NUTRITIONAL SUPPORT IN CRITICALLY ILL PATTIENTS

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CONTENT:

1. Introduction.

2. Physiological changes.
2 a. Changes during starvation
2 b. Metabolic changes during critical illness

3. Clinical assessment.

4. Nutrition assessment.

5. Nutrition requirement.

6. Systemic inflammatory response syndrome and compensatory anti-inflammatory response syndrome.

7. Gut mucosal barrier and its relationship to sepsis, SIRS, MOF.

8. General nutrition intervention.

9. immune-enhancing nutrition.

10. Monitoring nutrition support.

11. Conclusion.

12. References.

1. INTRODUCTION.

Critically ill patients in the intensive care unit are a very heterogeneous group with respect to illness, age and nutrition status. Nutrition support in the ICU has become a vital part of the treatment in patients with critical illness and injury. Among the patients who are previously well nourished before ICU admission, nutritional disorders develop rapidly because of the metabolic demands of illness and healing, rapid fluid shifts, and the loss of specific vitamins and trace elements.

In the broadest sense, malnutrition in the ICU represents the deficiency or excess of energy, protein, vitamins, or minerals. These disorders may occur independently, or in any combination, depending on the clinical state of the patient. Malnutrition in critical illness results in loss of body cell mass, alterations in mineral homeostasis, and derangements in organ system function. Typical manifestations of these derangements in critically ill patients include impaired immune function, prolonged dependence on mechanical ventilation, and increased rates of infection. These effects often are difficult to differentiate from the concurrent illness and injury, but attempts must be made by practitioners to identify and correct nutritional disorders because they make patients vulnerable to infectious complications, increased health care costs, and lead to increased patient morbidity and mortality.

The provision of specialized nutrition support to patients in the ICU is a complex and sometimes overwhelming task. Nutrition support benefits critically ill patients by facilitating wound healing, ameliorating the maladaptive metabolic response to injury, maintaining the structure and function of the gastrointestinal tract, and decreasing overall morbidity. Although nutrition support can prevent the morbidity and mortality associated with prolonged malnutrition, the use of either parenteral nutrition (PN) or enteral nutrition (EN) can cause mechanical, infectious, and metabolic complications. The goal of providing nutrition support to critically ill patients is to improve patient outcomes. Markers used in assessing these outcomes include preserving lean body mass, treating or preventing micronutrient or macronutrient deficiencies, and preventing complications associated with the provision of nutrition support.

The purpose of this review is to discuss nutrition support in general with emphasis put on critically ill patients especially in regard to the metabolic changes. The physiologic consequences of the flow phase insult serve as the basis for modern critical care medicine in which key features such as support of adequate cardiac hemodynamics, optimized ventilation strategies, fluid administration, monitoring of organ function, and nutrition are supported in the critically ill patient.

In addition the role of intestinal barrier failure and bacterial translocation in the development of systemic infection is shortly discussed here. Also new strategies in nutrition support in the critically ill are outlined here in the form of supplementation of particular amino acids that are able to support or regulate the immune response, such as glutamine and arginine, may have a role not only for their potential metabolic effect but also for their potential antioxidant role.

2 PHYSIOLOGICAL CHANGES

2. A Metabolic changes during starvation

Protein energy malnutrition varies greatly between healthy individuals and patients with critical illness or injury. Healthy individuals experiencing starvation adapt to this state through the use of nutritional reserves. Low intake of nutrients results in a reduction in resting energy expenditure (REE) and urinary nitrogen excretion. The degree of decrease in REE is determined by the severity of calorie restriction and the duration of that restriction. Typically, human beings maintain stores of glycogen in the liver that may be used to provide the glucose vital to the function of the brain. However, these stores are depleted in about 24 hours (1, 2). In unstressed patients, protein stores are sufficient to meet the body's needs for about 30 days, though this severity of restriction would cause death well before all this protein has been used. In the setting of caloric restriction, the only other source of energy to be used is fat, which is calorically dense and may be used without serious squeals. In a starving patient, the oxidation of these fat stores provides energy. The use of fat for energy production allows for the relative sparing of protein use. However, fat cannot be used to produce glucose. Early in starvation, hepatic gluconeogenesis from protein breakdown is a major source of glucose. As the starved state continues over longer periods, the body acts to preserve muscle mass by decreasing nitrogen excretion and increasing the production of ketones that the brain can use as a source of energy. The use of lipids as a major source of energy continues until fat stores are greatly diminished. Because of the caloric density of fat, the loss of body weight for the degree of energy produced is minimized. (1, 2)

