure. Many medications used in the ICU, such as theophylline, anticholinergics, calcium channel blocking agents, beta-adrenergic agonists, and alpha-adrenergic antagonists, cause a reduction in LES pressure. Finally, a history of aspiration places the patient at increased risk for recurrent episodes.

For most enterally fed patients, safety demands that the head be elevated at feeding time and for some period thereafter to prevent regurgitation. If this is not possible, an alternative nutrient delivery site should be considered. Nasogastric intubation, in particular, requires elevation of the head because the tube may render the upper and lower esophageal sphincters incompetent and liable to reflux. Even the presence of a tracheostomy or endotracheal tube does not ensure that regurgitated gastric contents will not be aspirated. Aspiration of liquid formulas can be verified if a bit of food coloring or methylene blue is included in the feeding mixture and subsequently detected in pharyngeal and tracheal secretions.[6]

ACCESS FOR FEEDING

In most general and thoracic surgical patients, access for feeding is most commonly obtained via the stomach or the jejunum. Methods of access for intragastric feedings include nasogastric tubes and feeding gastrostomies placed through a laparotomy or percutaneously with the aid of endoscopy, fluoroscopy, or laparoscopy.

Nasogastric tubes are the most commonly used access method for gastric feeding. Polyurethane or silicone rubber tubes are preferred because they are soft, nonreactive, and generally well tolerated; they are also less corrosive to the nasopharynx than rubber or polyvinyl chloride tubes. This very softness, however, often makes them hard to insert into critically ill patients and precludes checking of gastric residuum. Difficulties of tube passage into the stomach are increased when thin, floppy tubes are inserted into obtunded patients. Useful aids include stylets, judicious use of gravity and positioning, and designation of especially experienced and certified nursing personnel to assist in this task [*see Table 7*].

Passage of a tube through the pylorus into the jejunum may be necessary if the patient is at increased risk for aspiration (see above). Our practice is to place the tube into the stomach, to position the patient on the right side for several hours once or twice in the next 24 hours, and then to obtain an abdominal roentgenogram. If the tube has not passed, metoclopramide, 10 mg I.V., is given while the patient is still in the radiology department, and the roentgenogram is repeated. If the location of the feeding tube is not evident, a small amount of contrast material can be administered through the tube to verify its position. If the tube still has not passed through the pylorus, the aid of the fluoroscopist is enlisted. Finally, if all else has failed and no alternative route is appropriate, the endoscopist can capture the

Table 6 Composition of Modified Diets

Formula	Protein (g/L)	Carbohydrate (g/L)	Fat (g/L)	Ratio of Nitrogen (g) to Nonprotein Calories (kcal)	Caloric Density (kcal/ml)	Product* (Manufacturer)
Elemental	50	127	34	1:100	1.0	Subdue (Mead Johnson Nutritionals)
	40	127	39	1:131	1.0	Peptamen (Nestlé Clinical Nutrition)
Stress	56	130	28	1:71	1.0	Impact (Novartis)
	66	177	37	1:97	1.3	Perative (Ross Laboratories)
Hepatic	44	168	36	1:148	1.2	Hepatic Aid II (B. Braun Medical Inc.)
Renal	19	365	46	1:800	2.0	Amin-Aid (R&D Laboratories)

*Partial listing.

Table 7 Procedure for Inserting Nasoenteric Tubes

Provide privacy.
Explain procedure and its purpose.
Place patient in sitting position with neck flexed slightly and head of bed elevated to 45°.
Lubricate stylet and insert into feeding tube.
Inspect nares and determine optimal patency by having the patient breathe through one nostril while the other is temporarily occluded.
Estimate the length of tubing required to reach into the stomach by measuring the distance from the tip of the nose to the earlobe and then from the earlobe to the xiphoid process. Add 25 cm to this length for nasoduodenal intubation.
If the patient seems uncooperative, instill generous amounts of lidocaine jelly into the nares and nasopharynx before tube insertion. Lubricate the end of the tube and pass it posteriorly. Ask a cooperative patient to swallow water to facilitate passage of the tube.
Once the tube is beyond the nasopharynx, allow the patient to rest.
Have the patient continue neck flexion and swallowing while the tube is advanced.
If the patient begins to cough, withdraw the tube into the nasopharynx and then reattempt passage.
Confirm passage into the stomach by obtaining an abdominal x-ray.
Remove stylet.
Secure tube to bridge of nose or upper lip with nonallergenic tape and prevent undue pressure on external nares.

tube tip in the stomach with the biopsy forceps of the flexible endoscope (aided by a suture through the tube end) and guide the tube through the pylorus.

When any type of nasoenteric tube is placed for enteral nutrition, its location must be confirmed before feedings are started. The simplest means of accomplishing this is to aspirate gastric contents, the source of which can be determined by measuring the pH of the aspirate. Because small-bore, soft tubes tend to collapse under high negative pressure, a small syringe should be used to aspirate gastric contents. If gastric contents cannot be aspirated, radiographic confirmation of tube location is mandatory. Because feeding tubes are often radiopaque, a simple plain film of the abdomen may be adequate. If the exact location of the tube is still in doubt, a small amount of contrast material can be injected through the tube. Placement of the distal tip of the tube in the duodenum is usually confirmed by abdominal roentgenogram before transpyloric feedings are started. The tube should be inserted to a length sufficient to permit migration into the proximal jejunum.

Simple insufflation of air into the tube is not sufficient to verify its position. Auscultation over the stomach can detect sound transmitted through a tube that has been inadvertently passed into the bronchial tree. Many of these tubes are small enough to pass through the glottis and the trachea without markedly interfering with phonation or respiration. Enteral formulas delivered into the bronchial tree through a misplaced tube can cause severe pneumonitis and death.

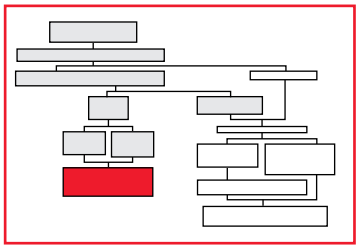
The development of percutaneous techniques for the placement of gastrostomies has been a major contribution to enteral nutrition. Percutaneous endoscopic gastrostomy (PEG) [*see 5:18 Gastrointestinal Endoscopy*] and Witzel techniques for these procedures are well documented.

Concurrent decompression of the stomach and feeding into the small intestine have been used to reduce the risk of aspiration in critically ill patients. This combination of procedures requires either insertion of a multilumen nasojejunal tube, surgical placement of combined gastrojejunal tubes, modification of PEG, or insertion of a nasogastric tube in conjunction with a surgical jejunostomy. Such access to the GI tract also provides a route for the delivery of crushed medications and the option to provide cyclic nocturnal enteral nutrition with gastric decompression (i.e., the patient receives nutrients by mouth during the day).

FEEDING REGIMENS

If the patient tolerates the initial trial of enteral nutrition, then the delivery site for future feeding is chosen according to the risk of aspiration, and the feeding regimen is gradually intensified. If the risk of aspiration is minimal, intragastric feedings are preferred: they are better tolerated physiologically, easier to administer, and less restrictive for the patient than continuous feeding into the small intestine. Patients fed into the stomach receive an isotonic formula delivered continuously at a rate of 30 ml/hr; the delivery rate is increased daily by 30 ml/hr [*see Table 8*]. If the risk of aspiration is increased, feedings are delivered via nasoduodenal or nasojejunal tubes. Patients fed into either the duodenum or the jejunum receive formulas of 300 mOsm/kg delivered at an initial rate of 30 ml/hr with the aid of a peristaltic pump; the rate is increased daily by 30 ml/hr [*see Table 8*]. Only isotonic feedings should be administered into the small bowel: hypertonic formulations have been associated with small bowel injury and necrosis.

MONITORING AND PREVENTION OF COMPLICATIONS



Patients receiving enteral nutrition require careful monitoring similar to that required by patients receiving parenteral nutrition. Particular attention is directed to metabolic status and fluid and electrolyte balance. A protocol should be established and followed to ensure that nutritional goals are met and complications minimized. A standard checklist is helpful and prevents omission of important details [*see Table 9*].

Four types of complications are related to enteral nutrition: GI, mechanical, metabolic, and infectious. The first two are the most common.

The most frequent GI complication is diarrhea, which may occur in as many as 75% of critically ill patients receiving enteral nutrition. Diarrhea is best defined as stool weight greater than 300 g/24 hr or volume greater than 300 ml/24 hr. Given that such measurements are impractical and difficult to obtain, a more practical definition is more than three loose bowel movements during a 24-hour period. There are many causes of diarrhea in critically ill patients receiving enteral nutrition; the most frequent association is with antibiotic therapy [*see Figure 2*]. The desired therapeutic approach is to adjust the enteral nutrition regimen as necessary

Table 8 Suggested Starter and Advancement Regimens for Intragastric and Intrajejunal Feeding

Feeding Regimen	Days			
	1	2	3	4
Intragastric				
mOsm/kg	300	300	300	480
ml/hr	30	60	90	90
Intrajejunal				
mOsm/kg	300	300	300	300
ml/hr	30	60	90	90

Table 9 Standard Orders for Enteral Nutrition

Obtain abdominal x-ray to confirm tube location before feeding.
Elevate head of bed 45° when feeding into the stomach.
Record type and strength of diet and rate of infusion.
Check gastric residuum every 4 hr in patients receiving gastric feedings. Withhold feedings for 4 hr if residuum is 50% greater than ordered volume. Notify physician if two consecutive measurements detect excessive residuum.
Check for abdominal distention. Check frequency, consistency, and volume of stool output.
Weigh patient on Monday, Wednesday, and Friday. Record weight on graph.
Record intake and output daily. For every shift, chart volume of formula administered separately from water or other oral intake.
Change administration tubing and cleanse feeding bag daily.
Irrigate feeding tube with 20 ml of water at the completion of each intermittent feeding, when tube is disconnected, after the delivery of crushed medications, of if feeding is stopped for any reason.
When patient is ingesting oral nutrients, ask the dietitian to provide calorie counts daily for 5 days, then weekly thereafter.
On a weekly basis, obtain complete blood count with red blood cell indices, SMA-12, serum iron, and serum magnesium.
Obtain SMA-6 every Monday and Thursday.
Once a week, collect urine for 24 hours, starting at 8:00 A.M., and analyze for urea nitrogen.

rather than to discontinue it completely. Only one variable of the feeding regimen (i.e., osmolality, volume, rate, or type of diet) should be altered at a time. In our experience, critically ill patients tolerate continuous feeding better than intermittent feeding. If the patient still has diarrhea when receiving 150 to 300 mOsm/kg at 30 ml/hr, antidiarrheal treatment is indicated.

