NUTRITION SUPPORT IN MECHANICALLY VENTILATED PATIENTS

Essay

Submitted for partial fulfillment of master degree in chest diseases and tuberculosis

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2007
Acknowledgment

Thanks are all to Allah for blessing this work until it reached its end.

I would like to express my deepest appreciation and gratitude to Prof. Ahmad El-Gazzar professor of chest diseases, faculty of medicine, Benha university for his close supervision and continuous encouragement through the whole work, It’s a great honor to work under his supervision.

My deepest appreciation and grateful thanks are to Prof. Abd El Sadek Al-Aarag. professor of chest diseases, faculty of medicine Benha university for his continuous care, guidance, supervision instructions, and taught me how to write an essay.
INTRODUCTION

In critically ill patients malnutrition is associated with impaired immune function, impaired ventilatory drive and weakened respiratory muscles leading to prolonged ventilatory dependence and increased infectious morbidity and mortality. Malnutrition is prevalent in ICU patients, has been reported as being as high as 40%, and is associated with poor patient outcomes.

The benefits of nutrition support in the critically ill include improved wound healing, a decreased catabolic response to injury, improved gastrointestinal structure and function, and improved clinical outcomes including a reduction in complication rates and length of stay with accompanying cost savings.

Nutrition support is not without adverse effects or risks. Early enteral nutrition can be associated with high gastric residual volumes, bacterial colonization of the stomach, and an increased risk of aspiration pneumonia.

Parenteral nutrition has been associated with gut mucosal atrophy, overfeeding, hyperglycemia, an increased risk of infectious complications and increased mortality in critically ill patients. Both forms of nutrition support can increase health care costs and workloads of care providers.

Recent review papers have documented that nutrition support dose influence morbidity and mortality in critically ill patients. Therefore, strategies to improve the delivery of nutrition support are relevant and may result in decreased morbidity and mortality. Systematically developed practice guidelines that focus on these strategies will allow practitioners to make decisions about appropriate nutrition support care and will aim at improving the quality of patient care and maximizing the efficiency with which resources are used.
AIM OF THE ESSAY

The aim of this essay was to identify the benefits and complications of different modalities of nutritional support in mechanically ventilated patients in order to know the preferred modality.
THE METABOLIC MEILIU

Acute stress caused by accidental or surgical injury, sepsis, burns or other serious illnesses, results in the outpouring of counter-regulatory endocrine hormones, cytokines and lymphokines. This results in changes in substrate utilization and substance synthesis rates, as well as catabolism and hypermetabolism. Consequently, there is loss of fat and lean body (muscle) mass, a problematic situation that has been named 'auto-cannibalism'. Thus, it is not surprising that this abnormal metabolic meilieu causes disordered utilization of exogenously administered nutrients. Conventional nutritional strategies, such as providing the equivalents of a usual human diet, frequently do not prevent or attenuate the loss of muscle and fat tissue. As a result, many investigational efforts have been directed at overcoming the obstacles placed by this disordered milieu.

Glucose metabolism

The metabolic response to stress → increased secretion of the counter-regulatory (to insulin) hormones cortisol, catecholamines and glucagon → ↑endogenous glucose production that is secondary to accelerated hepatic gluconeogenesis.

Glucose oxidation → (ATP) + H₂O + CO₂; converted to glycogen for storage in the liver and muscles; or converted to fat. The latter process is called lipogenesis and occurs in both liver and adipose tissue, although the latter appears to be the main site for lipogenesis. Under normal circumstances carbohydrate intake inhibits fat oxidation, increases glucose oxidation and promotes fat storage.

When carbohydrate intake exceeds total energy expenditure, lipogenesis becomes a more important pathway, and respiratory quotients may exceed 1.0, indicating net lipogenesis. This may be seen among patients receiving glucose infusions of > 4 mg/kg per min.

Exogenous glucose and carbohydrate administration

The administration of exogenous glucose and carbohydrates to injured or septic patients either does not or only minimally diminishes the rate of gluconeogenesis. This is in contradistinction to refeeding starved patients where carbohydrate administration reduces gluconeogenesis and lipolysis. Despite the reduced utilization of glucose, it is
still important to administer carbohydrates, because some body tissues are unable to use other substrates readily. Furthermore, glucose and carbohydrate intakes stimulate the secretion of additional insulin, an anabolic hormone that promotes protein synthesis and has an antilipolytic affect. Excessive glucose loads (> 4 mg/kg per min), especially when administered to acutely stressed patients receiving a total caloric intake greater than resting energy expenditure, results in a thermogenic response, further elevation of blood glucose concentrations and production of additional carbon dioxide. If the patient is no longer stressed respiratory quotients may exceed 1.0, indicating net lipogenesis. This additional carbon dioxide must be excreted via the lungs.

**Lipid metabolism**

Various stresses, including injury, sepsis and congestive heart failure, cause alterations in lipid metabolism. Lipolysis is accelerated secondary to increased β₂-adrenergic stimulation. Elevated concentrations of glucagon, TNF-α, IL-1, interferon-α and interferon-γ might also play a role in stimulating lipolysis.

Rapid glycerol and free fatty acid turnover rates reflect the accelerated lipolysis seen during stress. The increase in lipolysis also results in an increased systemic supply of free fatty acids. During stress, β-Adrenergic receptor blockade with propranolol decreases lipid oxidation and resting metabolic rates of burn patients.

In the stressed state the relative caloric contribution of fat oxidation to the resting energy expenditure is increased and the contribution of glucose oxidation is decreased. The fatty acids released by lipolysis undergo β-oxidation, which in the stressed patient is the predominant ATP-producing pathway.

**Exogenous lipid administration**

Intravenous exogenous lipid is administered as an emulsion of long-chain triglycerides (LCT). In the blood the lipid emulsion is converted to triglyceride-rich particles, and to phospholipid-rich particles called liposomes. The chylomicron-like particles are hydrolyzed by lipoprotein lipase and release fatty acids. The liposomes stimulate cholesterogenesis. Patients with sepsis and multiple organ dysfunction efficiently metabolize intravenous lipid emulsion, even when chronic hepatic failure is present.

Exogenous lipid is needed to prevent essential free fatty acid deficiency, so it is recommended that patients receiving TPN receive lipid emulsion infusion (500 ml 10% LCT emulsion) two to three times a week. Concern has been expressed over the possible immunosuppressive effects of lipid emulsions. Studies have demonstrated decreased neutrophil bacterial killing, depression of monokine expression and other...
immunodepressant effects.

Increased incidence of infections with lipid emulsion administration leads to recommendations to limit fat calories to 30% of total calories.

**Alternate fuels**

There has been interest in substituting MCT for some of the LCT. MCT do not require carnitine to enter the mitochondria and so may be advantageous in situations where carnitine is reduced, such as in some cases of sepsis. In an attempt to reduce the toxicity of the MCT, structured lipids have been developed. These are lipids with both LCT and MCT bonded to the glycerol backbone. They are known to have higher oxidation rates, faster clearance rates and lower reticuloendothelial system accumulation than MCT (Bellantone et al. 1999).

The soybean derived fat emulsions traditionally used for parenteral nutrition contain omega-6 polyunsaturated fatty acids, specifically arachidonic and linoleic acids. Arachidonic acid is the precursor for prostaglandins such as thromboxane-A\textsubscript{2} and prostaglandin-E\textsubscript{1}, which are associated with platelet aggregation and inflammation. Alternately, fish oils contain fatty acids (e.g., eicosapentaenoic and omega-3 linolenic acids). These are precursors of another class of prostaglandins that include thromboxane-A\textsubscript{3} which have less platelet-aggregating activity and cause less inflammation. The platelets from postoperative patients infused with fish oil-enriched soybean oil lipid emulsions for 7 days after surgery aggregated less than those administered only soybean oil lipid emulsion. Omega-3 Fatty acids also decreased the ex-vivo production of IL-1, IL-6, IL-2 and TNF by peripheral blood mononuclear cells. Oral eicosapentaenoic acid intake after surgery improved lymphocyte proliferation and natural killer cell activity. There has been some interest in using omega-3 fatty acids in adult respiratory distress syndrome to reduce pulmonary microvascular permeability and alveolar macrophage prostaglandin and leukotriene synthesis.

**Protein metabolism**

One of the hallmarks of the metabolic response to injury is catabolism (negative nitrogen balance). There is accelerated proteolysis of skeletal muscle, which provides some of the substrate for increased hepatic gluconeogenesis. The degree of nitrogen loss is proportional to the degree of stress.

The increased protein breakdown is thought to be modulated only partly by the
endocrine stress hormones, such as cortisol. Instead, other mediators such as the cytokines TNF-α, IL-1, IL-6 and interferon-γ are involved in mediating catabolic activity. It is the balance between these catabolic hormones and anabolic hormones such as insulin and insulin-like growth factors that determine the degree of catabolism. A number of metabolic pathways may be responsible for skeletal muscle proteolysis, including the lysosomal calcium-activated, ATP-ubiquitin-dependent proteolytic pathway. The liver also contributes to catabolism through the increase in clearance of α-amino nitrogen (urea). After surgery the rate of this conversion is doubled.

During stress there is increased hepatic synthesis of the 'acute phase' proteins such as fibrinogen, complement, immunoglobulins and C-reactive protein. Increase in these proteins is thought to lead to increased ability to fight infection. Simultaneously, there is reduced synthesis of binding proteins, such as albumin prealbumin, and transferrin (Wiessman 1999).