2. B Metabolic changes during critical illness

Principles of ebb- and flow phase

The metabolic response to critical illness or injury is quite different from the response to starvation. This response has classically been discussed in two phases, the ebb and flow. In the first hours to a couple of days after injury, the ebb phase is marked by hypometabolism and increases in the activity of the sympathetic nervous system and hypothalamic-pituitary axis. The flow phase of critical illness is characterized by hypermetabolism, increased resting energy expenditure, proteolysis, gluconeogenesis, and lipolysis. These adaptations to severe physiological stress represent the body's survival mechanisms, activated to use nutrients to maintain organ systems and promote healing processes. The degree of this response is variable and depends on factors such as the type of insult, severity of insult, prior nutritional state of the host, and temporal relationship to any previous illness or injury (1, 2). Numerous changes in the activity of chemical mediators are involved in the stress response to critical illness and injury. These include increases in the counterregulatory hormones cortisol, adrenocorticotropic hormone, epinephrine, and glucagon. Increased production of pro-inflammatory cytokines, such as interleukin-1, interleukin-6, and tumor necrosis factor, also play a role in the occurrence and magnitude of the stress response. Energy expenditure may be increased to 150–200% of normal in the most severely injured or ill patients, whereas most patients in the ICU maintain REEs of 100–150% of normal. (2)

TABLE 1. METABOLIC ALTERATIONS FOLLOWING INJURY (2)

EBB PHASE	FLOW PHASE
Increased blood glucose	Normal/slightly increased blood glucose
Increased circulating free fatty acids	Normal/slightly increased free fatty acids
Decreased insulin	Normal/increased insulin
Increased catecholamines	Increased catecholamines
Decreased cardiac output	Increased cardiac output
Decreased oxygen consumption	Increased oxygen consumption
Decreased core temperature	Elevated core temperature

Protein metabolism

Protein loss is accelerated by increases in proteolysis. Even in the critical care setting, where protein and non-protein substrates are provided, negative nitrogen balance can be an expected result. Urinary nitrogen excretion can exceed 15–20 g/day. The excessive protein catabolism occurs because of not only gluconeogenesis, but also thermogenesis, immune function, acute phase protein synthesis, and tissue repair. These processes may result in a substantial loss of body protein within a relatively short duration of ongoing critical illness. Body composition studies in critical illness have revealed that a majority of these losses occur in skeletal muscle. Recommend that protein be given as amino acids at a rate of at least 0.10-0.15 g N/kg/day. (1)

Carbohydrate metabolism

Glucose is a primary source of fuel for the brain. It also provides energy for immune function, red blood cells, bone marrow, and for the healing wound. Hyperglycemia is very common among critically ill patients, due to insulin resistance in peripheral tissue despite increased insulin secretion in concert with increased rates of gluconeogenesis and increases in counter-regulatory hormones. (1, 2)

The catabolism of protein is a major source of the glucose produced in critical illness. In contrast to healthy patients administration of carbohydrates to critically ill patient does not suppress gluconeogenesis; indeed it may further exacerbate hyperglycemia. The degree and control of hyperglycemia in the ICU are being revealed as increasingly important to predicting outcomes related to critical illness. Administering high amount of glucose may lead to lipogenesis, hepatic steatosis, and hyperglycemia. Glucose level should be tightly controlled according to guidelines, which states that if blood glucose is higher more than 10 mmol/l then parallel insulin should be given to lower it but not to less than 2 g/kg/day. (1)

Lipid metabolism

Lipid metabolism also is altered in critical illness. Lipolysis is accelerated because of increased adrenergic stimulation. This increase in lipolysis is not suppressed by hypercaloric carbohydrate administration. The rate of turnover of glycerol and free fatty acids increases and reflects the degree of acceleration in lipolysis because of stress. The contribution of fat oxidation to energy production is increased in critically ill patients. The fatty acids liberated by lipolysis are oxidized as a primary source of ATP during stress. (2)
In patients fed parenterally, lipid emulsion must be provided to prevent the development of essential fatty acid deficiency. In general, Triglycerides should be above 5 mmol/l
But not above 10 mmol/l. (1)

Fluid changes

Fluid and electrolyte changes are a constant challenge in intensive care units. Critical illness predictably results in gains in total body water. Whether it is from fluid resuscitation or perioperative fluid loading, critically ill patients experience a 15–20% increase in extracellular water. The degree of fluid overload depends on the type and severity of illness or injury, the amount of exogenous fluid administered, and patient age. This change in volume status remains present even after patients have been stabilized. Older patients tend to take longer to resolve this excess extracellular water than younger patients. (2)