In many instances, antidiarrheal medication is given without a definite diagnosis; therefore, it is essential to select medications with both a wide therapeutic range and a low incidence of side effects. For these reasons, we prefer kaolin-pectin over opiates such as paregoric. Every 3 hours, 30 ml of kaolin-pectin solution is given through the feeding tube, followed by 25 ml of normal saline for irrigation. If this regimen is unsuccessful after 48 hours and opiates are not contraindicated, paregoric is added at a dose of 1 ml/100 ml formula [*see Figure 2*]. Opiates act by slowing intestinal motility. Because the normal motility pattern is a defense against bacterial growth in the small bowel, administering opiates to patients with a contaminated small bowel can lead to bacterial overgrowth and worsen diarrhea. In addition, opiates are respiratory depressants and are contraindicated in patients with infectious diarrhea.

Several diagnostic methods may help identify the cause of diarrhea associated with enteral nutrition, including the assaying of stool for *Clostridium difficile* enterotoxin, analysis of stool for fat malabsorption, the D-xylose test for carbohydrate malabsorption, and breath H_2 analysis for bacterial overgrowth. The D-xylose test and breath H_2 analysis are more commonly used in non–critically ill patients.

To prevent peptic ulcers and bleeding, gastric acidity is controlled with H_2 receptor blockers in critically ill patients. Although these drugs help control hyperacidity, which is a cause of diarrhea, they also lead to bacterial overgrowth in the intestine.[7] Therefore, they should not be used in patients who receive intragastric feedings, because the liquid formula in the stomach already provides a physiologic means of buffering acid. If necessary, antacids rather than H_2 receptor blockers should be used to titrate gastric pH to 4.5 to 6.5. Glutamine is also used to prevent or treat ulceration of the upper GI tract.

The most common mechanical complications related to enteral nutrition are tube dislodgment, clogging of the tube, and leakage of enteric contents around the tube's exit site. Tube dislodgment occurs more frequently in agitated patients and hypoxic patients. Inadvertent tube removal can usually be prevented by adequate taping or, in agitated patients, by suturing the tube or using a Velcro abdominal wall binder.

Clogging or plugging of the tube often results from failure to use saline irrigation after intermittent feedings or inadvertent delivery of crushed medications through a small-bore tube. The incidence of this complication is reduced by routine irrigations of 20 to 25 ml of normal saline or water after each intermittent feeding. Liquid medications may also help prevent this complication, though such medications are frequently hyperosmolar and may produce discomfort

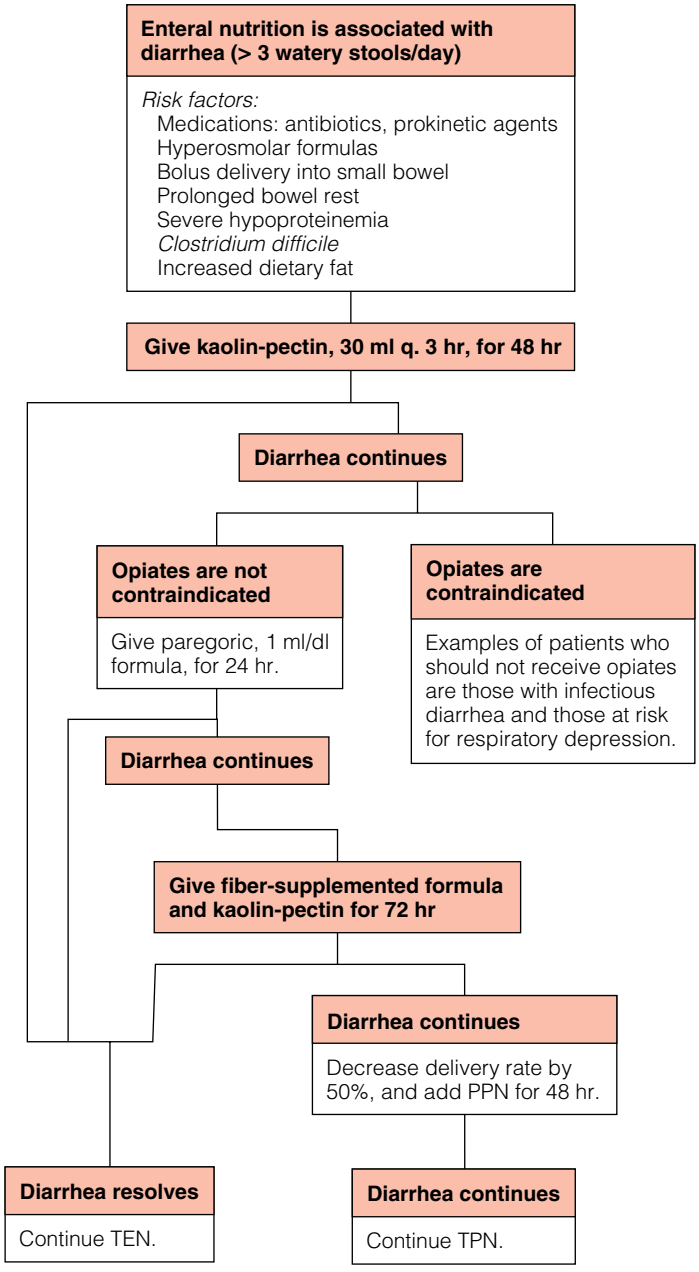
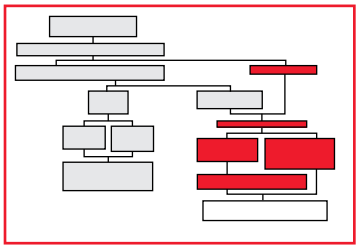


Figure 2 **Shown is the decision-making approach for pharmacologic and dietary treatment of diarrhea associated with enteral nutrition.**

and diarrhea when delivered rapidly into the jejunum. The injection of a small volume of a carbonated beverage into a plugged tube often clears the blockage. Occasionally, a guide wire and the help of the interventional radiologist will be needed.

Leakage of enteric contents onto the skin around the exit site is often uncomfortable for the patient and may produce a moderate amount of skin irritation. One cause of such leakage is inadequate approximation of the end of the tube to the gastric wall. Leakage around a tube is prevented by proper fixation of the end of the tube with a retention disk or bumper at the skin level. The aid of an enterostomal therapist is often useful, as are products such as karaya gum, zinc oxide, Stomahesive, and locally applied antacid. Also problematic is the inappropriate use of urinary catheters for enteral access; these devices were not designed to function as gastrostomy or enterostomy tubes.

Parenteral Nutrition



CENTRAL VENOUS VERSUS PERIPHERAL VENOUS INFUSIONS

Central venous infusions [*see 6:22 Vascular and Peritoneal Access*] are indicated in most critically ill patients who receive parenteral nutrition, because (1) patients in the ICU often require increased quantities of energy and cannot tolerate large fluid volumes and (2) solutions of much greater caloric density and tonicity can be infused into central veins than into peripheral veins. Nonetheless, peripheral venous infusions [*see* Peripheral Venous Nutrient Infusion, *below*] may be indicated in certain situations [*see Table 10*].

CENTRAL VENOUS NUTRIENT INFUSION

Hypertonic nutrient solutions are infused into the superior vena cava, where they are rapidly diluted. Usually, such solutions contain hypertonic glucose (25%), amino acids (5%), and other essential nutrients. Their tonicity (> 1,900 mOsm/kg) is so great that administration into peripheral veins would cause severe thrombophlebitis and venous sclerosis. These solutions contain at least 1 kcal/ml, and thus, infusion of 2.0 to 2.5 L/day provides 2,000 to 2,500 kcal and all essential nutrients. This calorie load is sufficient to meet energy requirements in more than 90% of surgical patients.

Once positioned, the catheter is used exclusively for administering the hypertonic nutrient solution: drawing blood, monitoring central venous pressure, and administering medication through this dedicated lumen are to be avoided. If a multiple-lumen central venous catheter is used, as is the case in most patients today, at least one port should be devoted solely to the infusion of hypertonic nutrient solutions. Some reports have suggested that the incidence of catheter-related infection is higher with multiple-lumen than with single-lumen feeding catheters[8,9]; others have not found such differences.[10] It appears that multiple-lumen catheters can be used in the ICU for central venous nutrient infusions if strict protocols are maintained to ensure that one lumen is dedicated to nutrient infusion, that other lumens are handled safely, and that catheters are removed when no longer required.

Occasionally, infusion of a hypertonic nutrient solution may be required in a situation where percutaneous puncture of central veins is impossible or contraindicated. In such cases, catheterization of an antecubital vein and insertion of a peripherally inserted central catheter (PICC) with the tip positioned in the superior vena cava should be considered. These catheters are readily inserted by the interventional radiologist, and they eliminate the complications associated with subclavian and internal jugular vein insertions. The PICC line has become the primary route of central venous access in many institutions.

Silastic catheters have been safely kept in place for extended periods and provide an additional option for central venous access. Catheterization of the femoral vein may provide a route for central venous access in some situations. Because of the high density of skin pathogens in the groin area, these catheters should be replaced every 2 to 3 days. If the catheter tip is positioned in the iliac vein or the inferior vena cava, the concentration of solution infused through the catheter should not exceed 15%. Strict care of the entrance site should be maintained because of the high complication rate associated with lines placed in the groin.