**Exogenous protein administration**

Amino acids and protein are basic components of nutritional support regimens. The aim of administering exogenous protein or amino acid is to attenuate the breakdown of endogenous proteins by providing an alternate source of amino acids for gluconeogenesis and protein synthesis. Unfortunately, in the stressed state exogenously administered amino acids and protein are not well utilized and nitrogen balance remains negative. In the catabolic state an intake of 1.2-1.5 g/kg per day protein/amino acid is recommended and higher amounts do not promote further nitrogen retention. Instead the added protein/amino acid is metabolized to urea, so the blood urea nitrogen may rise. Situations associated with large external losses of protein, such as extensive burns and large draining abscesses, make it necessary to increase protein/amino acid intake. One of the important consequences of glucose and carbohydrate administration is the stimulation of insulin secretion. At lower doses insulin decreases protein breakdown by inhibiting the major catabolic pathway, the ATP-ubiquitin proteasome proteolytic pathway. At higher doses it is thought also to stimulate protein synthesis.

**Alternate approaches**

The inability of the usual intake of protein/amino acids to attenuate nitrogen losses significantly has led investigators to examine ways of either decreasing proteolysis or increasing protein synthesis. An initial attempt was to provide branched-chain amino acid enriched solutions. This resulted in some improvement in nitrogen balance, but no improvements in outcome. More recent attempts have focused on administering anabolic substances to reduce protein oxidation and improve protein synthesis. During the flow phase of stress, concentrations of growth hormone are
reduced and there is resistance to its actions. Because of its anabolic properties (mediated through insulin-like growth factor-1) there has been much study of growth hormone administration in catabolic patients. The aim of administering growth hormone is to increase nitrogen retention and promote wound healing. Growth hormone administration in critically ill patients receiving nutritional support has been observed to reduce nitrogen loss and improve phosphate retention. A disadvantage of growth hormone is its diabetogenic and lipolytic properties. In the studies performed thus far with growth hormone administration in the critically ill, no definitive improvement in patient outcome was observed.

**The effect of critical illness on the gut (Thompson 1995).**

The mucosal cells of the gastrointestinal tract have one of the highest turnover rates of any body tissue. Endothelial renewal depends on the division and migration of stem cells within the mucosal crypts. Therefore an intact gut mucosa depends on a balance between cell renewal and exfoliation. The intact mucosal layer, tight junctions between cells, lymphocytes, macrophages, and neutrophils in the submucosa and Peyer's patches, and gut-generated IgA all contribute to barrier function of the gut. A fall in perfusion and tissue oxygenation, which occurs in many forms of critical illness, is a significant insult to the gut. Splanchnic hypoperfusion may persist after apparently adequate fluid resuscitation, and even short periods of circulatory compromise may result in prolonged gut ischemia/hypoxia. This may cause cell injury, necrosis, and loss of mucosal integrity, a state which may be exacerbated by coexisting malnutrition, bacterial overgrowth of the gut, and (possibly) reperfusion injury following periods of hypovolemia and hypotension. Bacterial translocation (the migration of viable bacteria across the intestinal barrier to the liver, spleen, or mesenteric lymph nodes) and endotoxin translocation may occur following loss of barrier function. When such processes occur to a limited extent, which may be an everyday event, the Kupffer cells in the liver prevent spill-over into the systemic circulation. When there is a major deficiency in gut barrier function, systemic spill-over occurs because (i) the liver is overwhelmed by the amount of bacteria and/or endotoxin presented to it and (ii) often the cause of gut barrier failure (e.g. hypoperfusion) will also induce hepatic dysfunction, preventing efficient phagocytosis of bacteria and removal of endotoxin in portal blood.
NUTRITION AND ENERGY REQUIREMENTS

The fundamental goal of nutritional support is to provide individual patients with their daily nutritional requirements. (Mandt et al.1992).

Oxidative combustion

According to the Laws of Thermodynamics, energy can neither be produced nor destroyed. Therefore, the only way to obtain energy is to transfer it from an energy source in nature. nd this releases energy from the fuel that is then used to power the human body.

Table -1 Energy yield from organic fuel (Marino and Kenneth 2006)

<table>
<thead>
<tr>
<th>Fuel</th>
<th>VO2(L/g)</th>
<th>VCO2(L/g)</th>
<th>*RQ</th>
<th>Energy Yield(kcal/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid</td>
<td>2.00</td>
<td>1.40</td>
<td>0.70</td>
<td>9.1</td>
</tr>
<tr>
<td>Protein</td>
<td>0.96</td>
<td>0.78</td>
<td>0.80</td>
<td>4.0</td>
</tr>
<tr>
<td>Glucose</td>
<td>0.74</td>
<td>0.74</td>
<td>1.00</td>
<td>3.7</td>
</tr>
</tbody>
</table>

*Respiratory quotient: RQ=VCO2/VO2

Organic fuels

The three organic (carbon-based) fuels used by the human body are carbohydrates, proteins, and lipids. The information in this table can be stated as follows:

1gm glucose + 0.74 L of O2 yields 0.74 L of CO2 + 3.75 kcal

The summed metabolism of all three organic substrates determines the total-body O2 consumption (VO2), CO2 production (VCO2), and energy expenditure (EE) for any given period. The 24-hour EE then determines the daily calorie requirements that must be provided by nutrition support.(Marino and Kenneth 2006)

DAILY ENERGY EXPENDITURE

can be estimated or measured.

1-Perdictive equations.

simplified predictive equation for the BEE is as follows:
BEE(Kcal/day)=25 X wt (kg)

**Adjustments in BEE**

To allow for the thermal effect of food intake, the BEE is multiplied by 1.2 to derive the resting energy expenditure (REE), which is the energy expenditure of basal metabolism in the resting but not fasted state.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Adjustment Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>BEE X 1.1</td>
</tr>
<tr>
<td>Mild stress</td>
<td>BEE X 1.2</td>
</tr>
<tr>
<td>Moderate stress</td>
<td>BEE X 1.4</td>
</tr>
<tr>
<td>Severe stress</td>
<td>BEE X 1.6</td>
</tr>
</tbody>
</table>

The actual adjustments for severe illness can vary widely in individual patients (Mann et al. 1985). Comparing predicted and actual energy expenditure in critically ill patients have shown that the predictive equations (with adjustments for degree of stress) overestimate daily energy needs by 20 to 60%. For this reason, measurements of energy expenditure are more accurate than predictive equations in patients (Weissman et al. 1986).

**Table-2. Equations for daily energy expenditure** (Bursztien et al. 1989)

<table>
<thead>
<tr>
<th>Basal Energy Expenditure BEE:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men BEE(Kcal/24h)=66+(13.7 X wt)+(5.0 X ht)-(6.7 X age)</td>
</tr>
<tr>
<td>Women BEE(Kcal/24h)=655+(9.6 X wt)+(1.8 X ht)-(4.7 X age)</td>
</tr>
</tbody>
</table>

(Wt=weight in kilogram, ht=height in inches)

<table>
<thead>
<tr>
<th>Resting Energy Expenditure(REE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>*REE(Kcal/24hr)=[(3.9 X VO2)+(1.1 X VCO2)-61] X 1440</td>
</tr>
<tr>
<td>**REE(Kcal/24hr)=BEE X 1.2</td>
</tr>
</tbody>
</table>

*the VO2 and VCO2 are measured in mL/min, and the multiplier 1440 is used to convert the time period to 24 hr  **REE=BEE+ the thermal effect of food

**2- Indirect calorimetry**

Because it is impossible to measure metabolic heat production in clinical practice, the metabolic energy expenditure is measured indirectly by measuring the whole-body VO2 and VCO2. This technique is called indirect calorimetry (Healhy et
The REE can be derived from the whole-body VO₂ and VCO₂ by using the equation shown in Table 2. (Bursztein et al.1989).

**Method:**

Indirect calorimetry is performed with specialized instruments called metabolic carts that measure the exchange of O₂ and CO₂ across the lungs. These instruments can be placed at the bedside, and gas exchange measurements are obtained over 15 to 30 minutes. The VO₂ and VCO₂ are then extrapolated to a 24-hour period, and the 24-hour REE is calculated by using an equation similar to the one shown in Table 2. (Marino and Kenneth 2006).

**Limitations:**

Indirect calorimetry is the most accurate method for determining the daily energy requirements of individual patients in the ICU. However, several factors limit the popularity of indirect calorimetry in the clinical setting. First and foremost, the technique requires relatively expensive equipment and specially trained personnel, and it is not universally available. In addition, the oxygen sensor in most metabolic carts is not reliable at inspired oxygen levels above 50%, so indirect calorimetry can be unreliable in patients with respiratory failure who require inhaled oxygen concentrations above 50% (McClave et al.1992). Because of all these limitations, daily caloric needs are often estimated using predictive formulas such as the Harris-Benedict equations, whereas indirect calorimetry (if available) is reserved for selected patients who require careful titration of daily energy intake (e.g., ventilator-dependent patients)(Marino and Kenneth 2006).

**VITAMIN REQUIREMENTS:**

Twelve vitamins are considered an essential part of the daily diet. The recommended daily dose of individual vitamins in enteral and parenteral nutritional regimens is shown in Table-4 (Headly 2003). It is important to emphasize that the daily vitamin requirements may be much higher than indicated in this table in seriously ill, hypermetabolic patients. In fact, deficiencies in several vitamins have been documented in hospitalized patients, despite the daily provision of vitamins in nutritional support regimens (Dempsey et al.1987).

Table-4 Recomended daily requirments for vitamins (Dark and Pingleton 1993)
Thiamine (vitamin B1) is a component of thiamine pyrophosphate, an essential cofactor in carbohydrate metabolism. Thiamine deficiency is likely to be common in patients in the ICU for the following reasons, 1- the normal body content of thiamine is only approximately 30 mg. Assuming a daily thiamine requirement of 3 mg in patients in the ICU, lack of thiamine intake could result in depletion of endogenous thiamine stores after just 10 days. 2- the use of thiamine is increased beyond expected levels in hypercatabolic conditions 3- urinary thiamine excretion is increased by furosemide, which is a commonly used diuretic in the ICU. 4- magnesium is necessary for the conversion of thiamine into thiamine pyrophosphate, so magnesium depletion (which is common in patients in the ICU) causes a "functional" form of thiamine deficiency.