Electrolyte changes

Electrolyte abnormalities are common in patients in the ICU. The clinical manifestations of these abnormalities include arrhythmias, gastrointestinal dysfunction, and mental status changes. The goals of fluid and electrolyte therapies in the ICU are to maintain normal serum concentrations. Potassium, magnesium, and phosphorus are particularly important in critically ill patients because they are involved in processes that maximize protein anabolism.
Nutritional Assessment With the ultimate goal of providing nutritional support and minimizing the loss of lean body mass in burns, major trauma, sepsis, acute respiratory distress syndrome, and other forms of critical illness, nutritional screening and assessment should take place in every patient in the ICU. Many complex processes occur simultaneously in critically ill patients, and they must be considered both clinically and metabolically.

3. CLINICAL ASSESSMENT

Weight history

Although difficult to obtain in critically ill patients, an accurate usual body weight and weight change history may be useful as prognostic markers. Fluid shifts, resuscitation, leaky capillary syndrome, and excess drainage contribute to inaccuracies that make weight a less useful monitoring parameter in patients in the ICU. Involuntary weight loss of more than 5% over 1 month or 10% over 6 months in critically ill patients is the most common marker used that correlates with increased morbidity and mortality. However, interpretation of weight history may be difficult in patients whose acute illness has prompted rapid fluid shifts before admission (vomiting, diarrhea, and heart failure). When an accurate body weight and height have been measured, the body mass index (weight [kg] ÷ height [m] 2) may be calculated. The body mass index provides clinicians with useful information in interpreting the patient's body composition, whether underweight (body mass index less than 18.5) or obese (body mass index of 30 or more). The body mass index also may serve as a prognostic indicator. For example, in a severely underweight patient, a body mass index less than 14 would be associated with a low probability of survival. (6)

Clinical history and physical examination

Closely related to the weight history and body composition assessment is a thorough physical examination of patients in the ICU. A thorough examination can reveal numerous problems of nutritional relevance, such as abnormalities in skin and mucous membrane appearance reflective of vitamin and mineral deficiencies, decubitus ulcers, diabetic foot ulcers, or ascites. A good history of the patient's eating habits and changes which may have resulted recently is important, along with a closer examination of the musculoskeletal system, which may reveal muscle wasting indicative of underlying chronic illness.

Function of bowel.

Before clinicians initiate any form of nutrition, they must determine whether diarrhea, constipation, emesis, ileus (surgical, functional, or medical/pharmacological), or gastrointestinal bleeding precludes oral feeding if patients are not mechanically ventilated or hemodynamically unstable. Constipation can have a serious impact on the ability to absorb macro- and micronutrients from EN, and can be extremely uncomfortable for the patient. Emesis, if severe enough, can cause malnutrition and impact long-term nutritional status, as can ileus. Active gastrointestinal bleeding may prevent initiation of EN as well.

Injury and illness type and severity

Patients with co morbidities, such as cirrhosis or chronic liver disease, chronic renal failure, diabetes mellitus, congestive heart failure, chronic obstructive pulmonary disease, cancer, or human immunodeficiency virus, may be predisposed to even greater catabolic breakdown of protein and gluconeogenesis when a critical insult occurs. Sepsis or the systemic inflammatory response syndrome causes the release of inflammatory mediators or cytokines (tumor necrosis factor and interleukins), potentiating the observed metabolic alterations. It is the combination of these derangements coupled with chronic disease(s) that makes nutritional assessment such a challenging part of supportive care.

The most critical injuries, such as burns (second or third degree), major trauma (including long bone fractures and traumatic head injury), sepsis and septic shock, require nutritional intervention as expeditiously as clinically feasible with the goal of minimizing further protein loss.

4. NUTRITION ASSESSMENT.

Nutrition assessment allows determination of the changes in body composition parameters and the resulting associated organ function impairment that may adversely influence the clinical outcome. The principal aims of nutrition assessment are to identify patients who need to have nutrition intervention, to quantify and qualify malnutrition, to enable the health worker to better determine nutrition requirements, provide means for the clinician to monitor the efficacy of nutrition support and finally nutrition assessment makes it possible to evaluate metabolic abnormalities present with common diseases, to compare outcome of patients among different institutions and to analyze the metabolic effect of artificial nutrition.

Serum Proteins

Serum protein concentrations frequently are used as markers of nutritional state in the ICU. Proteins most frequently monitored are albumin, prealbumin (also known as transthyretin or thyroxine-binding prealbumin), retinolbinding protein and transferrin.