Central Venous Solutions

Central venous solutions are formulated in the hospital pharmacy. They are commonly combinations of 500 ml of 50% dextrose and 500 ml of a 10% amino acid mixture [*see Table 11*] to which electrolytes, vitamins, and trace elements are added (see below). Each day, 2 L of the solution can be infused. Administration of fat emulsion (500 ml, 20%) 1 day each week meets essential fatty acid requirements. Alternatively, the three major nutrients may be mixed together in a 3 L bag (triple mix or three-in-one) and the entire contents of the single bag infused over the 24-hour period [*see Table 11*]. In addition, an automated mixing device may be used to compound various proportions of 70% glucose, 10% amino acids, and 20% fat emulsions into 3 L bags. Such devices allow the hospital pharmacy to manufacture a variety of nutrient combinations with minimal effort. More concentrated solutions can be made, and the computer will generate a label for the bag that allows nurses to verify the order.

Electrolytes and minerals are added to the base formula as required [*see Table 12*]. Sodium and potassium salts are added as chloride or acetate, depending on the acid-base status of the patient. The solution should usually consist of approximately equal quantities of chloride and acetate; if chloride losses from the body are increased, as in a patient requiring nasogastric decompression, the solution should contain proportionately more chloride. Sodium bicarbonate is incompatible with the nutrient solutions; if additional base is re-

Table 10 Indications for Central Venous or Peripheral Venous Infusions

Central Venous Infusions

- To provide adequate intravenous nutritional support for 10 days or more
- To satisfy nutrient requirements in patients with increased energy needs and normal or decreased fluid requirements
- To support the patient with single- or multiple-organ failure by infusing modified nutrient solutions in a limited fluid volume

Peripheral Venous Infusions

- To provide initial feeding (< 5 days) before catheter insertion in a patient who will require central venous feedings
- To infuse less concentrated solutions via a multiuse central catheter (i.e., a line for blood drawing, medication, and nutrients) into an individual in whom other venous access cannot be easily or safely obtained
- To supplement enteral feedings that are inadequate because of gastrointestinal dysfunction
- To satisfy energy requirements that are near basal (1,500–1,800 kcal/day) in a nondepleted patient who can tolerate 2.5–3.0 L I.V. solution each day

Table 11 Composition of Central Venous Solutions

	Standard Solution	Triple-Mix Solution
Volume		
Amino acids 10% (ml)	500	1,000
Dextrose 50% (ml)	500	1,000
Fat emulsion 20% (ml)	—	250
Total (ml)	1,000	2,250
Contents		
Amino acids (g)	50	100
Dextrose (g)	250 (25%)	500
Total nitrogen (g)	8.4	16.8
Total calories (kcal)	1,050	2,600
Ratio of nitrogen to calories	1:125	1:154
Caloric density (kcal/ml)	1.0	1.15
Osmolarity (mOsm/kg)	≈1,970	≈1,900

quired, acetate, which generates bicarbonate when metabolized, is given. Phosphate is usually given as the potassium salt; if potassium phosphate is contraindicated, sodium phosphate is given. Phosphate is also present in fat emulsions.

Commercially available preparations of vitamins, minerals, and trace elements are also added to the nutrient mix for daily administration unless they are contraindicated. A solution containing both fat- and water-soluble vitamins should be added. Vitamin K_1 (phytonadione), 10 mg, is given once a week but is contraindicated in patients receiving warfarin.

Trace elements are given daily. Usual requirements are satisfied by adding commercially available mixtures either to 1 L of standard solution or to the triple-mix bag each day. Trace elements are indicated for all patients receiving central venous nutrient solutions, except those with chronic renal failure or severe liver disease. At especially high risk for zinc deficiency are alcoholics and patients with pancreatic insufficiency with malabsorption, massive small bowel resection, renal failure with dialysis, or nephrotic syndrome; at high risk for copper deficiency are patients with short-bowel syndrome, jejunoileal bypass, malabsorptive conditions with severe diarrhea, or nephrotic syndrome. Copper and manganese are excreted primarily via the biliary tract. Therefore, in patients with biliary tract obstruction, excess retention of these elements should be prevented by decreasing intake of these ions, monitoring blood levels, or both. Although the main excretory route for zinc and chromium is via the feces, renal excretion minimizes dangers from modest excesses of these elements. In patients with renal insufficiency, however, daily zinc and chromium administration may be contraindicated. ICU patients usually do not require iron. Iron supports bacterial growth and thus is contraindicated in patients with systemic infection. It may be required to treat iron deficiency anemia, particularly during convalescence from this condition, but rarely does the anemia associated with chronic disease and inflammation respond to iron therapy during its active stages.

Table 12 Electrolytes Added to Central Venous Solutions

	Usual Electrolyte Concentration	Usual Range of Electrolyte Concentration
Sodium (mEq/L)	30	0–150
Potassium (mEq/L)	30	0–80
Phosphate (mmol/L)	15	0–20
Magnesium (mEq/L)	5	0–15
Calcium* (mEq/L)	4.7	0–10
Chloride (mEq/L)	50	0–150
Acetate (mEq/L)	70	70–220

*As gluconate.

Like other invasive therapies, total parenteral nutrition (TPN) is associated with potential complications deriving from either central venous access or the composition of the formula. Most such complications are preventable with appropriate attention to detail [*see Table 13*].

PERIPHERAL VENOUS NUTRIENT INFUSION

Slightly hypertonic nutrient solutions (approximately 600 to 900 mOsm/kg) can be prepared for peripheral venous infusion from commercially available amino acid mixtures (5%), dextrose solutions (10%), and fat emulsions (20%). These nutrient mixtures have a low caloric density (approximately 0.3 to 0.6 kcal/ml) and thus provide only 1,200 to 2,300 kcal in 2,000 to 3,500 ml of solution. Such solutions are particularly useful in patients whose tube feedings are insufficient and who need additional nutrients.

These dilute nutrient mixtures can be infused through plastic cannulas placed in large-bore peripheral veins. The catheter insertion site and the surrounding tissue should be inspected periodically for signs of phlebitis or infiltration, and the infusion site should be rotated every 48 to 72 hours to prevent thrombophlebitis. Only fat emulsion can be administered simultaneously through the same I.V. site as a peripheral venous solution. The nutrient solution should be temporarily stopped if the catheter is used for administration of antibiotics, chemotherapeutic agents, blood, or blood products. The infusion line should then be flushed with saline and nutrient infusion resumed.

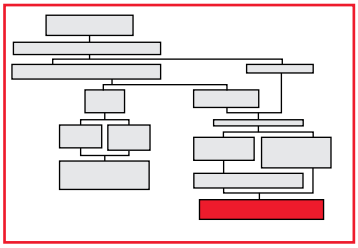
If the fat emulsion is infused in a piggyback manner, administration should take place over a period of 8 to 12 hours and be concluded in the early morning hours (e.g., 3:00 A.M.) to allow clearance of the emulsion from the bloodstream. Blood sampling should be avoided during short-term fat infusion because the associated hypertriglyceridemia will interfere with many of the serum measurements. In patients who are receiving peripheral venous solutions by triple mix, hypertriglyceridemia is rare because the rate of infusion is reduced and infusion extended over a 24-hour period.

Patients receiving peripheral venous feedings should be monitored in much the same fashion as those receiving central venous feedings (see below). Mechanical and infectious complications are uncommon. Fluid imbalances and alterations in serum electrolyte concentrations are similar to those seen with standard I.V. support, and corrections are made by altering the volume of the infusion or adding or omitting electrolytes. Hyperglycemia and glycosuria are rarely observed unless the patient is diabetic.

Table 13 Diagnosis, Treatment, and Prevention of Potential Mechanical and Metabolic Complications Associated with Total Parenteral Nutrition

	Complications	Diagnosis	Treatment	Prevention
Mechanical	Pneumothorax	Dyspnea, chest x-ray	Tube thoracostomy Observation	Avoid emergency procedures Trendelenburg's position
	Hemothorax	Dyspnea, chest x-ray	Remove catheter Observation	Insert catheter using appropriate technique
	Venous thrombosis	Inability to cannulate	Remove catheter Heparin therapy	Use silicone catheters Add heparin to solution
	Air embolism	Dyspnea, cyanosis, hypotension, tachycardia, precordial murmur	Trendelenburg's position Left lateral decubitus position	Trendelenburg's position Valsalva maneuver Tape intravenous connections
	Catheter embolism	Sheared catheter	Fluoroscopic retrieval	Never withdraw catheter through needle
	Arrhythmias	Catheter tip in right atrium	Withdraw catheter to superior vena cava	Estimate distance to SVC before insertion; confirm position with x-ray
	Subclavian artery injury	Pulsatile red blood	Remove needle Apply pressure Chest x-ray	Review anatomy
	Catheter tip misplacement	Chest x-ray	Redirect with a guide wire	Direct bevel of needle caudally
Metabolic	Hyperglycemic, hyperosmolar, nonketotic coma	Dehydration with osmotic diuresis, disorientation, lethargy, stupor, convulsions, coma, glucose 1,000 mg/dl, osmolarity 350 mOsm/kg	Discontinue TPN; infuse D5 in 0.45% S at 250 ml/hr Insulin 10–20 U/hr Bicarbonate Monitor glucose, potassium, pH	Monitor glucose
	Hypoglycemia	Headache, sweating, thirst, convulsions, disorientation, paresthesias	D50W I.V.	Taper TPN by ½ for 12 hr; then 12 hr of D5W at 100 ml/hr
	CO_2 retention	Ventilator dependence, high respiratory quotient	Taper glucose	Provide 30%–40% of calories with fat
	Azotemia	Dehydration, elevated BUN	Increase nonprotein calories	Monitor fluid balance
	Hyperammonemia	Lethargy, malaise, coma, seizures	Discontinue amino acid infusions Infuse arginine	Avoid casein or fibrin hydrolysate
	Essential fatty acid deficiency	Xerosis, hepatomegaly, impaired healing, bone changes	Fat administration	Provide 25–200 mg/kg/day of essential fatty acids
	Hypophosphatemia	Lethargy, anorexia, weakness	Supplemental phosphate	Treat causative factors: alkalosis, gram-negative sepsis, vomiting, malabsorption Provide 20 mEq/kcal
	Abnormal liver enzymes	Fatty infiltrate in liver	Evaluate for other causes	Provide balanced TPN solution
	Hypomagnesemia	Weakness, nausea, vomiting, tremors, depression, hyporeflexia	Infuse 10% $MgSO_4$	Supply 0.35–0.45 mEq/kg/day
	Hypermagnesemia	Drowsiness, nausea, vomiting, coma, arrhythmia	Dialysis Infuse calcium gluconate	Monitor serum levels

PATIENT MONITORING: OPTIMIZING NUTRITIONAL SUPPORT, PREVENTING COMPLICATIONS, AND RESOLVING COMMON PROBLEMS



General Measures

Patients receiving central venous feedings should be weighed daily, and accurate intake and output records should be maintained. Blood glucose should be monitored daily. If levels are persistently elevated, a more stringent schedule of monitoring blood glucose should be instituted and specific therapy initiated.