Disorders of thiamine deficiency

Four clinical disorders are associated with thiamine deficiency: (a) Cardiac dysfunction (beriberi heart disease), (b) Metabolic (Wernicke's) encephalopathy, (c) Lactic acidosis [Thiamine serves as a co-factor for the enzyme pyruvate dehydrogenase that initiates pyruvate oxidation in the mitochondria so thiamine deficiency should be considered in unexplained hyperlactatemia in ICU]. (d) Peripheral neuropathy. These conditions are common in patients in the ICU, and thiamine deficiency should be considered in each case in which one of these disorders is unexplained (Butterworth and Thiamin 2006).

Diagnosis

The most reliable assay of functional intracellular thiamine stores is the erythrocyte transketolase assay (Boni et al.1980). This assay measures the activity of a thiamine pyrophosphate-dependent (transketolase) enzyme in the patient's red blood
cells in response to the addition of thiamine pyrophosphate (TPP). An increase in enzyme activity of greater than 25% after the addition of TPP indicates a functional thiamine deficiency. Plasma thiamine levels are used to screen for thiamine depletion and transketolase assay is reserved for determining the end-point of thiamine repletion in patients with documented thiamine deficiency (Oriot et al. 1991).

Anti oxididant Vitamins:

Two vitamins serve as important endogenous antioxidants: vitamin C and vitamin E, vitamin E is the major lipid soluble antioxidant in the body, and vitamin C is water soluble and serves as one of the major antioxidant in the extracellular fluid. Considering the important role that oxidation-induced cell injury may have in multiorgan failure in serious illnesses, it is wise to maintain adequate body stores of the antioxidant vitamins in critically ill patients. The increased rates of biological oxidation that are common in critical illness are likely to increase the daily requirements for vitamin C and vitamin E (Dark and Pingleton 1993).

ESSENTIAL TRACE ELEMENTS:

A trace element is a substance that is present in the body in amounts less than 50 ug per gram of body tissue (Fleming 1989). Seven trace elements are considered essential in humans (i.e., associated with a deficiency syndrome.

Iron

A reduced serum iron level in a critically ill patient should not prompt iron replacement therapy unless there is evidence of total-body iron deficiency. This latter condition can be detected with a plasma ferritin level; that is, a plasma ferritin below 18 ug/L indicates probable iron deficiency, whereas a plasma ferritin above 100 ug/L means that iron deficiency is unlikely (Guytatt et al. 1990).

Selenium

Selenium is an endogenous antioxidant by virtue of its role as a co-factor for glutathione peroxidase, one of important endogenous antioxidant enzymes. Selenium use is increased in acute illness, and plasma selenium levels can fall to subnormal levels within 1 week after the onset of acute illness (Yusuf et al. 2002). Since selenium supplementation is not routinely included in parenteral nutrition support regimens,
prolonged parenteral nutrition is accompanied by selenium deficiency. The combination of increased selenium use and lack of daily selenium supplementation may make selenium deficiency common in patients in the ICU. Such a condition will promote oxidant cell injury (Ishida et al. 2003).

The acute selenium status is best monitored by measuring the plasma selenium levels. The normal range is 89-113 mg/L (Geoghegan et al. 2006). The minimum daily requirements is likely to be much higher in hypermetabolic patients in the ICU. The maximum daily dose of selenium that is considered safe is 200 ug, and this dose is probably more appropriate for ICU patients which can be given intravenously as sodium selenite at dose of 200 ug IV daily if needed (Ishida et al. 2003).

**Nutrient Toxicity**

In healthy subjects, less than 5% of exogenously administered glucose is metabolized to form lactate. However, in acutely ill patients, up to 85% of an exogenous glucose load can be recovered as lactate.

Patients undergoing abdominal aneurysm surgery were given intraoperative fluid therapy with either Ringer's solutions or 5% dextrose solutions. In the patients who received the 5% dextrose solution (total amount of dextrose infused averaged 200 g), the blood lactate increased by 3 mmol/L, whereas in the patients who received an equivalent volume of the glucose-free (Ringer's) solution, the blood lactate level increased only 1 mmol/L. Thus an organic nutrient (carbohydrate) can be used to generate a metabolic toxin (lactic acid) when nutrient processing is abnormal (during the stress of abdominal aneurysm surgery) (Degoute et al. 1989).
Figure 2 Effect of carbohydrate infusion on arterial lactate levels during abdominal aortic surgery. Each point represents the mean lactate level for 10 patients receiving Ringer's solution and 10 patients receiving 5% dextrose solution. Total volume infused is equivalent with both fluids. (Manchon et al, 1989)
CHAPTER 3

ENTERAL TUBE NUTRITION

One of the important features of the gastrointestinal (GI) tract is the role of the intestinal epithelium as a barrier to invasion by pathogenic microorganisms. The barrier function of the bowel mucosa is maintained by the intake and processing of bulk nutrients along the digestive tract. Therefore, providing nutrients via the enteral route not only provides nutritional support for the vital organs, but also supports host defenses against invasive infection (Bistrian and McCowen 2006).

TROPHIC EFFECT OF ENTERAL NUTRIENTS

Complete bowel rest is accompanied by progressive atrophy and disruption of the intestinal mucosa (Alpers 2002). This effect becomes evident after just a few days and is not prevented by parenteral (intravenous) nutrition (Alverdy et al. 2003). One of the nutrients that may play an important role in this process is the amino acid glutamine, which is considered the principal metabolic fuel for intestinal epithelial cells (Herskowitz et al. 1990).

Translocation

The process of translocation, where enteric pathogens move across the bowel mucosa and into the systemic circulation, has been documented during periods of bowel rest in critically ill patients (Wiest et al. 2003). This means that enteral nutrition could help prevent translocation and subsequent sepsis by maintaining the functional integrity of the bowel mucosa. The potential for enteral nutrition to prevent sepsis of bowel origin is one of the major reasons why enteral nutrition has become favored over parenteral (intravenous) nutrition in critically ill patients (Deitch et al. 1987).
Figure 3 Photomicrographs showing the normal appearance of the small bowel mucosa (upper), and the mucosal disruption after 1 week of a protein-deficient diet (lower). Quoted from Deitch et al. 1987.

Figure 4 The triple threat of translocation. This diagram of an intestinal microvillus shows three conditions that predispose to blood stream invasion by enteric microorganisms. (Wiest et al. 2003)
**PATIENT SELECTION**

In the absence of contraindications, enteral tube feedings are indicated when nutrient intake has been inadequate for 1-3 days. Table 7 (Heyland, et al. 2003) In patients who are at risk of bacterial translocation across the bowel (e.g., burn victims), tube feedings should be started as soon as possible after the onset of inadequate nutrient intake (Kreymann et al. 2006). The decision to initiate enteral feeding depend also on parameters for nutritional status.

### Table 7  Parameters for nutritional status. (Erich et al. 2002)

<table>
<thead>
<tr>
<th>BMI</th>
<th>Protein(g/l)</th>
<th>Albumin(g/l)</th>
<th>Prealbumin(mg/l)</th>
<th>Undernutrition</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 19</td>
<td>67-83</td>
<td>&gt; 35</td>
<td>&gt; 160</td>
<td>None</td>
</tr>
<tr>
<td>17-19</td>
<td>60-66</td>
<td>30-35</td>
<td>140-160</td>
<td>Mild</td>
</tr>
<tr>
<td>16-16.9</td>
<td>50-59</td>
<td>25-29</td>
<td>110-139</td>
<td>Moderate</td>
</tr>
<tr>
<td>&lt; 16</td>
<td>&lt; 50</td>
<td>&lt; 25</td>
<td>&lt; 110</td>
<td>Severe</td>
</tr>
</tbody>
</table>

**Contraindications** (Bistrian et al. 2006)

Enteral feedings in any amount are contraindicated in patients with 1. circulatory shock, 2. intestinal ischemia, 3. complete mechanical bowel obstruction, or ileus.

Total enteral nutrition is not advised in patients with the following conditions: 1. partial mechanical bowel obstruction 2. severe or unrelenting diarrhea 3. pancreatitis, 4. high-volume (more than 500 mL daily) enterocutaneous fistulas. Partial (low volume) enteral support is, however, possible in these conditions. In the case of pancreatitis, enteral feedings can be delivered into the jejunum.

**FEEDING TUBES** (Dotson et al. 1996)

Standard nasogastric tubes (14 to 16 French) are no longer favored for enteral tube feedings because of patient discomfort. The feeding tubes that are currently favored are narrower (8 to 10 French) and more flexible than standard nasogastric tubes. Because these tubes are so flexible, a rigid stylet is also provided to facilitate insertion.
**Insertion**

Feeding tubes are inserted through the nares and advanced into the stomach or duodenum. The distance that the tube must be advanced to reach the stomach can be estimated by measuring the distance from the tip of the nose to the earlobe and then to the xiphoid process (typically 50-60 cm). (Stroud et al. 2003). Proper placement in the stomach is sometimes possible to determine by measuring the pH (with litmus paper) of a specimen aspirated from the tip of the feeding tube. If the specimen has a pH less than 5, the tip of the tube is likely to be in the stomach. Feeding tubes that are equipped with a pH sensor are also available. (Metheny et al. 1994)

**Tracheal intubation**

The principal complication of feeding tube placement is accidental tracheal intubation in 1%. Because feeding tubes are narrow, they readily pass through the larynx and around the inflated cuffs on tracheal tubes. (Baskin 2006)

**Figure 5** Accidental placement of feeding tube in the trachea. (Kolbitsch et al. 1997)

Accidental intubation of the trachea is often asymptomatic (probably because of sedation, depressed consciousness, or an abnormal cough reflex), and in the absence of symptoms, tubes can be advanced into the distal airways. If feeding tubes are advanced too far into the lungs, the rigid stylet makes it easy to puncture the visceral pleura and produce a pneumothorax (Kolbitsch et al. 1997). Because of the risk of asymptomatic intubation of the lungs, a postinsertion chest x-ray study is often required to evaluate tube placement (unless pH testing confirms gastric placement). Auscultation of the upper abdomen while insufflating air through the tube is not a reliable method for excluding tube malposition in the lungs because sounds emanating from a tube in the
lower airways can be transmitted into the upper abdomen (Fisman and Ward 1996).