Albumin

Albumin found both intravascularly and extravascularly, is the most widely studied serum protein marker. It is the only one of the monitored proteins for which a decreased concentration on admission (less than 2.5 g/dl) has been correlated with increasing mortality. Serum albumin is a good prognostic marker but a poor marker of nutritional recovery because of its long half-life (18 days) and large body pool (6). The normal concentration range of albumin is 3.5 g/dl to 5 g/dl.

Transferrin

Transferrin binds and transports the ferric ion, is synthesized in the liver, and has a half-life of 8–9 days. Transferrin concentrations have been used as a predictor of morbidity and mortality, with concentrations less than 100 mg/dl indicative of severe serum protein depletion, 100–150 mg/dl suggestive of moderate depletion, and values of 150–200 mg/dl, indicating mild nutritional depletion. In periods of physiological stress, this marker may not be reflective of nutritional repletion because of reprioritization of hepatic protein synthesis. It also is Important to note that transferrin is elevated in states of iron deficiency secondary to increased hepatic synthesis. Overall, these serum protein markers can be used independently or in combination with nitrogen balance to assess the aggressiveness of protein repletion necessary. The usefulness of these serum protein markers in assessing nutritional status is limited by a lack of research correlating protein concentrations with clinically important outcomes,
By decreased protein synthesis that may occur in patients with hepatic dysfunction, and by decreased protein clearance that may occur in patients with renal dysfunction. (2)

5. NUTRITIONAL REQUIREMENTS.

Energy requirements

Energy expenditure of critically ill patients depends on the underlying disease state of the patient, nutritional status before injury or illness, and the degree of stress incurred.
For the patient with critical illness, increases in oxygen consumption and REE are to be expected. Critically ill patients typically have REEs up to 150% of predicted values, except for patients with head injury or thermal injury in whom even greater increases are observed. Weight-based estimates or predictive equations for assessing energy needs for patients in the ICU traditionally have been used; however, they should be used with caution.

Predictive equations

Basal energy expenditure (BEE) is the energy expended by the body in the resting state under basal conditions, varying with the weight of the individual and as a function of body surface area. Resting energy expenditure relates to BEE by adding the thermogenesis from nutrient assimilation, as well as from fever and sepsis. About 200 equations have been derived to predict BEE or REE. Age, height, weight, sex, and clinical condition are factors involved in predicting energy output in patients in the ICU. Studies have shown that most predictive equations tend to overestimate REE by an average of more than 1000 kcal/day. With the current emphasis on avoiding overfeeding, the clinical usefulness of these equations must be carefully considered. (2, 1)

Harris-Benedict equation.

The BEE can be estimated by using one of these two formulas, one for men and women.
Men BEE = 66 + [13.8 × weight (kg)] + [5 × height (cm)] – (6.8 × age)
Nutrition Management Women BEE = 655 + [9.6 × weight (kg)] + [1.8 × height (cm)] – (4.7 × age)
These equations do not take into consideration either activity or stress factors that vary based on injury type and infection, but were developed in healthy volunteers in a fasting, resting state. A commonly used method of estimating energy needs in an average patient in the ICU is 1.2–1.3 times the BEE. This estimate has limitations, including what effects drugs may have (neuromuscular blockers or sedatives may decrease REE), overestimation of actual energy expenditure (as determined by various studies of critically ill patients where time after acute injury may affect REE), and severity of illness (lack of correlation of Acute Physiology and Chronic Health Evaluation II score and estimated REE).
The major criticism for use of the Harris-Benedict equations is their limited applicability to clinical practice in critically ill patients. Many modifiers to the Harris-Benedict equations have been developed to account for activity and stress. These stress factors are observer-dependent and do not accurately estimate patient needs compared to indirect calorimetry. It typically is not recommended that the Harris-Benedict equations, with or without modifiers, be used to estimate energy needs in the ICU.