The quantity of energy administered to most ICU patients should minimize the loss of lean body mass and adipose tissues. Thus, variations in body weight usually reflect alterations in fluid balance. If sustained weight loss occurs (as characterized by a gradual fall in body weight over a period of 2 weeks or more), caloric intake may be inadequate. Additional calories (500 to 1,000 kcal/day) should be administered to maintain weight. Alternatively, the metabolic rate can be calculated from oxygen consumption ($\dot{V}O_2$) and calorie intake, then matched to equal energy expenditure:

$$\text{Metabolic rate (kcal/hr)} = \dot{V}O_2 \text{ (ml/min)} \times 60 \text{ min/hr} \times 1 \text{ L/1,000 ml} \times 4.83 \text{ kcal/L}$$

This calculation is required in only 5% of our patients.

Sample Calculation of Nitrogen Balance

A 65-year-old man with an infected aortic graft and ileus is receiving 2.2 L triple-mix solution containing 16.8 g nitrogen each day. His UUN is 500 mg/dl, and his urine output is 2,000 ml/day. Is he receiving adequate nitrogen?

24-hour UUN = 500 mg/dl × 2,000 ml/day × 1 g/1,000 mg × 1 dl/100 ml
= 10 g/day

Nitrogen output
= 24-hr UUN + (0.20 × 24-hr UUN) + 2 g/day
= 10 g/day + (0.20 × 10 g/day) + 2 g/day
= 14 g/day

Nitrogen balance
= 16.8 g/day (N intake) – 14 g/day (N output)
= 2.8 g/day

The patient is in positive nitrogen balance, retaining approximately 2 to 3 g nitrogen/day. If positive nitrogen balance had not been achieved, his protein and caloric intake would have had to be increased and the nitrogen balance recalculated.

In non–ventilator-dependent patients, oxygen consumption and, in turn, the metabolic rate can be derived from measurements of respiratory gas exchange. In patients with a Swan-Ganz catheter in place, oxygen consumption can be calculated from cardiac output, mixed venous oxygen content ($C_{mv}O_2$), and arterial oxygen content (C_aO_2):

$$\dot{V}O_2 \text{ (ml/min)} = \text{cardiac output (L/min)} \times (C_aO_2 \text{ [ml/dl]} - C_{mv}O_2 \text{ [ml/dl]}) \times 1 \text{ L/10 dl}$$

Another objective of nutritional support in the ICU patient is the maintenance of lean body mass, reflected by nitrogen balance equilibration or positive nitrogen balance. Although complete nitrogen balance determination is a complex and sophisticated study, nitrogen equilibration can be estimated by simply subtracting total nitrogen loss (or output) from total nitrogen intake [*see Sidebar* Sample Calculation of Nitrogen Balance]. Calculation of total nitrogen loss requires several steps. The urine urea nitrogen (UUN) concentration is multiplied by the total urine output during a given day to yield the 24-hour UUN (i.e., the total amount of urea excreted during that period). Because urea accounts for only approximately 80% of the nitrogen excreted in the urine, the value for the 24-hour UUN is then increased by an additional 20%. This quantity and an additional 2 g/day are added to the value for the 24-hour UUN to account for nonurea nitrogen, stool, and integumentary losses:

$$\text{24-hour UUN (g/day)} = \text{UUN (mg/dl)} \times \text{urine output (ml/day)} \times 1 \text{ g/1,000 mg} \times 1 \text{ dl/100 ml}$$

$$\text{Total nitrogen loss (g/day)} = \text{24-hour UUN (g/day)} + (0.20 \times \text{24-hour UUN [g/day]}) + 2 \text{ g/day}$$

Metabolic Monitoring

A wide variety of metabolic complications may occur during parenteral feeding [*see Table 14*]. They are minimized by frequent monitoring [*see Table 15*] and appropriate adjustment of nutrients in the infusion.

The most common metabolic problems in ICU patients are hyperglycemia and glucosuria. The combination of excessive counterregulatory hormone release and overproduction of tumor necrosis factor (TNF)–α, interleukin (IL)-1, and IL-6 characteristic of critical illness is a major cause of stress-induced hyperglycemia in nondiabetic hosts.[11] Hypergylcemia has been associated with infectious complications,[12,13] worsened outcome after head injury and stroke,[14] and increased proteolysis.[15] Moreover, prevention of hyperglycemia by means of aggressive insulin treatment has been associated with reduced mortality in ICU patients.[16] Initially, elevated blood glucose levels should be treated by administering insulin (5.0 U s.c. every 4 to 6 hours for glucose 200 to 250 mg/dl; 7.5 U for 250 to 300 mg/dl; 10.0 U for 300 to 350 mg/dl). When the nutritional solution is ordered for the next 24-hour period, half of the quantity of insulin administered subcutaneously is added to the mixture. The initial insulin dose should be least 10 U of regular insulin/L of solution, and in some cases, as much as 40 U/L may be required. If larger doses of insulin are needed (> 100 U/day), a separate insulin infusion or drip should be employed.

In most patients with severe glucose intolerance, the rate of glucose administration should not exceed 5 mg/kg/min (~ 500 g/day). Additional calories should be administered as fat emulsion. The commercially available fat emulsions are all generally well tolerated by critically ill patients. Triglyceride levels should be monitored, and the emulsion should be administered at a reduced rate or temporarily discontinued if levels exceed 500 mg/dl. Fat emulsion should be used with caution in patients with known hypertriglyceridemia or in those with gram-negative bloodstream infection that is associated with hyperlipidemia.

Infusion of excess glucose or lipid may alter pulmonary function and in some patients prevent weaning from a mechanical ventilator. Excessive carbohydrate loads (usually > 500 g/day) increase CO_2 production. If more CO_2 is produced than the lungs can excrete, hypercapnia results. Fat emulsion may also interfere with diffusion of gas across the alveolar membranes. This interference is generally related to the concentration of the emulsion in the bloodstream; hence, it can be minimized by monitoring triglyceride levels and preventing hypertriglyceridemia.

Catheter Care and Catheter Infection

The most serious problem associated with central venous feedings is catheter infection [*see 8:18 Intra-abdominal Infec*]. Primary catheter infection is defined as the signs and symptoms of infection (usually a febrile episode), with the indwelling catheter being the only anatomic infectious focus; after removal of the catheter, the symptoms usually attenuate. Cultures of the catheter tip with semiquantitative techniques yield at least 10^3 organisms,[17] and the organisms are the same as those recovered in blood drawn from a peripheral vein during initial evaluation of the infection. Secondary catheter infection is associated with a primary infectious focus that causes bacteremia and thus seeds or contaminates the catheter; the infection clears after specific treatment of the primary infection. The microorganisms cultured from the catheter tip are similar to those cultured from the primary source.

Primary catheter infection is prevented or at least greatly reduced by following strict protocols governing use and manipulation of the central venous feeding catheter and by employing a systematic method of care and surveillance of the catheter entrance site. Usually, catheter care and its supervision and certification are performed by a nurse with expertise in maintenance of long-term I.V. access. Every 48 to 72 hours, the dressing covering the entrance site of the catheter is removed, the site inspected, the area around the entrance site cleaned, a topical antibiotic or antiseptic ointment applied, and the site redressed with a new sterile dressing. This procedure is documented in the clinical