**Duodenal Placement**

For those who prefer tube feedings placed in the duodenum instead of the stomach, gastric tubes must be advanced past the pylorus and into the duodenum. This can sometimes be accomplished by specialized maneuvers at the bedside or may require fluoroscopic guidance. Tube passage into the duodenum can be confirmed by an increase in the pH of feeding tube aspirates to above 6.0, or by radiographic localization. (Baskin et al.2006)

**Importance:**

1. It improves delivery of enteral nutrition.
2. It reduces the risk of ventilator-associated pneumonia in the setting of enteral nutrition.

Figure 6 Abdominal X-ray small bowel feeding tube.(Daren et al 2005)
Feeding Site

The proposed advantage of duodenal feedings is a reduced risk of reflux of feeding solution into the esophagus and subsequent pulmonary aspiration (Jabbar and McClave 2005). Clinical studies show that the risk of aspiration in duodenal feedings is the same as that in gastric feedings. Therefore, the time and effort devoted to advancing gastric tubes into the duodenum is not justified. (Kreymann et al.2006)

FEEDING FORMULAS

Features of enteral feeding formulas.

1-Caloric density

The caloric density of feeding formulas is determined primarily by the carbohydrate content. Most formulas provide 1 to 2 kilocalories per ml of solution. The formulas that provide 1 to 1.5 kcal/ml (standard caloric density) and the formulas that provide 1.5 to 2 kcal/ml (high caloric density). The energy-rich formulas are well-suited for patients with excessive daily energy needs and for patients who are volume-restricted. (Kreymann et al.2006).

2-Osmolality

The osmolality of liquid feeding formulas varies from 280 to 1100 mOsm/kg H2O. The major determinant of osmolality is the carbohydrate content. Because carbohydrates also determine caloric density, osmolality and caloric density are directly related. Formulas with the lowest caloric density (1 kcal/ml) have the lowest osmolalities (approximately 300 mOsm/kg H2O) and are usually isotonic to the body fluids. Formulas with the highest caloric density (2 kcal/ml) have the highest osmolalities (1000 mOsm/kg H2O) and are markedly hypertonic to the body fluids (Malon 2005). Hypertonic formulas should be infused into the stomach to take advantage of the dilutional effects of the gastric secretions. (Marino and Kenneth 2006)

Table 8 Characteristics of selected enteral feeding formulas (Malon et al.2005)

<table>
<thead>
<tr>
<th>Formula</th>
<th>Caloric Density (kcal/ml)</th>
<th>Protein(g/L)</th>
<th>Osmolarity (mOsm/L)</th>
<th>Volume to meet US RDA*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ensure plus HN</td>
<td>1.5</td>
<td>63</td>
<td>525</td>
<td>1000</td>
</tr>
<tr>
<td>Isocal</td>
<td>1.1</td>
<td>34</td>
<td>270</td>
<td>1890</td>
</tr>
<tr>
<td>Isocal HN</td>
<td>1.1</td>
<td>44</td>
<td>270</td>
<td>1180</td>
</tr>
<tr>
<td>Nutren</td>
<td>1.0</td>
<td>40</td>
<td>315</td>
<td>1500</td>
</tr>
<tr>
<td>Osmolite</td>
<td>1.1</td>
<td>37</td>
<td>300</td>
<td>1890</td>
</tr>
<tr>
<td>Osmolite HN</td>
<td>1.1</td>
<td>44</td>
<td>300</td>
<td>1320</td>
</tr>
</tbody>
</table>
Peptamen | 1.0 | 40 | 270 | 150
Ultraceal | 1.1 | 37 | 500 | 1180
Vivonex TEN | 1.0 | 38 | 630 | 2000
Vital HN | 1.0 | 42 | 500 | 1500

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

Table 9 Enteral formulas with a high caloric density (Malon 2005)

<table>
<thead>
<tr>
<th>Formula</th>
<th>Caloric Density (kcal/ml)</th>
<th>Osmolality (mOsm/kg H2O)</th>
<th>Volume to meet US RDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nepro</td>
<td>2</td>
<td>665</td>
<td>1000</td>
</tr>
<tr>
<td>Novasource Renal</td>
<td>2</td>
<td>700</td>
<td>1000</td>
</tr>
<tr>
<td>TwoCal HN</td>
<td>2</td>
<td>725</td>
<td>950</td>
</tr>
</tbody>
</table>

3-Protein (Malon 2004)

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

Protein complexity (Malon 2005)

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

4-Lipids

The lipid emulsions used in feeding formulas are rich in long-chain triglycerides derived from vegetable oils. These lipids represent a concentrated source of calories, with an energy yield (9 kcal/g) that is almost three times that of carbohydrates (3.4 kcal/g). Because excessive fat ingestion is not well tolerated (i.e., it promotes diarrhea), the lipid content of most feeding formulas is limited to 30% of the total calories.
(Gadek et al.1999).

**Table 10 Feeding formulas with an altered lipid composition** (Malon 2005)

<table>
<thead>
<tr>
<th>Formula</th>
<th>Feature</th>
<th>Proposed Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune Aid</td>
<td>Contains omega3 fatty acids, RNA, arginine, and glutamine</td>
<td>Enhances immune function, limits inflammatory-mediated tissue injury</td>
</tr>
<tr>
<td>Oxepa</td>
<td>Contains omega 3 fatty acids, arginine, antioxidants</td>
<td></td>
</tr>
<tr>
<td>Impact</td>
<td>Contains omega 3 fatty acids, arginine, antioxidants</td>
<td></td>
</tr>
<tr>
<td>Pulmocare</td>
<td>High lipid content lipid provide 55% of the calories in the formula</td>
<td>Limits nutrition-induced CO2 retention in respiratory failure</td>
</tr>
</tbody>
</table>

**Lipid-Rich Formula**

One liquid feeding formula with a high fat content is pulmocare, which uses lipids to provide 55% of the total calories. This formula is intended for patients with respiratory failure. The proposed benefit is based on the low rate of CO2 production relative to O2 consumption associated with lipid metabolism. Thus when lipids replace carbohydrates as the principal nutrient substrate, metabolic CO2 production will decline and there will be less of a tendency for CO2 retention in patients with compromised lung function (Malon 2005).

**Alternative Lipids**

(ImmunAid-Pulmocare) contain dietary fat from sources other than vegetable oils. Polyunsaturated fatty acids from vegetable oils can serve as precursors for inflammatory mediators (eicosanoids) that are capable of producing widespread cell injury. The omega-3 fatty acids do not promote the production of harmful inflammatory mediators, and thus they might be preferred to the standard dietary fats to limit the risk of inflammatory-mediated tissue injury (Bistrian et al. 2006). Several feeding formulas contain omega-3 fatty acids oils, and are included in Table 10.[Oxepa, Impact, Immune-Aid] These formulas are intended for patients with systemic inflammation or ARDS who are at risk for inflammatory-mediated tissue injury (Zaloga et al. 2004)
ADDITIVES

1-Glutamine

Glutamine is the principal fuel for the bowel mucosa (Herskowitz and Souba, 1990). Daily supplementation with glutamine seems a reasonable measure for maintaining the functional integrity of the bowel mucosa. Although glutamine is not an essential amino acid (because it is produced in skeletal muscle), tissue glutamine stores decline precipitously in acute, hypercatabolic states (De-Souza and Greene, 2005).

Glutamine Enriched Formulas

All feeding formulas that contain intact protein will also contain glutamine (Swails et al, 1992). With the exception of AlitraQ (Ross Laboratories) or Impact glutamine (Novartis Laboratories), the glutamine content of enteral feeding formulas is low and may be insufficient to provide a benefit (Garcia-de-Lorenzo et al, 2003). The average glutamine dosage (oral and intravenous) was 0.35 g/kg/day, or 24.5 g/day for a 70-kg subject. Assuming a daily caloric intake of 2000 kcal, the only feeding formula that will provide a glutamine dosage of 0.35 g/kg/day is AlitraQ and Impact glutamine. In the setting of hypercatabolism, the glutamine provided by most enteral formulas will be even more inadequate. Therefore, although the use of glutamine-fortified enteral formulas seems reasonable, the amount of glutamine provided by most formulas may be inadequate (Ziegler et al, 1990).

Table 11 Glutamine-Enriched feeding formulas (Malon et al, 2005)

<table>
<thead>
<tr>
<th>Formula</th>
<th>Manufacturer</th>
<th>Glutamine (g/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AlitraQ</td>
<td>Rose</td>
<td>15.5</td>
</tr>
<tr>
<td>Impact Glutamine</td>
<td>Novartis</td>
<td>15</td>
</tr>
<tr>
<td>Replete</td>
<td>Nestle</td>
<td>3.3</td>
</tr>
<tr>
<td>Vivonex TEN</td>
<td>Novartis</td>
<td>3.3</td>
</tr>
</tbody>
</table>

2-Dietary Fiber (Palacio and Rombeau, 1990).

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

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

**Nonfermentable fiber** (lignins) is not degraded by intestinal bacteria, but it can create an osmotic force that adsorbs water from the bowel lumen. This type of fiber can therefore reduce the tendency for watery diarrhea. Thus fiber has several actions that can reduce the tendency for diarrhea during enteral feedings. Furthermore, fermentable fiber can serve as a source of metabolic support for the mucosa of the large bowel. This latter effect could play an important role in limiting the tendency for translocation across a disrupted large bowel mucosa.