Weight-based estimates

Recommendations for estimating energy expenditure have been presented in numerous clinical trials, reviews, and clinical practice guidelines. The American College of Chest Physicians recommends administering 25 kcal/kg/day (7). Most clinicians implement total energy provision of 25–35 kcal/kg/day across different ICU populations.
The current thinking on caloric provision to critically ill patients is to meet patients' needs, but to avoid overfeeding as long as adequate protein is provided to maintain or replenish lean mass. Complications such as fatty liver infiltration with cholestasis, hyperglycemia, and prolonged mechanical ventilation from excess carbon dioxide production are problems that can arise when more than 40 kcal/kg/day are administered. Patient obesity is a factor that needs to be addressed increasingly when estimating patient energy needs in the ICU. Traditionally, an adjusted body weight calculation of:
ideal body weight + 0.25(actual body weight – ideal body weight) has been used in patients weighing more than 120% of their ideal body weight. Recent data in obese patients have shown that an adjusted body weight equal to the ideal body weight plus 50% of excess body weight may be used to more accurately estimate energy needs. An increasingly accepted strategy for obese patients is to use a hypocaloric, high-protein nutritional feeding intervention, wherein goal energy provision is about 20 kcal/kg of adjusted body weight. (7)

Indirect calorimetry

A patient's energy expenditure is most accurately assessed by using indirect calorimetry by a metabolic cart. Indirect calorimetry measures oxygen consumption and carbon dioxide production. The measurements, taken at 30-minute intervals, are then extrapolated to determine 24-hour energy expenditure. The benefit of indirect calorimetry for critically ill patients is that energy expenditure is measured, rather than estimated as with predictive equations. In addition to the REE, the respiratory quotient also is calculated as carbon dioxide production ÷ oxygen consumption. This ratio is an indicator of substrate oxidation, ranging from about 0.7 to 1 or more. At least in part due to metabolic changes because of stress and increases in oxygen consumption in critically ill patients, it is unusual for observed respiratory quotients greater than about 0.9, which would be indicative of overfeeding total calories. Overfeeding may lead to prolonged mechanical ventilation because of the excessive production of carbon dioxide. Although many clinicians consider an elevated respiratory quotient to be the result of an excessive proportion of carbohydrate calories delivered, studies reveal that hypercaloric nutrition support leads to increased carbon dioxide production, regardless of the relative proportion or fat and carbohydrate calories delivered. This is in contrast to stable mechanically ventilated patients who received three eucaloric nutritional regimens with variable carbohydrate fat ratios, and had no significant changes in carbon dioxide production. A respiratory quotient of 0.7 indicates predominant fat use. The usual target respiratory quotient, reflecting a state of mixed substrate oxidation, is about 0.85. Various analyses have shown that respiratory quotient reflected substrate use accurately in 77% of studies assessed by indirect calorimetry. (7)
Indirect calorimetry has its limitations. It requires trained personnel and specialized equipment; therefore, interoperator differences need to be addressed. Indirect calorimetry should occur under steady-state conditions, avoiding involuntary skeletal muscle activity, occurring in a rested or thermoneutral environment for at least 30 minutes, and without changes to feeding formulas surrounding the study. Ventilator changes and fraction of inspired oxygen stability should be demonstrated, along with chest tube or other ventilatory

leaks excluded, and any supplemental oxygen provided. Finally, drugs that can impact energy expenditure and nutritional supplementation during the study need to be noted. Indirect calorimetry should be recommended to assess patients who may be receiving excessive total calories or in whom estimating energy needs is more difficult.

Protein requirements

Each gram of nitrogen lost correlates to the loss of 30 g of lean tissue, with the majority of loss coming from skeletal muscle. The goal in providing protein to critically ill patients should be to limit protein catabolism.
Most patients in the ICU require the provision of at least 1.5–2 g/kg/day of protein. Protein needs of enterally fed critically ill patients should be addressed first, then the total calories determined. A controversy exists over whether to include protein calories or separate them from total energy requirements. Most practitioners would include the 4 kcal provided by each gram of protein as part of the total energy calculation.
Acute renal failure and renal replacement therapies require a careful assessment of the clinical state of the patient and the interventions being made to determine the best provision of protein. Patients with acute renal failure who are not dialyzed should be given 0.5–0.8 g/kg/day, with titration based on changes in blood urea nitrogen. Patients receiving hemodialysis should receive about 1.2 g/kg/day. With the increasing use of continuous renal replacement therapies, this mode of therapy leads to even greater loss of amino acids than other forms of dialysis. Patients receiving continuous renal replacement therapies should be given 1.5–2.5 g/kg/day, titrated based on changes in blood urea nitrogen and changes in nitrogen balance. Recent studies indicate that administering protein at doses that achieve positive nitrogen balance has a positive effect on patient outcome. Patients receiving continuous renal replacement therapies require fewer total calories from feeding regimens because of dextrose retention from dialysate. Therefore, it is recommended that they be given 20–25 kcal/kg/day. (2, 1, 7)

Weight determination

The patient weight that is used to calculate protein requirement depends on whether the patient is obese. For patients whose total weight is at or near their ideal body weight, then total weight should be used. For patients who are malnourished or below their ideal body weight, ideal body weight should be used. For obese patients the use of a hypocaloric, high-protein regimen can be used instead of debating adjusted body weight calculations. With these regimens, goal protein provision is about 2 g/kg of ideal body weight. This approach results in decreases in length of ICU stay and antimicrobial use, with no differences in nutritional markers or mortality when compared with traditional feeding regimens.