Table 14 Metabolic Complications of Total Parenteral Nutrition

Problems	Possible Causes	Solutions
Glucose		
Hyperglycemia, glycosuria, osmotic diuresis, hyperosmolar nonketotic dehydration and coma	Excessive total dose or rate of infusion of glucose; inadequate endogenous insulin; increased glucocorticoids; sepsis	Reduce amount of glucose infused; increase insulin; administer a portion of calories as fat emulsion
Ketoacidosis in diabetes mellitus	Inadequate endogenous insulin response; inadequate exogenous insulin therapy	Give insulin; reduce glucose input
Postinfusion (rebound) hypoglycemia	Persistence of endogenous insulin production secondary to prolonged stimulation of islet cells by high-carbohydrate infusion	Administer 5%–10% glucose before infusate is discontinued
Fat		
Pyrogenic reaction	Fat emulsion, other solutions	Exclude other causes of fever
Altered coagulation	Hyperlipidemia	Restudy after fat has cleared bloodstream
Hypertriglyceridemia	Rapid infusion, decreased clearance	Decrease rate of infusion; allow clearance before blood tests
Impaired liver function	May be caused by fat emulsion or by an underlying disease process	Exclude other causes of hepatic dysfunction
Cyanosis	Altered pulmonary diffusion capacity	Discontinue fat infusion
Essential fatty acid deficiency	Inadequate essential fatty acid administration	Administer essential fatty acids in the form of one 500 ml bottle of fat emulsion every 2–3 days
Amino Acids		
Hyperchloremic metabolic acidosis	Excessive chloride and monohydrochloride content of crystalline amino acid solutions	Administer Na^+ and K^+ as acetate salts
Serum amino acid imbalance	Unphysiologic amino acid profile of the nutrient solution; differential amino acid utilization with various disorders	Use experimental solutions if indicated
Hyperammonemia	Excessive ammonia in protein hydrolysate solutions; deficiency of arginine, ornithine, aspartic acid, or glutamic acid, or a combination of these deficiencies in amino acid solutions; primary hepatic disorder	Reduce amino acid intake
Prerenal azotemia	Excessive amino acid infusion with inadequate calorie administration; inadequate free water intake, dehydration	Reduce amino acid intake; increase glucose calories; increase intake of free water
Calcium and Phosphorus		
Hypophosphatemia	Inadequate phosphorus administration; redistribution of serum phosphorus into cells or bones, or both	Administer phosphorous (≥ 20 mEq potassium dihydrogen phosphate/1,000 I.V. calories); evaluate antacid or calcium administration, or both
Hypocalcemia	Inadequate calcium administration; reciprocal response to phosphorus repletion without simultaneous calcium infusion; hypoalbuminemia	Administer calcium
Hypercalcemia	Excessive calcium administration with or without high doses of albumin; excessive vitamin D administration	Decrease calcium or vitamin D
Vitamin D deficiency; hypervitaminosis D	Inadequate or excessive vitamin D	Alter vitamin D administration
Miscellaneous		
Hypokalemia	Potassium intake inadequate relative to increased requirements for protein anabolism; diuresis	Alter nutrient administration
Hyperkalemia	Excessive potassium administration, especially in metabolic acidosis; renal failure	Alter nutrient administration
Hypomagnesemia	Inadequate magnesium administration relative to increased requirements for protein anabolism and glucose metabolism; diuresis; cisplatin administration	Alter nutrient administration
Hypermagnesemia	Excessive magnesium administration; renal failure	Alter nutrient administration
Anemia	Iron deficiency; folic acid deficiency; vitamin B_{12} deficiency; copper deficiency; other deficiencies	Alter nutrient administration
Bleeding	Vitamin K deficiency	Alter nutrient administration
Hypervitaminosis A	Excessive vitamin A administration	Alter nutrient administration
Elevations in AST (formerly SGOT), ALT (formerly SGPT), and serum alkaline phosphatase	Enzyme induction secondary to amino acid imbalance or to excessive deposition of glycogen or fat, or both, in the liver	Reevaluate status of patient

record; if drainage or crusting appears at the entrance site, appropriate cultures are taken. In addition, the dressing is changed if it becomes wet or soiled or no longer remains intact. In patients who have either draining wounds in close proximity to the catheter entrance site or tracheostomies, the entire dressing may be covered with a transparent barrier drape to minimize contamination.

If signs and symptoms of infection develop in a recipient of central venous parenteral nutrition, a history should be taken and a physical examination performed [*see Figure 3*]. Appropriate tests (e.g., complete blood count and urinalysis) and diagnostic studies (including roentgenogram) should also be performed. If blood cultures are needed, samples should be drawn from a peripheral vein. If trained nurses have maintained the catheter and there is no evidence of infection at the exit site, the dressing should not be removed, and the catheter should not be manipulated. Blood cultures should never be taken through the catheter—except, possibly, when the initial presentation of infection is characterized by marked hyperpyrexia or hypotension, in which case, contamination of the catheter is immaterial because the catheter will be removed. If no other infectious focus is identified, the physician may elect to remove all indwelling lines, including the feeding catheter. In addition, either drainage around the catheter or a previous positive culture from the catheter exit site may

Table 15 Variables to Be Monitored during Intravenous Alimentation and Suggested Frequency of Monitoring

Variables	Suggested Monitoring Frequency	
	First Week	Later
Energy Balance		
Weight	Daily	Daily
Metabolic Variables		
Blood measurements		
Plasma electrolytes (Na^+, K^+, Cl^-)	Daily	3 × weekly
Blood urea nitrogen	3 × weekly	2 × weekly
Plasma osmolarity*	Daily	3 × weekly
Plasma total calcium and inorganic phosphorus	3 × weekly	2 × weekly
Blood glucose	Daily	3 × weekly
Plasma transaminases	3 × weekly	2 × weekly
Plasma total protein and fractions	2 × weekly	Weekly
Blood acid-base status	As indicated	As indicated
Hemoglobin	Weekly	Weekly
Ammonia	As indicated	As indicated
Magnesium	2 × weekly	Weekly
Triglycerides	Weekly	Weekly
Urine measurements		
Glucose	Daily	Daily
Specific gravity or osmolarity	Daily	Daily
General measurements		
Volume of infusate	Daily	Daily
Oral intake (if any)	Daily	Daily
Urinary output	Daily	Daily
Prevention and Detection of Infection		
Clinical observations (activity, temperature, symptoms)	Daily	Daily
WBC and differential counts	As indicated	As indicated
Cultures	As indicated	As indicated

*May be predicted from 2 × Na concentration (mEq/L) + (blood glucose [mg/dl] ÷ 1).

also indicate immediate removal. If another primary source of infection is diagnosed, specific therapy should be instituted and parenteral nutrition continued. If no source of infection is identified, the catheter should be removed and the catheter tip cultured [*see 8:18 Intra-abdominal Infection*].

A dilemma arises if another source of infection is identified and if signs and symptoms of infection persist despite what appears to be appropriate therapy. If blood cultures are positive, we favor removal of the catheter to avoid the complications associated with a contaminated indwelling catheter. If, however, peripheral blood cultures are negative, the catheter can be changed over a guide wire and the catheter tip cultured; central venous feeding can be continued during this interval. If the cultured catheter tip is positive ($\geq 10^5$ organisms), the catheter should be removed.

Changing the central venous catheter over a guide wire can aid in the diagnosis of primary catheter infection.[18] Because most ICU patients have multiple potential sources for infection, this technique allows culture of the catheter tip but minimizes the risks associated with reinsertion of a new central catheter. With strict care of catheters, the incidence of catheter infection should be less than 6%.[19] Catheter-related bloodstream infection (CRBSI) is most commonly caused by growth and invasion of organisms along the catheter tract. Occasionally, bacteria are infused through the catheter because of a breach in sterility during care of the infusion apparatus. The most common bacterial organisms causing catheter sepsis are *Staphylococcus epidermidis, S. aureus, Klebsiella pneumoniae,* and *Candida albicans*. In some rare cases, the I.V. solutions may be contaminated. Moreover, most patients requiring central venous alimentation are immunocompromised hosts; their resistance is lowered further by disease, severe malnutrition, or treatment or by some combination of these factors. Coexisting conditions such as urinary tract infection, abscess, pneumonia, or mucositis secondary to chemotherapy predispose to bacteremia, which may contaminate the central venous catheter.

Immunosuppressed critically ill patients receiving multiple broad-spectrum antibiotics are also at risk for *Candida* CRBSI. Blood cultures positive for *C. albicans* in an ICU patient are an indication for catheter removal and treatment with fluconazole. An ophthalmologist should examine the eyegrounds of patients with proven candidemia to exclude the possibility of metastatic *Candida* ophthalmitis [*see 8:19 Fungal Infection*].

Home Nutritional Support

HOME PARENTERAL NUTRITION

Home parenteral nutrition is indicated for patients who are unable to eat and absorb enough nutrients for maintenance. Most of the adult surgical patients who require home parenteral nutrition suffer from short-bowel syndrome caused by (1) extensive Crohn disease, (2) mesenteric infarction, or (3) severe abdominal trauma. Pseudo-obstruction, radiation enteritis, carcinomatosis, necrotizing enterocolitis, and intestinal fistulas are other indications for home parenteral nutrition. Patients with these conditions cannot receive adequate nutrition enterally, though sometimes compensatory mucosal growth occurs that may reduce or eventually eliminate the need for continued home parenteral nutrition.

Patients must receive extensive evaluation, teaching, and training during hospitalization if home parenteral nutrition is to prove successful. These services should be provided by a team consisting of a physician, a nurse, a dietitian, a pharmacist, and a social worker. The team's instructions should cover the basic principles of parenteral nutrition as well as provide mechanical guidelines for catheter care, asepsis, and use of infusion pumps. Patients should be objectively evaluated before discharge to ensure that they adequately understand the principles of I.V. nutrition and can carry out home parenteral nutrition properly.

Once a patient is judged to be a suitable candidate for home TPN, a Silastic catheter is placed that is designed for more permanent use than the central venous catheter employed during hospitalization. Typically, the catheter is 90 cm long, with a thin 55 cm intravascular segment that is inserted either by venous cutdown into the internal or external jugular vein or the cephalic vein or by venipuncture directly into the subclavian vein. Its intravascular portion is cut so that the tip will lie at the junction of the superior vena cava and the right atrium.