**Table 12** Fiber-Enriched Enteral Feeding Formulas (Marino and Kenneth 2006).

<table>
<thead>
<tr>
<th>Formula</th>
<th>Fiber (g/L)</th>
<th>Formula</th>
<th>Fiber (g/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrich</td>
<td>14.3</td>
<td>Isosouece 1.5 Cal</td>
<td>8</td>
</tr>
<tr>
<td>Fibrosource</td>
<td>10</td>
<td>Jevity</td>
<td>14.4</td>
</tr>
<tr>
<td>Fibrosource HN</td>
<td>10</td>
<td>Nutren1.0 Fiber</td>
<td>14</td>
</tr>
<tr>
<td>Glucerna</td>
<td>14.3</td>
<td>Ultracal</td>
<td>14.4</td>
</tr>
</tbody>
</table>

**3-Miscellaneous**

**Branched Chain Amino Acids**

The branched chain amino acids (BCAAs) isoleucine, leucine, and valine are available in feeding formulas intended for trauma victims and patients with hepatic encephalopathy. In trauma victims, the BCAAs can be used as a fuel source in skeletal muscle, thereby sparing the degradation of other muscle proteins to provide energy. In hepatic encephalopathy, the BCAAs can antagonize the uptake of aromatic amino acids (e.g., tryptophan) into the central nervous system, and this helps prevent the subsequent breakdown of the aromatic amino acids to form false neurotransmitters, which have been implicated in the pathogenesis of hepatic encephalopathy (James 2002).

**Carnitine**

Carnitine is necessary for the transport of fatty acids into mitochondria for fatty acid oxidation. Humans normally synthesize carnitine from lysine and methionine (essential amino acids) in sufficient amounts so that the dietary intake is not required (Rebouche 2006).

Deficiency of carnitine (plasma concentration below 20umol/L) can occur in prolonged states of hypercatabolism or during prolonged haemodialysis when carnitine
intake is eliminated. The clinical consequences of carnitine deficiency include cardiomyopathy, skeletal muscle myopathy, and hypoglycemia (Kazmi et al. 2005). The recommended daily dose of carnitine is 20-30mg/kg in adults.

**FEEDING REGIMEN**

Tube feedings are usually infused for 12 to 16 hours in each 24-hour period. Continuous infusion without a period of bowel rest is an unrelenting stress to the bowel mucosa and promotes malabsorption and diarrhea. Intermittent bolus feedings more closely approximate the normal condition, but the volumes required are often too large to be given safely (Rees et al. 1986).

**Gastric Retention**

Before gastric feedings are started, it is necessary to determine how much volume will be retained in the stomach over a 1-hour period because this will determine how fast the feedings can be administered. A volume of water that is equivalent to the desired hourly feeding volume should be infused over 1 hour. After the infusion is complete, the feeding tube should be clamped for 30 minutes. The tube should then be unclamped, and any residual volume should be aspirated from the stomach. If the residual volume is less than 50% of the volume infused, gastric feeding can proceed. If the residual volume is excessively high, duodenal or jejunal feedings may be more appropriate. When the gastric residual volume is measured, it is important not to administer the volume as a bolus because this will produce acute gastric distension and lead to overestimation of the residual volume (Stroud et al. 2003).

**Starter Regimens (Mizock 1993)**

The traditional approach to initiating tube feedings is to begin with dilute formulas and a slow infusion rate and gradually advance the formula concentration and infusion rate over the next few days until the desired nutrient intake is achieved. This presumably allows the atrophic bowel mucosa time to regenerate after a period of bowel rest. The drawback with starter regimens is the fact that nutrient intake is inadequate for the time required to advance to full nutritional support. In the malnourished patient, this added period of inadequate nutrition adds to the malnutrition. Full feedings can be delivered immediately without troublesome vomiting.
or diarrhea. This is presumably due to the ability of gastric secretions to dilute the feeding formula and reduce the osmotic load associated with the feedings. Therefore, starter regimens are unnecessary for gastric feedings. Because of the limited reservoir function of the small bowel, starter regimens are usually required for duodenal and jejunal feedings.

COMPLICATIONS

The complications associated with enteral feedings include 1- occlusion of the feeding tube, 2- reflux of gastric contents into the airways [aspiration] and 3- and diarrhea.

1- Tube Occlusion

Narrow-bore feeding tubes can become occluded by accumulation of residue from the feeding formula (Marcuard and Perkins 1998). Standard preventive measures include flushing the feeding tubes with 30 mL of water every 4 hours, and using a 10-mL water flush after medications are instilled (Benson et al. 1990).

Relieving the Obstruction

If there is still some flow through the tube, warm water should be injected into the tube and agitated with a syringe. This can relieve the obstruction in 30% of cases. If this is ineffective, pancreatic enzyme can be used.

2- Aspiration

Retrograde regurgitation of feeding formula is reported in as many as 80% of patients receiving gastric or duodenal feedings (Metheny 1993). The risk of reflux in gastric feedings is the same as that in duodenal feedings (Metheny 2002). Elevating the head of the bed to 45 degrees can reduce—although not eliminate the risk of reflux (Castel et al. 2005).

Detection of aspiration

Aspiration of feeding formulas into the airways can be detected by testing tracheal aspirates with glucose oxidase reagent strips. The results are measured with an
automated glucose meter. A glucose concentration greater than 20 mg/dL in tracheal aspirates is evidence of aspiration. (Potts et al.1993).

**3-Diarrhea**

Diarrhea occurs in approximately 30% of patients receiving enteral tube feedings (Edes et al.1990). Although the hypertonicity of enteral feeding formulas can induce an osmotic diarrhea, in most cases of diarrhea associated with enteral feedings, the feeding formula is not responsible for the diarrhea (Eisenberg 1993). The cause of the diarrhea in many cases is a medicinal elixir that contains sorbitol (an osmotic agent) to improve palatability. Most cases, the daily dosage of sorbitol can be enough to induce an osmotic diarrhea. (Cheng et al.1999).

**Stool Osmolal Gap**

Clostridium difficile enterocolitis is also a possible cause of diarrhea during enteral feedings. To differentiate the secretory diarrhea caused by C. difficile enterocolitis from the osmotic diarrhea caused by hypertonic feedings or medicinal elixirs calculate the stool osmolal gap:

\[ \text{Osmolal gap} = \text{Measured stool osmolality} - 2(\text{stool}[\text{Na}] - \text{stool}[\text{K}^+]) \]

A stool osmolal gap greater than 160 mOsm/kg H2O suggests an osmotic diarrhea secondary to hypertonic tube feedings or medicinal elixirs, whereas a smaller (or negative) osmolal gap suggests a secretory diarrhea caused by C. difficile enterocolitis (Eisenberg 1993).
JEJUNOSTOMY FEEDINGS

Although abdominal surgery usually is accompanied by 24 to 48 hours of gastric hypomotility, the motility of the small bowel is often unimpaired. Infusion of liquid feeding formulas into the jejunum takes advantage of the continued small bowel motility after abdominal surgery and allows immediate postoperative nutrition. Jejunal feedings can also be performed for nutritional support of patients with pancreatitis (Sagar et al. 1992).

**Needle Catheter Jejunostomy**

A feeding jejunostomy can be performed as a "complimentary" procedure during laparotomy. A needle catheter jejunostomy is shown in Figure 7. A loop of jejunum (15 to 20 cm distal to the ligament of Treitz) is mobilized to the anterior abdominal wall, and a 16-gauge catheter is tunneled through the submucosa of the...
jejunum for a distance of 30 to 45 cm and then advanced into the bowel lumen. The jejunum is then secured to the peritoneum on the underside of the abdominal wall, and the catheter is secured to the skin. (Nance et al.1995)

**Figure 7** A needle catheter jejunostomy(Nance et al.1995)

Feeding Method

The small bowel does not have the reservoir capacity of the stomach, so starter regimens are recommended for jejunal feedings. Feedings are usually initiated at a rate of 15 to 25 mL/hour, and the infusion rate is gradually increased over the next few days until full nutritional support is achieved. Catheters are flushed with 10 mL of saline every 6 hours to promote catheter patency. (Collier et al.1994)

Complications

The principal complications of needle catheter jejunostomies are diarrhea and occlusion of the narrow feeding catheters. Because of the latter complication, needle catheter jejunostomies are used only for temporary nutritional support (approximately 1 week). If more prolonged jejunal feedings are desired, a needle catheter jejunostomy can be converted to a standard jejunostomy (which uses a 12 French feeding tube) using a special technique (Antinori et al.1992).
Figure 6. Quoted from Heyland et al. 2003.
Figure 7  Quoted from Heyland, et al. 2003
Figure 8. Quoted from Heyland et al. 2003
CHAPTER 4

TOTAL PARENTERAL NUTRITION

When full nutritional support is not possible with enteral tube feedings, the intravenous delivery of nutrients can be used to supplement or replace enteral nutrition. (Dudrick 2003).

Indications of parenteral nutrition

Gastrointestinal tract interruption, patients with high protein losses and high caloric requirements (Burns, sepsis, major surgery or trauma), considered the major indications of TPN in critically ill patients (Tayek 1998).