Nitrogen balance

Nitrogen balance assessment is the standard technique used to assess the adequacy of protein provision. The goal of protein provision in critically ill patients is to maintain a positive nitrogen balance of 2–4 g/day; however, this frequently cannot be achieved. In many critically ill the goal is revised to minimize the degree of negative nitrogen balance.
Nitrogen balance requires a timed collection of urine over 24 hours, which is analyzed for urea nitrogen loss, and knowledge of the amount of protein provided to the patient during the collection period.

From the results of the urine collection, clinicians may calculate a nitrogen balance by simply subtracting the amount of nitrogen lost from the amount provided. This balance is most commonly calculated as:
Nitrogen balance = (protein intake [g/day]) / 6.25 – urine urea nitrogen (g/day) – 4 (g/day).

This equation assumes that the protein source used is 16% nitrogen, which may need to be reassessed for different protein sources. The 4 g/day in the equation represents non-urea nitrogen lost through the urine (2 g) and through the stool, integument, and insensible losses (2 g).
This 4 g/day factor must be reevaluated in certain clinical situations, wherein it may underestimate the true degree of nitrogen loss. Patients with diarrhea, enterocutaneous fistulae, and drain losses may lose significantly greater amounts of nitrogen than 2 g/day. Patients with thermal injury have increased integumentary nitrogen losses. In highly catabolic patients (more than 30 g urinary urea nitrogen loss/day), it has been recommended that non-urea nitrogen losses are more accurately estimated as 6 g/day.
Finally, in patients with evolving renal dysfunction, the calculation of nitrogen balance requires that accumulation of urea nitrogen in the blood be accounted for in assessing the total daily nitrogen losses of the patient.
The calculation for urea nitrogen accumulation over 24 hours is:
Urea accumulation (g/day) = 0.6 (L/kg) × initial weight (kg) × [final BUN – initial BUN) × 0.01] + [(final BUN × 0.01) × (final weight – initial weight).
BUN = blood urea nitrogen.
Practical limitations to the accuracy of nitrogen balance assessment include inadequate urine collection, drugs that may alter nitrogen excretion in the urine, and inaccuracy in the estimation of non-urea nitrogen loss. (2)

Fluid requirements

Fluid needs in critically ill patients may vary greatly. The goals of fluid administration are to maintain adequate urine output and electrolyte concentrations. Daily fluid needs in adults are estimated to be 30–40 ml/kg/day, with decreasing needs as patients age. Fluid needs also may be calculated using the Holliday-Segar method where the minimal daily fluid requirement equals 100 ml/kg for the first 10 kg of weight, an additional 50 ml/kg for 11–20 kg, and an additional 20 ml/kg/day for every kg greater than 20 kg.
However, many factors affect fluid needs. Fluid needs are increased in patients with fever, severe sweating, hyperventilation, and losses of fluid because of nasogastric suctioning or enterocutaneous fistula output. Third spacing of fluids also necessitates adjustment of total fluid replacement. Although total body water is unchanged, the effective intravascular volume may be decreased. Hydration may be difficult to assess in many critically ill patients and invasive monitoring of hemodynamic parameters and fluid status may be necessary. Patients with renal, hepatic, or cardiac dysfunction may have reduced fluid needs because of volume overload inherent with the pathophysiology of organ system dysfunction. Because of the large volume of other intravenous fluids frequently required in the ICU, and the data showing the degree of fluid overload common in these patients, nutrition support formulations may frequently need to be maximally concentrated.