Catheter placement is done in the OR with the patient under local anesthesia (1% lidocaine) and adequate sedation. The catheter is tunneled subcutaneously from a small incision lateral to the sternum to the site of venous insertion. The exit site is chosen on the basis of the patient's sex, physique, and hand dominance. In women, lower paraxiphoid or upper abdominal exit sites permit a more natural appearance. If coagulation status is abnormal, the cephalic vein is isolated in the deltapectoral groove and tied distally, and the catheter is inserted proximally by means of venotomy; otherwise, it is inserted into the subclavian vein percutaneously. Proper position-

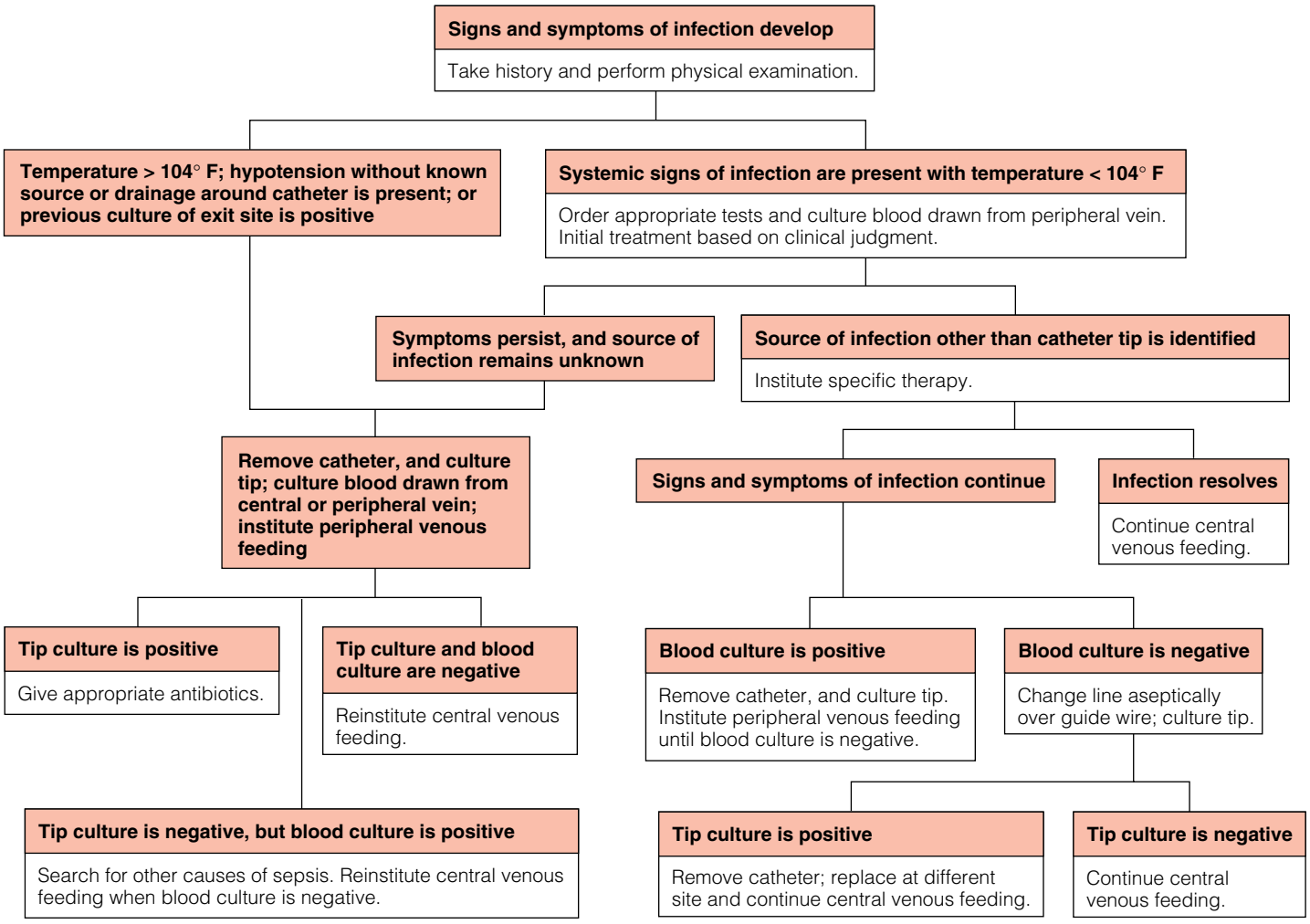


Figure 3 **Shown is an algorithm for evaluating a febrile patient receiving central venous parenteral nutrition.**

ing of the catheter is confirmed by fluoroscopy, and the incisions are closed with absorbable sutures. The catheter is sutured to the exit site, and the sutures are left attached for at least 2 weeks while tissue ingrowth into the cuff takes place. After the sutures are placed, sterile dressings are applied.

Calorie, protein, and fluid needs are carefully estimated for each patient, and the administration schedule is arranged so that the total volume may be infused nocturnally over 10 to 12 hours. Electrolytes, micronutrients, and trace minerals are added as indicated. Fat emulsions may be given either separately or admixed with glucose and protein and are used to reduce the requirement for dextrose calories and to prevent essential fatty acid deficiency.

The complications of home TPN are much the same as those of in-hospital TPN and may be divided into four categories: mechanical, infectious, metabolic, and psychosocial. Mechanical complications, which are generally easy to remedy, include catheter occlusion and dislodgment and damage to the external portion of the catheter. Infectious complications superficial to the cuff usually respond well to antibiotics. Catheter infections may necessitate removal of the device after the diagnosis is confirmed by blood cultures, but the usual therapeutic approach is to initiate a trial of parenteral antibiotics. Metabolic complications related to individual nutrient deficiencies may be corrected by adding the appropriate substance to the solution. The role of serum levels of trace minerals and micronutrients in delineating nutrient deficiency states is unclear. In patients receiving insulin, hyperinsulinemia after infusion may be prevented by reducing the rate of administration gradually over the last hour of infusion. Psychosocial complications may vary from slight depression to suicidal tendencies, which must be treated with appropriate counseling.

The costs of a home TPN program may also be divided into four categories: patient training, equipment, supplies, and follow-up. It has been estimated that the average annual cost of home TPN is 70% less than that of in-hospital TPN. The growth of private companies that deliver equipment and supplies to the home, maintain inventory, bill patients, and help with health insurance reimbursement has considerably facilitated home care.

HOME ENTERAL NUTRITION

Home enteral nutrition is frequently used as either the sole source or a partial source of nutritional support. It is the preferred method when GI tract function is adequate. In patients undergoing surgery of the aerodigestive tract for cancer, jejunostomy feedings can supplement oral feedings, especially during adjuvant chemotherapy and radiation treatment. Patients are taught to cycle feedings over 12-hour periods, using an enteral pump system to provide 20 to 30 kcal/kg/day. Use of an appropriate feeding tube and immediate flushing of the tube after use reduce the incidence of clogging at home. If blockage occurs,

proteases or carbonated beverages can be introduced into the tube in an attempt to open it. Jejunostomy feedings reduce the risk of aspiration and help maintain nutritional status during periods of inadequate oral intake. Use of inexpensive nutritionally complete commercial formulas is encouraged. For patients with more permanent disabilities that prevent adequate oral intake, a gastrostomy (or PEG [*see 5:18 Gastrointestinal Endoscopy*]) may be preferable; this reduces the GI complications of feeding by making use of the reservoir and admixing functions of the stomach.

Discussion

Evidence-Based Nutritional Support

EARLY ORAL FEEDINGS AFTER ELECTIVE OPERATIONS

Anesthetics, prolonged bed rest, and fluid shifts make the intestine susceptible to ileus after most operations, particularly abdominal ones. In the past, patients commonly underwent gastric decompression with a nasogastric tube until they showed obvious signs of bowel function. Over the past 10 years, however, several authors have questioned the necessity of postoperative nasogastric decompression.[20,21] Others have suggested not only that nasogastric decompression is unnecessary but also that perhaps patients should be fed earlier than is usually done.[22-24]

The traditional approach to postoperative feeding has been to start with a clear liquid or full liquid diet, continue this until the appearance of consistent flatus or bowel movements, and then switch to a regular diet. There is, however, no evidence that such a stepwise progression is necessary or leads to better outcomes. In fact, a 2002 study found no significant differences in time to diet tolerance, complications, or hospital stay between this approach and one in which postoperative feeding started with a regular diet.[25]

Use of opioids can have significant deleterious effects on nutrition. Opioid-induced constipation can lead to lower abdominal discomfort, fecal impaction, diarrhea, nausea, and inadequate absorption of oral drugs. The ensuing bowel dysfunction is a consequence both of CNS-mediated alteration of autonomic flow to the gut[26] and of a direct local opioid effect on the bowel.[27] Opioid receptor antagonists (e.g., naloxone and naltrexone) can reverse these changes, but at the cost of some reduction in analgesia. Newer agents (e.g., methylnaltrexone) are poorly lipid soluble and unable to penetrate the CNS and thus do not antagonize the central effects of opioids.[28] A 1996 study suggested, however, that I.V. methylnaltrexone could prevent opioid-induced delay in bowel motility without affecting analgesia.[29] Such drugs may be particularly useful as adjuncts, minimizing the side effects of opioids when these agents must be given.

Finally, early feeding has been combined with other therapies to enhance recovery [*see 1:10 Fast Track Surgery*]. Patients who undergo epidural anesthesia, receive early oral feedings, and take part in an active exercise program experience much shorter convalescent recovery periods and require less hospitalization.[30]

DATA ON NUTRITIONAL SUPPORT IN SPECIFIC SETTINGS

Preoperative TPN

A number of studies have been conducted to evaluate the effect of preoperative TPN; most have involved patients with GI cancer who were considered at least moderately malnourished. A pooled analysis of the data showed that in patients who received preoperative TPN, the complication rate dropped from approximately 40% to 30%; in five studies, the differences reached statistical significance.[31] The pooled analysis found no significant difference in mortality between the TPN groups and the control groups.

Intraoperative TPN

Although not yet tested in clinical trials, intraoperative TPN should be avoided. The stress associated with surgery and anesthesia results in hyperglycemia even without the infusion of dextrose. When infused during surgery the dextrose in the TPN solution can increase blood glucose levels severalfold, and these extreme increases have been associated with impaired immune function. Furthermore, it appears that hypotension or cardiac arrest during concentrated dextrose infusion can result in more irreversible damage to the CNS.

Postoperative TPN

TPN in the immediate postoperative period without preoperative TPN has been evaluated in multiple trials—again, mostly involving GI cancer patients who were considered at least moderately malnourished.[31] In contrast to the pooled analysis of the preoperative data, a pooled analysis of the postoperative data showed that in patients who received TPN after operation, the complication rate rose from approximately 30% to 40%.

Perioperative Enteral Nutrition

Two studies compared preoperative enteral nutrition with an ad libitum oral diet,[32,33] and in one,[32] postoperative complications were significantly lower in patients who received enteral tube feeding. Other studies compared early postoperative jejunal tube feeding with a standard oral diet that was advanced as tolerated and found no consistent differences in postoperative morbidity or mortality.[34-37] Yet another evaluated the use of postoperative jejunostomy tube feeding with a special formula enriched with arginine, ribonucleic acids, and omega-3 fatty acids after operation for upper GI tract cancer.[38] When only successfully fed patients were evaluated, those who received the enriched formula had fewer complications and a shorter hospital stay than those who received the standard formula.