INTRAVENOUS NUTRIENT SOLUTIONS

Dextose Solutions

The standard nutritional support regimen uses carbohydrates to supply approximately 70% of the daily (nonprotein) calorie requirement. These are provided by dextrose (glucose) solutions, the dextrose solutions must be concentrated to provide enough calories to satisfy daily requirements. The dextrose solutions used for TPN are hyperosmolar and should be infused through large central veins. (Heyland et al. 2003)

Table 14 Intravenous Dextrose solutions (Heyland et al. 2003)

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

*Based on an oxidation energy yield of 3.4 kcal/g for dextrose

Amino Acid Solutions

Amino acid solutions are mixed together with the dextrose solutions to provide the daily protein requirements. The standard amino acid solutions contain
approximately 50% essential amino acids (N = 9) and 50% nonessential (N = 10) plus semiessential (N = 4) amino acids. The nitrogen in essential amino acids is partially recycled for the production of nonessential amino acids, so the metabolism of essential amino acids produces less of a rise in the blood urea nitrogen concentration than metabolism of nonessential amino acids. For this reason, amino acid solutions designed for use in renal failure are rich in essential amino acids. Nutritional formulas for hypercatabolic conditions (e.g., trauma) and hepatic failure can be supplemented with branched chain amino acids (isoleucine, leucine, and valine).

Table 15. Standard and specialty amino Acid solutions (Borgsdrof et al. 2006)

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

**Glutamine**

Glutamine is the principal metabolic fuel used by intestinal epithelial cells, and lack of glutamine may be at least partly responsible for the atrophy of the bowel mucosa that accompanies prolonged periods of bowel rest. Glutamine-enriched TPN has been shown to reduce the atrophic changes in the bowel mucosa during periods of bowel rest and preventing bacterial translocation (De-Souza and Green 2005). (Wischmeyer 2006). Available evidence support the role of glutamate containing amino acid solutions in reducing infectious complications and mortality in the ICU patients (Dechelotte et al. 2006)
Lipid Emulsions

Intravenous lipid emulsions consist of submicron droplets (=0.45 mm) of cholesterol and phospholipids surrounding a core of long-chain triglycerides (Driscoll 2003).

The triglycerides are derived from vegetable oils (safflower or soybean oils) and are rich in linoleic acid, an essential polyunsaturated fatty acid that is not produced by the human body. Lipid emulsions are available in 10% and 20% strengths (the percentage refers to grams of triglyceride per 100 mL of solution). The 10% emulsions provide approximately 1 kcal/mL, and the 20% emulsions provide 2 kcal/mL. Unlike the hypertonic dextrose solutions, lipid emulsions are roughly isotonic to plasma and can be infused through peripheral veins and can be infused separately (at a maximum rate of 50 mL/hour) or added to the dextrose–amino acid mixtures. The triglycerides introduced into the bloodstream are not cleared for 8 to 10 hours, and lipid infusions often produce a transient, lipemic-appearing (whitish) plasma. (Warshawsky 1992)

Table 16 Amino Acid Solutions with Glutamic Acid (Borgsdorf, et al. 2006)

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Manufacturer</th>
<th>Glutamate Content (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminosyn-PF 7%</td>
<td>Abbott</td>
<td>576</td>
</tr>
<tr>
<td>Aminosyn II 10%</td>
<td>Abbott</td>
<td>738</td>
</tr>
<tr>
<td>Aminosyn II 15%</td>
<td>Abbott</td>
<td>1107</td>
</tr>
<tr>
<td>Novamine 11.4%</td>
<td>Clintec</td>
<td>570</td>
</tr>
<tr>
<td>Novamine 15%</td>
<td>Clintec</td>
<td>749</td>
</tr>
</tbody>
</table>

Table 18 Intravenous Lipid For Clinical Use (Borgsdorf et al. 2006)
Lipid restriction

Lipids are used to provide up to 30% of the daily (nonprotein) calorie requirements. However, because dietary lipids are oxidation-prone and can promote oxidant-induced cell injury. Restricting the use of lipids in critically ill patients (who often have high oxidation rates) seems wise. Although lipid infusion is necessary to prevent essential fatty acid deficiency (cardiomyopathy, skeletal muscle myopathy), this can be accomplished with minimal amounts of lipid. To prevent EFA deficiency, approximately 4% of the total daily calories should be provided by linoleic acid (Barr et al.1981)

ADDITIVES

Commercially available mixtures of electrolytes, vitamins, and trace elements are added directly to the dextrose–amino acid mixtures. (Marino and Kenneth 2006)

Electrolytes

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

Recommended daily parentral requirment in adult.
Sodium 60-150 mEq. Potassium 40-100 mEq. Magnesium 8-24 mEq. Calcium 5-15 mEq. Phosphorus 10-40 mmol. (Heyland et al.2005)
**Vitamines**

Aqueous multivitamin preparations are added to the dextrose-amino acid mixtures. One unit vial of a standard multivitamin preparation will provide the normal daily requirements for most vitamins, with the exception of vitamin K (Heiphingstine and Bistrian 2003).

Table 19 Trace Element Preparation and Daily Requirements. (Mirtallo et al.2004)

<table>
<thead>
<tr>
<th>Trace Element</th>
<th>Daily Parenteral Requirement</th>
<th>MTE-6* concentrated</th>
<th>MTE-6* concentrated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromium</td>
<td>10–15 μg</td>
<td>10 μg</td>
<td>10 μg</td>
</tr>
<tr>
<td>Copper</td>
<td>300–500 μg</td>
<td>1 mg</td>
<td>1 mg</td>
</tr>
<tr>
<td>Iodine</td>
<td>150 μg</td>
<td>—</td>
<td>75 μg</td>
</tr>
<tr>
<td>Iron‡</td>
<td>2.5–8 mg</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Manganese</td>
<td>60–100 μg</td>
<td>500 μg</td>
<td>500 μg</td>
</tr>
<tr>
<td>Selenium</td>
<td>20–60 μg</td>
<td>60 μg</td>
<td>60 μg</td>
</tr>
<tr>
<td>Zinc</td>
<td>2.5–5 mg</td>
<td>5 mg</td>
<td>5 mg</td>
</tr>
</tbody>
</table>

**Trace Elements**

A variety of trace element additives are available, and two commercial mixtures are shown. Most trace element mixtures contain chromium, copper, manganese, and zinc, but they do not contain iron and iodine. Some mixtures contain selenium, and others do not. Considering the importance of selenium in endogenous antioxidant protection, it seems wise to select a trace element additive that contains selenium. Routine administration of iron is not recommended in critically ill patients because of the prooxidant actions of iron. (Mirtallo et al.2004)

**CREATING A TPN REGIMEN (Marino and Kenneth 2006)**

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

**Step 1**

The first step is to estimate the daily protein and calorie requirements. For this example, the daily calorie requirement will be 25 kcal/kg, and the daily protein requirement will be 1.4 g/kg. Therefore, for the 70-kg patient, the protein and calorie requirements are as follows:
Caloric requirements = 25 (kcal/kg) x 70 (kg) = 1750 kcal/day

Protein requirements = 1.4 (g/day) x 70 (g) = 98 g/day

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

\[
\text{Volume of A10 – D50} = \frac{98 \text{ (g/day)}}{50 \text{ (g/L)}} = 1.9 \text{ L/day}
\]

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

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

\[
\text{Amount of dextrose} = 250 \text{ (g/L)} \times 1.9 \text{ (L/day)} = 475 \text{ g/day}
\]

\[
\text{Dextrose calories} = 475 \text{ (g/day)} \times 3.4 \text{ (kcal/g)} = 1615 \text{ kcal/day}
\]

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

**Step 4**
If a 10% lipid emulsion (1 kcal/mL) is used to provide 135 kcal/day, the daily volume of the lipid emulsion will be 135 mL/day. Because the lipid emulsion is available in unit volumes of 50 mL, the volume can be adjusted to 150 mL/day to avoid wastage. Thus volume can be infused at half the maximum recommended rate (50 mL/hour) to minimize the tendency to develop lipemic serum during the infusion.
Step 5
The daily TPN orders for the previous example can then be written as follows:
1. Provide standard TPN with A10-D50 to run at 80 mL/hour.
2. Add standard electrolytes, multivitamins, and trace elements.
3. Give 10% Intralipid: 150 mL to infuse over 6 hours.

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

**COMPLICATIONS**

**1. CATHETER-RELATED COMPLICATIONS**

Because the dextrose and amino acid solutions are hyperosmolar, TPN is administered through central veins. One complication that can be particularly frustrating is the misdirected catheter, a catheter inserted into the right subclavian vein has entered the internal jugular vein and advanced in a retrograde direction up into the neck, this catheter should not be used for administration of TPN because the increased risk of venous thrombosis.

**Catheter Repositioning.**

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

X-ray of a central venous catheter misdirected into the neck.
2-CARBOHYDRATE INFUSIONS

Hyperglycemia

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

Hypophosphatemia

The effects of TPN on the serum phosphate level is shown in Figure 8. This effect is due to enhanced uptake of phosphate into cells associated with glucose entry into cells. The phosphate is then used to form thiamine pyrophosphate, an important cofactor in carbohydrate metabolism. (Knochel 1987).

The cumulative effect of (TPN) on the serum phosphate level. (Knochel 1987).
Fatty Liver

When glucose calories exceed the daily calorie requirements, there is lipogenesis in the liver and this can progress to fatty infiltration of the liver and elevated levels of transaminase enzymes in the blood (Perry, et al. 1990).

Hypercapnia

Excess carbohydrates promote CO2 retention in patients with respiratory insufficiency. Although this has been attributed to the high respiratory quotient associated with carbohydrate metabolism, this may be a reflection of overfeeding in general and not specific overfeeding with carbohydrates (Taplers et al. 1992).

3-LIPID INFUSIONS

Oxidant Injury

One of the major (and often overlooked) toxicities associated with lipid infusions is an increased risk of oxidation-induced cell injury (Carpentier and Dupont 2000).

Impaired Oxygenation

Lipid formulations used in TPN are rich in oxidizable lipids, and infusion of such lipids can promote organ injury similar to that seen in critically ill patients. For example, infusion of oleic acid, a fatty acid that is abundant in lipid emulsions used in TPN, is the standard method for producing the acute respiratory distress syndrome (ARDS) in animals, and this might explain why lipid infusions in TPN formulations are associated with impaired oxygenation and prolonged respiratory failure (Suchner et al. 2001).
4-GASTROINTESTINAL COMPLICATIONS

Mucosal Atrophy

The absence of bulk nutrients in the bowel produces atrophy and disruption of the bowel mucosa. These changes can predispose to translocation of enteric pathogens across the bowel mucosa and subsequent septicemia. Glutamine-supplemented TPN may help reduce the risk of this complication (De-Souza and Greene 2005).