Electrolyte requirements

Specific recommendations for electrolyte requirements in patients in the ICU cannot be made because of a lack of evidence. Therefore, electrolyte assessment must be conducted on an individual basis for each patient and should be based on established norms. The goal of electrolyte administration in the ICU is to maintain adequate serum concentrations. Specific attention must be paid to intracellular electrolytes, phosphorus, potassium, and magnesium, as they frequently are reduced in critically ill patients at initiation of nutrition support. (1, 2)

Vitamin and trace element requirements

No specific guidelines are available for the requirements of vitamins and trace elements in patients in the ICU. As part of any nutrition support regimen, patients should be given vitamins and minerals, regardless of the administration route.
These micronutrients should be administered in doses to meet recommended daily allowance, dietary reference intake, or the American Medical Association National Advisory Group parenteral vitamin and mineral recommendations. The goal of this supplementation is to optimize the use of macronutrients and support the integrity of the body's defenses.
There are critically ill populations that require alterations in trace element administration. Patients suffering from the most severe metabolic insults or who suffer excessive gastrointestinal fluid losses require additional zinc supplementation. Removing selenium from parenteral nutrition formulations is recommended for patients with renal dysfunction who are not receiving dialysis. Patients with cholestatic liver disease should not receive chromium or copper to avoid toxicities because of decreased hepatobiliary clearance. (1, 2)

6. SYSTEMIC INFLAMMATORY RESPONSE SYNDROME (SIRS) AND COMPENSATORY ANTIINFLAMMATORY SYNDROME (CARS)

Inflammatory cells are a vital part of the defense against infection but, when inappropriately or excessively activated, can induce a state of uncontrolled systemic inflammation.
Serious infections, such as pneumonia and septicemia, are the most common cause for admission to intensive care. Such infections and other non-infective *(e.g.* multiple trauma and burns) conditions commonly progress in the critically ill to a state of generalized inflammatory activation. This is characterised by the presence of a severe clinical illness and the presence of two or more of the following: a temperature of greater than 38°C or less than 36°C, a heart rate greater than 90 beats/min, tachypnoea of greater than 20 breaths/min or an arterial blood gas with a partial pressure of carbon dioxide (PaCO2) of less than 32 mmHg, or a white blood cell count of greater than 12 x 1071 or less than 4 x 109 /I or more than 10% band forms on the peripheral blood film. This multi-system inflammatory state is now known as the systemic inflammatory response syndrome (SIRS) and it is characterized by excessive immuno-inflammatory cascade activation leading to a widespread reduction in cellular oxygen utilization, ATP depletion, cell injury and death. As a consequence of this generalized activation, SIRS is commonly associated with multi-organ dysfunction syndrome (MODS), typified by the acute respiratory distress syndrome (ARDS).
Inflammation requires the activation of numerous component systems including the leukocytes, the endothelium and multiple mediator networks that are normally quiescent, leading to the classic clinical condition recognized as *calor, rubor, tumor and dolor.*

The inflammatory cells are the main driving force behind this process and comprise the circulating leukocytes (neutrophils, monocytes and lymphocytes), in addition to tissue fixed macrophages, dendritic cells, mast cells and eosinophils. Neutrophils and monocytes constitute the bulk of circulating inflammatory cells. They normally exist in a non-activated state and in the absence of stimulation have a life-span limited by apoptosis to a day or so. These cells are rapidly transformed by invading bacteria, specific bacterial products, foreign material, endogenous mediators or in response to trauma or hypoxia into highly active phagocytes with a greatly enhanced capacity to release mediators, enzymes and reactive oxygen intermediates (ROI)

Activation increases the number of neutrophils by speeding the maturation process, increasing the release of precursors from bone marrow. Likewise the number of monocytes entering the circulation from the bone marrow is doubled during inflammation. Chemotactic agents and adhesion molecules focus these cells upon sites of infection where they phagocytose and kill bacteria. Monocytes mature into macrophages, which having engulfed, killed and digested micro-organisms, present their foreign antigen to lymphocytes and engender highly specific adaptive immune responses. These inflammatory cells also release a wide range of mediators which act to regulate the whole inflammatory process, controlling cellular activation, endothelial and leukocyte adhesion molecule expression and function, acting as chemotaxins, prolonging the lifespan of inflammatory cells, stimulating fibroblasts and promoting wound healing and angiogenesis. Thus activation of the inflammatory cascade depends upon appropriate activation of the endothelium, the immune system, the Cytokine/chemokine and other soluble mediator systems along with activation of inflammatory cells. However, inflammatory cell activation is the central trigger driving this whole process. (4)

Hyper and hypo-responsiveness

The ability to activate and de-activate the inflammatory process is central to homeostasis. A state of persistent inflammatory cell activation would be unsustainable and life threatening, by adversely influencing the normal flow of leukocytes through capillary networks resulting in widespread leukocyte plugging, globally increasing metabolic demand and leading directly to tissue to damage through the release of free radical species. Clinical conditions occurring as a consequence of excessive activation of the inflammatory processes are now well described and include ARDS, disseminated intravascular coagulation (DIC), ischaemia\ reperfusion injury and MODS.