Nutrition in Cancer Patients

Trials addressing perioperative nutritional support have been conducted in patients undergoing surgery for pancreatic, hepatocellular, and upper GI malignancies. In one, patients undergoing major pancreatic resection were randomly assigned either to a group that received TPN on postoperative day 1 or to a non-TPN group.[39] Patients in the TPN group derived no demonstrable benefit and experienced more complications (primarily infectious). It was concluded that routine postoperative TPN could not be recommended for patients undergoing major pancreatic resection for malignancy.

Another trial examined the effects of cyclic versus continuous enteral nutrition on postoperative gastric function after pylorus-preserving pancreaticoduodenectomy.[40] Patients were evaluated with

respect to gastric emptying, resumption of normal diet, and length of hospital stay. Cyclic nutrition was associated with shorter periods of nasogastric intubation, earlier resumption of normal diet, and reduced hospital stay. It was concluded that cyclic enteral nutrition was clinically efficacious in this selected group of patients.

Nutritional support has been shown to reduce the catabolic response, improve protein synthesis, and enhance liver regeneration. In a 1994 study, 124 patients undergoing hepatectomy for hepatocellular carcinoma were randomly assigned either to a control group or to a group receiving perioperative I.V. nutritional support in addition to their oral diet.[41] The overall postoperative morbidity rate was reduced in the perioperative nutrition group (34% versus 55%), mainly because the rate of infection-related complications was lower (17% versus 37%). These benefits were mainly seen in patients with underlying cirrhosis who underwent major hepatectomy. It was concluded that perioperative nutritional support can reduce complications after major hepatectomy in such patients.

Early Postoperative Enteral Nutrition

In a nonrandomized, uncontrolled study of 38 patients who underwent colorectal surgery over a 3-month period,[42] the 31 patients who were able to tolerate an early feeding regimen had shorter postoperative stays (5.7 versus 10.6 days); the seven who were not had longer operative procedures and lost more blood intraoperatively (possibly as a result of a more difficult operation, which itself might lead to prolonged recovery and decreased tolerance of early enteral feeding). The investigators concluded (1) that early postoperative feeding is safe and is tolerated by the majority of patients and (2) that if early feeding is tolerated, it shortens hospital stay and may decrease health care costs.

In another study, 28 patients undergoing esophagectomy or pancreaticoduodenectomy received either immediate postoperative enteral feeding via jejunostomy or no feedings during the first 6 days after operation.[43] Postoperative vital capacity and forced expiratory volume in 1 second (FEV_1) were consistently lower in the fed group than in the unfed group, but there were no significant differences in grip strength and maximal inspiratory pressure between the two groups. Patients in the fed group were less mobile after operation and tended to recover less rapidly; however, there were no significant differences in fatigue or vigor between the two groups. The investigators concluded that immediate postoperative jejunal feeding is associated with impaired respiratory mechanics and postoperative mobility and does not influence the loss of muscle strength or the increase in fatigue occurring after major surgery; they further concluded that immediate postoperative enteral feeding should not be routine in well-nourished patients who are at low risk for nutrition-related complications.

Another trial evaluated early enteral feeding after resection of upper GI malignancies with the aim of determining whether early postoperative enteral feeding with an immune-enhancing formula supplemented with arginine, RNA, and omega-3 fatty acids could decrease morbidity, mortality, and length of hospital stay.[44] A total of 195 patients with upper GI cancer were randomly selected to receive either the immune-enhancing formula via jejunostomy or standard I.V. crystalloid solutions. There were no significant differences between the two groups with respect to number of minor, major, or infectious wound complications; length of hospital stay; or mortality.

In yet another trial, 43 patients with nontraumatic intestinal perforation and peritonitis were randomly assigned after laparotomy either to a control group or to a study group that received a feeding jejunostomy, with enteral feeding started 12 hours after operation.[45] Mortality was high in both the control group and the study group (18% versus 19%).[45] The control group had more infectious complications (22 versus 8).

Nutrition in ICU Patients

A meta-analysis of 26 relevant randomized clinical trials involving 2,211 patients cared for in ICUs demonstrated that parenteral nutrition did not reduce morbidity or mortality, though the data did suggest that the most malnourished groups of patients might derive some benefit.[46] Therefore, use of this expensive therapy in the ICU should be carefully limited to patients who have specific nutritional needs and cannot accept enteral feedings.

Conclusions

Parenteral and enteral nutritional support is a valuable adjunctive—and sometimes lifesaving—therapy in selected surgical patients. It is generally agreed that patients who cannot ingest adequate nutrients for a prolonged period require nutritional therapy. It is not entirely clear, however, precisely how "adequate" and "prolonged" should be defined. In practice, definitions are likely to vary from patient to patient, depending on the amount of body energy stores and lean body mass, the presence or absence of preexisting medical illnesses, the number and severity of postoperative complications, and the nature of the surgical procedure.

Summation of data from numerous trials suggests that giving nutritional support for 7 days before operation decreases postoperative complications. Severely malnourished patients (defined on the basis of percentage of body weight lost or nutritional risk index score) may derive greater clinical benefit from preoperative nutritional support, but support for this view comes largely from retrospective analysis of prospective data. In addition, certain subsets of patients may derive particular benefit from nutritional support (e.g., patients undergoing hepatic resection for hepatocellular carcinoma and elderly patients with hip fractures). The increased complication rates in patients receiving postoperative TPN and the case reports of small bowel necrosis in patients receiving early postoperative enteral nutrition are evidence that nutritional support has risks and should not be given indiscriminately.

Nutritional Pharmacology and Immunonutrition

The role of nutrient administration to surgical patients has evolved from maintenance of a positive energy and nitrogen balance to modulation of tissue metabolism and organ system function. This new role is referred to as nutrition pharmacotherapy. Like other forms of adjuvant therapy, nutrition pharmacotherapy is usually a multitargeted therapeutic modality. For instance, one form of nutrition pharmacotherapy, immunonutrition, makes use of combinations of specific amino acids, fatty acids, and, in some enteral formulas, nucleotides. Another form, so-called bowel rehabilitation, uses an amino acid (glutamine) in combination with growth hormone and a modified diet. Inclusion of a specific nutrient as part of a plan of nutrition pharmacotherapy is based either on clinical studies or, more often, on extrapolations from experimental observations. In what follows, we discuss each of the nutrients used, or proposed for use, in nutrition pharmacotherapy, with emphasis on chemical characteristics, physiologic effects, available forms for exogenous administration, and, if available, clinical data supporting its use for this purpose.

GLUTAMINE

Glutamine is the most abundant amino acid in the body and appears to be the most versatile. Most free glutamine is synthesized and stored in skeletal muscle.[47] Skeletal muscle releases net glutamine for

transport to the gut, immune cells, and the kidneys. The cells of the gut and the immune system proliferate rapidly, and glutamine acts as their main fuel source and as a biosynthetic precursor. One of the compounds derived from glutamine is glutathione, a tripeptide with potent antioxidant effects. Finally, glutamine participates in acid-base regulation via release of ammonia, which combines with H^+ to form NH_4^+ and is lost in urine.

Catabolism induced by major injury, surgery, sepsis, or burns results in increased release of glutamine from skeletal muscle.[48] This output of glutamine into the circulation is associated with increased uptake and consumption by the gut, the immune system, the liver, and the kidneys. The net effect is a profound fall in intracellular muscle stores of glutamine. This deficit exceeds all other amino acid deficits and persists even when stores of all other amino acids have already been replenished.[49]

Standard amino acid formulations have always included all of the essential amino acids and most of the nonessential ones. For a long time, glutamine was excluded from parenteral formulations because of its instability in aqueous solutions. However, the pharmaceutical industry has now begun to develop ways of keeping glutamine stable in an aqueous solution. For instance, Glamin (Pharmacia & Upjohn, Sweden), an amino acid formulation that is commercially available in Europe, includes the dipeptide glycyl-L-glutamine, which is readily hydrolyzed to free glutamine in plasma and tissues. These dipeptide formulations are not yet approved for use in the United States.

Several clinical studies of supplementation of parenteral formulas with glutamine have been published. Striking results have been reported in patients undergoing bone marrow transplantation. A randomized, double-blind, controlled study from 1992 investigated the effects of glutamine on metabolic parameters and clinical outcome in 45 adult patients undergoing bone marrow transplantation for hematologic malignancies.[50] Patients were randomly selected to receive either a formula supplemented with L-glutamine or a standard glutamine-free isonitrogenous formula for an average of 4 weeks after operation. The patients who received the glutamine-supplemented formula had a better nitrogen balance than the control group; more important, they also had a lower incidence of microbial colonization and clinical infection and a shorter hospital stay. These findings were subsequently confirmed by a study performed by a different group of investigators.[51]

Equally striking results have been reported in patients with the short-bowel syndrome that develops after massive small bowel resection. Although the advent of parenteral nutrition has improved survival for many patients with this syndrome, it has also created a dependency on such therapy, which in the long term can have life-threatening complications. For this reason, many surgical scientists have searched for ways of augmenting these patients' intestinal absorption capacity so as to reduce or eliminate the need for parenteral nutrition. A growing understanding of the roles of glutamine, dietary fiber, short-chain fatty acids, and growth factors in the process of intestinal adaptation led to clinical trials aimed at evaluating the effects of supplementation of these substances on patients with this syndrome.

In a randomized, double-blind, prospective multicenter trial, 41 patients with short-bowel syndrome were given an optimal diet and then randomly selected to receive oral glutamine, 30 g/day, plus placebo growth hormone; placebo glutamine plus growth hormone (GH), 0.1 mg/kg/day; or the two active agents together.[52] Patients were weaned from TPN according to standard criteria. At the end of 4 weeks, all subjects had decreased I.V. nutrient requirements, with the glutamine-GH group showing a greater reduction than the GH group, which in turn showed a greater reduction than the glutamine-placebo group.