Acalculous Cholecystitis

The absence of lipids in the proximal small bowel prevents cholecystokinin-mediated contraction of the gallbladder and the bile stasis that results may promote acalculous cholecystitis (Phelps et al. 1991).
Figure 9 quoted from Heyland, et al. 2003
CHAPTER 5

Strategies to maximize the benefits and minimize the risks of enteral nutrition and total parenteral nutrition.

A- Enteral nutrition

1-TIMING OF ENTERAL NUTRITION

While enteral feeding is the preferred route of nutrient administration, how soon it should be started after an acute injury or insult is not clear. Early EN was associated with a trend towards a reduction in mortality when compared to delayed nutrient intake. (Drover et al. 2003).

It was also associated with a trend towards a reduction in infectious complications when compared to delayed nutrient intake. Combined an aggressive early feeding protocol with the use of small bowel feedings and documented that head-injured patients fed aggressively, compared to standard (slower) provision of EN, not only had better nutritional status, but also had fewer complications and a more rapid recovery from their illness.

2-REDUCING RISK OF ASPIRATION

It is important on initial evaluation to assess the patient’s risk for aspiration on EN. Aspiration may occur from the antegrade passage of contaminated oropharyngeal secretions or the retrograde passage of contaminated gastric contents into the larynx. Regurgitation occurs more frequently than aspiration. (Lukan et al. 2002)

Major risk factors include; 1-documented previous episode of aspiration, 2-decreased level of consciousness (including sedation or increased intracranial pressure), 3-neuromuscular disease, 4-structural abnormalities of the aerodigestive tract, 5-overt vomiting or regurgitation, 6-need for prolonged supine position, 7-persistently high gastric residual volumes. Additional risk factors include; 1-presence of a nasoenteric tube, 2-noncontinuous or bolus intermittent feeding, 3-
abdominal/thoracic surgery or trauma. 4-delayed gastric emptying 6- poor oral care, 7-
advanced age, 8- inadequate nursing staff, 9- large bore feeding tube, 10- malpositioned
ental tube (back into the esophagus), or 11- transport out of the ICU. (McClave et
al. 2002)

3-ROLE OF SMALL BOWEL FEEDING

By delivering enteral feeds into the small bowel, beyond the pylorus, the
frequency of regurgitation and aspiration, as well as the risk of pneumonia, is
decreased while at the same time nutrient delivery is maximized. (Heyland et al,2001).

Significant reduction in VAP associated with small bowel feedings compared
to gastric feeding. It seems more prudent to reserve small bowel feeds for patients at
high risk for intolerance to EN (due to use of inotropes, continuous infusion of
edatives, paralytic agents, high gastric residual volumes, or patients with high
asogastric drainage) or at high risk for regurgitation and aspiration (nursed in
prolonged supine position). (Heyland et al. 2003)

Strategies to Optimize the Benefits and Minimize the Risks of EN and TPN.

<table>
<thead>
<tr>
<th>Enteral Nutrition</th>
<th>Total Parenteral Nutrition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Initiate early, within 24–48 hours of admission</td>
<td>1-Hypocaloric dose</td>
</tr>
<tr>
<td>2-Use small bowel feedings</td>
<td>2-Do not use lipids for short term use (&lt;10 days)</td>
</tr>
<tr>
<td>3-Elevate head of the bed</td>
<td>3-Tight control of blood sugars</td>
</tr>
<tr>
<td>4-Use motility agents</td>
<td>4-Supplement with glutamine</td>
</tr>
<tr>
<td>5-Use feeding protocol that enables consistent evaluation of gastric residual</td>
<td>5-Continue to trickle concentrated amounts of enteral nutrition if able</td>
</tr>
<tr>
<td>volumes and specifies</td>
<td></td>
</tr>
<tr>
<td>6-when feeds should be interrupted Use concentrated feeding formulae.</td>
<td></td>
</tr>
<tr>
<td>7-Consider formulae with immune additives</td>
<td></td>
</tr>
</tbody>
</table>

4-BODY POSITION

Several studies document that elevation of the head of the bed, to 45° is
associated with less regurgitation and pulmonary aspiration. Thus, a simple maneuver
(i.e., elevating the head of the bed to 30° to 45°) can reduce the risks associated with
ternal feedings.
5-MOTILITY AGENTS

Gastrointestinal prokinetic agents improve gastric emptying, improve tolerance to enteral nutrition, reduce gastroesophageal reflux and pulmonary aspiration, and therefore may have the potential to improve outcomes in critically ill patients. (Booth, et al. 2002). Since cisapride is no longer available and due to the concerns of bacterial resistance with the use of erythromycin, metoclopramide is probably the drug of choice. Reducing narcotic dosages and potentially reversing their effect at the level of the gut by infusing naloxone through the feeding tube, and switching from bolus intermittent feeds to continuous infusion may also be effective in improving gastric function and tolerance to EN, while reducing risk of aspiration.

6-FEEDING PROTOCOLS

Several observational studies document that EN is frequently interrupted for high gastric residual volumes, procedures, nausea and vomiting, and other miscellaneous reasons. (Heyland, et al. 1999).

Nurse-directed feeding protocols or algorithms have been shown to increase the amount of EN delivered on a daily basis. Instituting a feeding protocol in ICUs that provides specific instructions on the patient’s management related to EN to the bedside nurse has the potential to improve nutrient delivery and decrease complications. (Spain et al. 1999)

7-ROLE OF IMMUNE STIMULANTS AND ANTIOXIDANTS

Glutamine, arginine, and omega-3 fatty acids, as well as selenium, vitamins E, C, and A, and beta-carotene in supraphysiologic concentrations. Unfortunately, with the possible exception of glutamine, these nutrients have been combined together and marketed as an immune-enhancing diet. The term immunonutrition is used as a general term to describe all these enteral products.

a-ARGININE

L-arginine is an active secretagogue that stimulates the release of growth hormone, insulin growth factor, and insulin, all of which may stimulate protein
synthesis and promote wound healing. Conversion of arginine to ornithine by arginase provides two further functions. This pathway enables shuttling of nitrogen to urea, and ornithine is utilized in polyamine synthesis (which is involved in deposition of hydroxyproline, collagen, and the laying down of connective tissue to heal wounds). Arginine has also been shown to have significant immunostimulatory effects. Arginine has a trophic effect on the thymus gland that promotes the production and maturation of T lymphocytes. In the nitric oxide synthase pathway, the precursor arginine may contribute to improved bacterial killing. ([Suchner et al. 2002]) The arginase pathway is driven by a Th2 cytokine profile, mediated by further release of IL-4, IL-10 and TGF-β. The Th2 cytokine profile has the effect of reducing the overall inflammatory immune response. In contrast, the nitric oxide synthase pathway is mediated by a Th1 cytokine profile, and is perpetuated by further release of IL-1, TNF, and IFN-γ . This pathway has the capability of promoting the inflammatory response and inducing the formation of nitric oxide. Increased levels of nitric oxide may exert a negative inotropic and chronotropic effect on the cardiovascular system, and promote vasodilation (which may contribute to the hypotension and shock associated with sepsis syndrome). Nitric oxide in larger amounts may act as a mitochondrial toxin and inhibit several steps in the oxidative phosphorylation chain. Nitric oxide may also damage gut epithelium, increasing bacterial translocation and reducing overall gut integrity. Nitric oxide can also have nonspecific cytotoxic effects of inhibiting growth or killing cells indiscriminately. ([Ochoa et al. 2001])

**Clinical Review**

Arginine-containing products may worsen outcomes in critically ill septic patients. ([Heyland and Novak et al. 2001]).
In sepsis endotoxin exposure and cytokine activation have led to elevated levels of inducible nitric oxide synthesis, supplemental arginine may lead to the production of excessive amounts of nitric oxide, shock, and early death. Thus arginine-supplemented specialized diets should not be used in critically ill patients who are clearly septic. If a critically ill patient receiving an arginine supplemented diet develops sepsis, the arginine-containing diet should be discontinued. (Dent et al. 2003)

**b-OMEGA-3 FATTY ACIDS**

Omega-3 fatty acids may be provided in the form of fish oil or canola oil. These agents do not have direct stimulatory effects.

Omega-6 fatty acids are involved in the cyclooxygenase pathway, generating prostaglandin E2 (PGE2) and leukotriene B4 (LTB4) from arachidonic acid. These are proinflammatory cytokines that lead to immune suppression and nosocomial infection, systemic inflammatory response syndrome (SIRS), and organ dysfunction. Through diet supplementation, omega-3 fatty acids compete with the omega-6 fatty acids for incorporation into cell membranes. Upon activation of the cyclooxygenase pathway, omega-3 fatty acids instead lead to the formation of PGE3 and LTB5. These compounds have 1/10 the biologic activity of the PGE2 and LTB4 series, and as a result have a much less immunosuppressive effect. (Schloerb 2001).