The studies just cited were all conducted according to research protocols that used L-glutamine, which is not practical for I.V. administration, rather than the dipeptide form now commercially available (in Europe), which is stable in an aqueous solution. A meta-analysis of all the appropriate studies involving I.V. glutamine showed a significant reduction in postoperative infection associated with a decreased length of stay.[53] Reduced long-term (6 month) mortality was noted in critically ill patients—a finding that has not been recently associated with the administration of other specific nutrients.

ARGININE

Arginine is a nitrogen-dense amino acid that is considered semiessential because it is required for growth.[54] Its effect on growth seems to be mediated by its role in polyamine and nucleic acid synthesis. In addition, it is a potent secretagogue of growth hormone, insulin, glucagon, prolactin, and somatostatin[55-57]; when this effect is abolished by hypophysectomy, the stimulatory effect on wound healing is lost.[58] Supplemental dietary arginine has thymotrophic effects and enhances the responsiveness of thymic lymphocytes to mitogens in rats.[59] A similar response occurs in peripheral blood mononuclear cells of healthy human volunteers[60] and postoperative patients,[61] as evidenced by an enhanced response to concanavalin A and phytohemagglutinin.

Arginine enhances cellular immunity, as demonstrated by an increased delayed hypersensitivity response in animals with burns.[62] Dietary supplementation with arginine improves the response to dinitrofluorobenzene (DNFB) and enhances the survival of guinea pigs with 30% body surface burns. However, in a model of acute peritonitis in guinea pigs, supplemental arginine did not improve DNFB response or survival.[63]

Studies of arginine in humans have not been conclusive, because this substance is often administered with other active substances (e.g., RNA and omega-3 fatty acids). However, oral arginine supplementation has enhanced markers of wound healing in human volunteers,[64] and both enteral and parenteral arginine administration have improved immunologic measures.[65] Although arginine has antitumor properties in animals, the only relevant study done to date in humans found that arginine supplementation stimulated growth of breast cancer.[66] Because there is now controversy over increased mortality in critically ill patients receiving arginine [*see* Enteral Formulations to Counteract Immunosuppression, *below*], careful patient selection and full informed consent are necessary with this agent.

NUCLEOTIDES

Purines and pyrimidines are precursors of DNA and RNA, which are essential for cell proliferation. Purines and pyrimidines are synthesized by the liver de novo from amino acids and reutilized by salvage pathways. Reduction of dietary nucleotides results in suppression of cellular immune responses and prolongation of allograft survival.[67] The mechanism of this immunosuppression seems to be an inability of T cells to undergo blastogenesis. Dietary supplements containing RNA or uracil (but not adenine) maintain resistance to infection by *C. albicans* or *S. aureus* in rodents.[68,69] However, they do not enhance the immune response in comparison with a standard control diet.

On the basis of the immunosuppressive effect of dietary nucleotide restriction, it has been postulated that nucleotide supplementation could provide an immunostimulant effect. This postulate has been tested in studies of the RNA–fish oil–arginine formula now available [*see* Enteral Formulations to Counteract Immunosuppression, *below*].

FATTY ACIDS

Fatty acids in the systemic circulation can be used in two forms: as fuels to be stored and oxidized as needed by the organism and as precursors for other essential compounds, such as eicosanoids (prostaglandins, leukotrienes, and thromboxanes) [*see 8:26 Molecular and Cellular Mediators of the Inflammatory Response*]. Fatty acids may be classified in several different ways. One classification is based on chain length: short (two to five carbons), medium (six to 11 carbons), and long (12 to 26 carbons). Another classification is based on the presence of double bonds in the carbon chain: those with double bonds are called unsaturated and are further subclassified as either monounsaturated fatty acids or polyunsaturated fatty acids (PUFAs), depending on the number of double bonds. Another classification is the omega classification, which indicates where the first double bond is located when carbons are counted from the noncarboxyl end of the chain (e.g., omega-3, omega-6).

Humans can synthesize only fatty acids with double bonds at position 7 (counting from the noncarboxyl end toward the carboxyl end). Therefore, omega-6 or omega-3 fatty acids must be supplied exogenously. Because linoleic acid and α-linolenic acid can be elongated and desaturated to produce the remaining omega-6 and omega-3 PUFAs, these are considered the essential fatty acids. Requirements for omega-6 PUFAs exceed those for omega-3 PUFAs by a ratio of approximately 5:1. Omega-6 PUFAs are abundant in vegetable oils, whereas omega-3 PUFAs are abundant in fish oils and seed oils.

The availability of 20-carbon PUFAs—arachidonic acid in the omega-6 series and eicosapentaenoic acid in the omega-3 series—is the determining factor for the synthesis of eicosanoids [*see 8:26 Molecular and Cellular Mediators of the Inflammatory Response*]. Cells obtain arachidonic acid and eicosapentaenoic acid from degradation of phospholipids by phospholipase A_2 and phospholipase C or by elongation and desaturation of linoleic acid and α-linolenic acid. Because mature immune cells (e.g., monocytes, macrophages, lymphocytes, and polymorphonuclear cells) lack an enzyme needed for transformation of 18-carbon PUFAs into 20-carbon PUFAs,[70] availability of precursors for eicosanoid synthesis in such cells is largely dependent on their lipid composition. The lipid composition of immune cells, in turn, is influenced by lipid intake, and thus, the type of PUFAs ingested can affect the immune response.[71,72]

Eicosanoids, especially prostaglandin E_2 (PGE_2), leukotriene B_4 (LTB_4), 5-hydroxyeicosatetraenoic acid (5-HETE), and 15-hydroxyeicosatetraenoic acid (15-HETE), are immunomodulatory; when produced in excess (as in posttraumatic states), they are generally immunosuppressive.[73] Dietary supplementation with omega-3 PUFAs has improved survival of endotoxic shock in guinea pigs.[74] Reduced intake of omega-6 PUFAs seems to be as important as increased intake of omega-3 PUFAs. When animals are made deficient in linoleic acid, mortality after endotoxin challenge is only 24%; however, when arachidonic acid is given 2 days before endotoxin challenge, mortality reaches 100%.[75] Similar results were reported in guinea pigs recovering from flame burns covering 30% of body surface area.[76] Compared with animals fed dietary safflower oil (74% linoleic acid) or linoleic acid alone, animals fed fish oil had less weight loss, better skeletal muscle mass, lower resting metabolic expenditure, better cell-mediated immune responses, better opsonic indices, higher splenic weight, lower adrenal weight, higher serum transferrin levels, and lower serum C3 levels.

The fat emulsions currently available for I.V. use in the United States are made with LCTs derived either from soybean oil alone or from soybean oil and safflower oil. All of the fatty acids in LCTs are in the form of PUFAs. Intravenously administered LCT emulsions are cleared in part through the reticuloendothelial system (RES).[77] When such emulsions are used as a calorie source, they may impair the ability of the RES to clear bacteria if given too rapidly or in excessively large amounts. Moreover, the PUFAs in LCT emulsions require carnitine-mediated transport to cross the mitochondrial membrane for oxidation. During sepsis, urinary excretion of free carnitine rises significantly, and the plasma acylcarnitine level falls.[78] One way of circumventing these problems is to use emulsions that contain MCTs.

MCT-containing emulsions possess an absorptive advantage over LCT-containing emulsions: whereas LCTs are absorbed via lacteals and the lymphatic system, MCTs are absorbed via the portal system. MCTs are obtained from coconut oil and contain saturated fatty acids (with octanoic acids predominating). Because MCTs are smaller than LCTs, they are more water soluble; they are also poorly bound to albumin and diffuse more easily across body compartments. Several reports on the use of I.V. administered MCT fat emulsions have been published. One study evaluated the effect of a 75% MCT/25% LCT emulsion on RES function as demonstrated by ^{99m}Tc-sulfur colloid (Tc-SC) clearance. Tc-SC clearance was significantly higher after 3 days of MCT/LCT administration than after 3 days of LCT administration.[79] Another study investigated the metabolic effects of MCT-containing emulsions on surgical patients.[80] Its main finding was the appearance of β-hydroxybutyrate in association with MCT infusion, which was indicative of a ketogenic effect. A tendency toward improved nitrogen balance was also observed but was not statistically significant.

In summary, specific fatty acids have significant potential for use in nutrition pharmacotherapy. Omega-6 fatty acids are potential immunosuppressants, whereas omega-3 fatty acids are potential immunostimulants. A reduction in the intake of omega-6 PUFAs appears prudent in patients who are immunocompromised or in posttraumatic states. Formulas for nutritional support should include omega-3 PUFAs, though the exact amount of omega-3 PUFAs and the precise ratio of omega-6 to omega-3 remain to be determined.

In the United States, the only emulsions commercially available for I.V. use at present are made of LCTs containing omega-6 PUFAs. MCTs offer some metabolic advantages over LCTs and obviate the side effects resulting from an excess of omega-6 PUFAs. Enteral diets containing omega-3 PUFAs appear to benefit stressed surgical patients, particularly those who are immunosuppressed as a result of therapy for cancer.

ENTERAL FORMULATIONS TO COUNTERACT IMMUNOSUPPRESSION

Impact (Sandoz Nutrition, Minneapolis, MN), a commercially available enteral formula enriched with omega-3 PUFAs, arginine, and RNA, was shown to reduce infectious complications in postoperative patients[81,82] and in some critically ill patients.[83] It was also shown to reduce hospital stay in selected patient groups.[84] However, concern was raised by the publication of data from a large meta-analysis of studies using this formula, which suggested that its use led to increased mortality.[85] The investigators suggested that the immunomodulation associated with this diet might be beneficial in some patients (generally the less seriously ill) but harmful in others (generally the more critically ill patients who require nutritional support).[86] Until this issue is resolved, patient selection is extremely important if this diet is to be administered to surgical patients.

Nutritional Support Guidelines

In 2002, the American Society for Parenteral and Enteral Nutrition (ASPEN) published an updated version of guidelines for use of nutritional support.[87] These guidelines are also available on the Internet (http://www.nutritioncare.org/publications/2002guidelines.pdf).

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Acknowledgments

Figure 2 Talar Agasyan.
Figure 4 Carol Donner.