**Clinical Review**

A study of omega-3 fatty acids was conducted in patients with acute lung injury (ALI)/acute respiratory distress syndrome (ARDS). The pathophysiology of this syndrome is thought to be related to the release of arachidonic acid–related metabolites from inflammatory cells. Eicosapentaenoic acid, docosahexanoic acid (DHA), borage oil, and antioxidants would have a favorable effect on markers of inflammation in the lung and an improvement in clinical outcomes. In this study, 146 patients meeting the standard definition of ARDS with evidence of active pulmonary inflammation as indicated by fluid from a bronchoalveolar lavage (BAL) that contained a neutrophil count >10%, were randomized to the experimental diet or a high-fat, low carbohydrate control feed. In the subset of “evaluable” patients, those who received the experimental diet had higher plasma levels of dihomogamma linolenic acid, eicosapentaenoic acid, and an increased eicosapentaenoic/arachidonic acid ratio. With respect to the clinically important outcomes, patients fed the experimental diet experienced a reduction in days receiving supplemental oxygen, required significantly fewer days of ventilatory support, and less time in the ICU, and had fewer new organ failures. There was also a trend towards a reduction in mortality associated with the experimental diet. This study confirms that short-term administration of dietary lipids in
critically ill patients can modify fatty acid levels with a resultant favorable effect on neutrophil recruitment in the lung and subsequent clinical outcomes.

**c-GLUTAMINE**

Importance
1-Plays a central role in nitrogen transport within the body.
2-Fuel for rapidly dividing cells (particularly lymphocytes and gut epithelial cells).
3-A precursor to glutathione

Plasma glutamine levels drop during critical illness, and lower levels of glutamine have been associated with immune dysfunction

Glutamine-supplemented formulas have resulted in
1- Improved nitrogen balance, and higher intramuscular glutamine levels.
2- Glutamine plays a crucial role in enhancing immune cell function with no elevation in proinflammatory cytokine production.
3-A significant reduction in mortality, at trends towards a reduction in infectious complications.

**d-ANTIOXIDANT VITAMINS AND TRACE MINERALS**

While there is a putative beneficial role of reactive oxygen species in modulating cell signaling, and thus regulating proliferation, apoptosis, and cell protection. Oxygen-derived radicals may cause cellular injury by numerous mechanisms, including

1-Destruction of cell membranes through the peroxidation of fatty acids,
2-Disruption of organelle membranes such as those covering lysosomes and mitochondria,
3- degradation of hyaluronic acid and collagen.
4- disruption of enzymes like Na+,K+-ATPase or alpha1- proteinase inhibitor.

To protect tissues from oxygen free radical–induced injury, The first line of intracellular defense is a group of antioxidant enzymes such as superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase, including their metal cofactors selenium, copper, and zinc. When these enzymatic antioxidants are overwhelmed, oxygen free radicals (OFRs) are free to react with susceptible target molecules within the cell (i.e., unsaturated fatty acids of the cell membrane). Thus there is a need for a second line of defense scavenging OFRs by means of nonenzymatic antioxidants that are either water soluble, such as glutathione and vitamin C, or lipid soluble, such as vitamin E and beta-carotene.
In critical illness, oxidative stress arises when the balance between protective antioxidant mechanisms and the generation of reactive oxygen species (ROS) is disturbed. This imbalance may be caused by excess generation of ROS by means of ischemia/reperfusion injury, inflammation, infection, and toxic agents (chemotherapy or drugs), or by low antioxidant capacity (secondary to comorbid illnesses, malnutrition, and excessive losses such as in the case of burns).

↓ antioxidants → ↑ morbidity and mortality.

**Single Antioxidant Nutrients**

**SELENIUM ALONE**: Selenium is an important co-factor in glutathione enzymatic function and has favorable effects on cellular immune function.

In a trial of 17 patients with acute necrotizing pancreatitis, parenteral supplementation of 500 μg of selenium was associated with a significant reduction in ICU mortality.

In a prospective randomized trial, reported a reduction in mortality (15% vs. 40%) after IV administration of 1000 μg of sodium selenite for 28 days in patients with SIRS compared to placebo.

In a trial of 42 patients with SIRS, subjects that received a higher dose of parenteral selenium (535 μg/d × 3 days, 285 μg/d × 3 days, 155 μg/d × 3 days, and 35 μg/d thereafter) versus a lower dose (35 μg/d) had a trend towards reduced hospital mortality. trials that compared supplementation of selenium alone to standard were aggregated. selenium was associated with a trend towards a reduction in mortality.

**ZINC ALONE**: Zinc is an essential trace element necessary for normal protein metabolism, membrane integrity, and the function of more than 200 metalloenzymes including enzymes involved in oxidative capacity. In a randomized, prospective, double-blinded controlled trial in severely head injured, ventilated patients, those receiving a higher zinc supplement (12 mg elemental zinc via PN for 15 days, then progressing to 3 months of oral zinc) had a trend towards a reduction in mortality when compared to those receiving a placebo (2.5 mg elemental zinc).

**Combined Antioxidant Nutrients**
Many randomized controlled trials have chosen to administer a combination of antioxidants via various routes of administration, thereby making it impossible to attribute the outcomes to a specific nutrient. When 11 trials of single and combined antioxidants were aggregated, overall antioxidants were associated with a trend towards a reduction in mortality and no effect on infectious complications. Thus, for critically ill patients, selenium supplementation in combination with other antioxidants (vitamin E/alpha tocopherol, vitamin C, N-acetylcysteine, and zinc) may be beneficial. (Heyland et al.2003)

8-ROLE OF PARENTERAL NUTRITION

Enteral nutrition is used preferentially to PN. However, to optimize the delivery of nutrients, some prescribe PN at the same time EN is initiated, to provide nearly all required calories and protein immediately. Then, as EN becomes successfully established, PN is reduced and eliminated.

Studies reported on mortality and the aggregated results demonstrated a trend towards an increased mortality associated with the use of combination EN and PN. had no effect on ventilator days.

What about the patient who has been started on EN, and after several days is only tolerating inadequate amounts of EN? Does PN have a role in this patient population? The preferred approach is to continue with EN and standard IV therapy. However, at some point (probably between 7 and 14 days postinjury) the risk from further deterioration of nutritional status outweighs the risk of providing PN, due to the cumulative effect on immune function, continued losses to the lean body mass, and development of specific key nutrient deficiencies in the critically ill patient receiving inadequate nutritional support by EN. This time frame may be considerably shortened in patients at tremendously increased risk for deterioration of nutritional status due to the presence of large open wounds, enteric fistula, or short bowel syndrome.

Parenteral nutrition has a very limited role in the critical care setting. PN should not be started in critically ill patients until all strategies to maximize EN delivery (such as the use of small bowel feeding tubes and motility agents) have been attempted. Waiting 2 weeks in someone tolerating inadequate amounts of EN is probably too long, but practitioners will have to weigh the safety and benefits of initiating PN in patients not tolerating EN on an individual case-by-case basis. (Daren et al.2005)
2-Total parenteral nutrition

If PN is associated with harm in critically ill patients, it may be due to a variety of potentially avoidable pathophysiologic mechanisms, including overfeeding, the immunosuppressant effects of lipids, hyperglycemia, absence of key nutrients like glutamine, and the association of gut disuse and systemic inflammation.

1-ROLE OF HYPOCALORIC PARENTRAL NUTRITION

Stressed critically ill patients → insulin resistance, providing large amounts of dextrose intravenously results in hyperglycemia →↑ the risk of infection, hepatic steatosis, hypertriglyceridemia, and hypercapnia. This has given rise to the hypocaloric or hypoenergetic PN as a strategy to minimize complications associated with PN.

2-PARENTRAL LIPIDS

A significant reduction in pneumonia, catheter-related sepsis, and a significantly shorter stay in both ICU and hospital was observed in trauma patients not receiving lipids compared to those receiving lipids. The group of Patients receiving no lipids (hypocaloric group) showed a trend towards a reduction in infections. No difference in length of stay was seen in, and it did not report on ventilator days, and reduction in mortality.

It is unknown what the effects of long-term fat-free parenteral nutrition would be, lipid-free PN is probably best indicated for those patients requiring PN for a short time (< 10 days), where the risk of fatty acid deficiency would be minimal.

3-TIGHT GLYCEMIC CONTROL

Hyperglycemia, which occurs more often with PN than EN, is associated with increased infectious complications. Compared intensive insulin therapy (target range 4.4 to 6.1 mmol/L) vs. conventional treatment (10.0 to 11.1 mmol/L) in critically ill patients receiving nutrition support. Intensive insulin therapy was associated with a lower incidence of sepsis trend towards a reduction in ventilator days, and a reduced ICU and hospital mortality, compared to conventional insulin therapy.

4-SUPPLEMENTATION WITH GLUTAMINE
Perhaps the lack of treatment effect of PN relates to the lack of key nutrients necessary for repair and recovery following critical illness. PN supplemented with glutamine is associated with increased survival in seriously ill hospitalized patients. It is difficult to provide high-dose free glutamine intravenously to critically ill patients due to problems with limited solubility and stability, especially in critically ill patients with volume-restricted conditions. However, recent advances in parenteral glutamine delivery have overcome some of these challenges, making the provision of bioavailable glutamine practical, even at higher doses. The treatment effect is likely greatest when high-dose (>0.2 g/kg per day) glutamine is given parenterally to patients with gastrointestinal failure. (Furst 2001)

5-USE OF EN IN PATIENTS ON PN

The adverse effect of PN may be related to the absence of nutrients in the bowel. The gastrointestinal mucosa is metabolically very active and the lack of enteral nutrients (as in the case of PN) would result in mucosal atrophy, increased permeability, bacterial overgrowth, translocation of bacteria and/or gut-derived factors that activate the immune system, atrophy of the gut-associated lymphoid tissue, and increased production of proinflammatory cytokines. An observational study suggested that low-volume EN is associated with less toxicity compared to PN alone.

Clearly its recommended that EN is used preferentially to PN, but in the patient who is not tolerating adequate amounts of EN over a prolonged period of time, if PN is going to be used, its suggest that attempts to provide EN be continued until EN is successful and the PN can be discontinued.
تغذية المرضى المضوعين على اجهزة التنفس الاصطناعي

رسالة مقدمة
توطنة للحصول على درجة الماجستير في الأمراض الصدرية والتدرن
من الطبيب
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2007