By contrast, an inability to activate inflammatory cells would leave the body defenseless, as exemplified by neutropenia. Consequently, many endogenous mediators act to regulate the pro-inflammatory cascade. This down-regulating response has led to the term compensatory anti-inflammatory response syndrome (CARS). As with over-activation, states of inappropriate hypo-responsiveness have been described. Critical illness can lead to impaired inflammatory cell responses with reduced neutrophil chemotaxis and bactericidal activity after burn injury or haemorrhage.

Persisting inflammation induces immune hypo-responsiveness with reduced monocytic capacity to present antigens and diminished superoxide generation. This is identified by reduced monocyte expression of HLA-DR, a state that may be reversed by treatment with interferon-y (IFN-y). It is, therefore, clear that inflammatory cell activation is not absolute; different cells being activated to different degrees via single or multiple different effector functions, all requiring a remarkable degree of co-ordination. (4)

Down regulating effects

Many endogenous controls on the inflammatory cascade exist as part of the CARS. Specific cytokines down-regulate many of the functions of activated inflammatory cells. For example, IL-10 when given prior to inflammatory challenge in animal models inhibits LPS induced release of TNFa, IL-ip, *TL-6* and IL-8 and reduces mortality. IL-4 inhibits LPS induced COX-2 expression and reduces macrophage responses. Other protective molecules include the antiproteases and specific proteins that can block exogenous activating agents; notably bactericidal permeability increasing protein BPI, a weak antibacterial protein found in neutrophil granules. BPI binds LPS avidly and may play a powerful role as an 'endotoxin scavenger' within the neutrophil itself, preventing the systemic release of LPS after intracellular bacterial killing and thus limiting cellular activation. The scavenger receptor type A has a similar capability.
The expression of this trimeric glycoprotein is upregulated with macrophage activation and it binds to both LPS and lipoteichoic. The body synthesises protective endogenous anti-oxidants including superoxide dismutase, catalase and glutathione peroxidase, the levels of which may be deficient in certain states including the premature infant and in children with cyanotic congenital heart disease. Another regulatory protein is the intracellular redox regulating molecule thioredoxin, a stress inducible protein that protects cells from oxidative stress induced apoptosis.
In addition to these protective molecules, many surface receptors are shed upon activation including cytokine receptors *(e.g.* both TNF receptors, IL-6 and M-CSF receptors) adhesion molecules *(e.g.* ICAM-1, VCAM-1 and L-selectin) and others including CD14. Some, such as the IL-6 receptor and CD 14 activate inflammatory cells when shed26>45, whilst others, such as sICAM-1 and soluble TNF receptors exert negative regulatory effects. IL-1 is regulated by the endogenous IL-1 receptor antagonist IL-lra, found in increased levels in febrile patients. Thus, it is the balance of pro- and anti-inflammatory cytokines that may be more important than the absolute levels of any single cytokine and there is evidence for this in that the ratio of IL-1 (3 to IL-lra favors unopposed inflammation in established ARDS. (4)

7. Gut mucosal barrier and its relationship to sepsis, systemic inflammatory response syndrome and multiple organ failure

The GIT is an organ worth special consideration as it carries an enormous microbiological load within its lumen that normally it maintains effectively separated from the body.
The anatomy of the microcirculation of the gut, with end arteries supplying the villi within the intestine mean that when the general circulation is compromised these vessels may not be able to maintain an adequate blood supply.
The intestinal mucosa provides a barrier between bacteria and bacterial products in the intestinal lumen and the body’s circulation and organs. It is proposed that a derangement of this barrier function occurs during critical illness that results in the amplification of the general inflammatory response and predisposes to multiple organ failure. This outcome might be a result of: (1) translocation of bacteria into the blood circulation, which is detectable by culture or by detecting their DNA; (2) translocation of bacterial products or antigens into the systemic circulation or (3) amplification of an abnormal intestinal pro-inflammatory response, with release of pro-inflammatory cytokines etc. into the circulation in response to normal or abnormal lumen bacteria.

The intestinal mucosa and the lamina propria contain large numbers of immune cells that interact with each other and with the lumen milieu. The pathogenesis of gut mucosal barrier dysfunction in critical illness has been well summarized. Partially-reduced derivatives of molecular oxygen, superoxide, H2O2 and hydroxyl radicals are important mediators of inflammation, and oxidant stress increases the permeability of intestinal monolayers, depletes intracellular ATP and inhibits Na+–H+ exchange. Oxidant stress-related abnormalities in permeability may relate particularly to which of the protein kinase C isoforms are expressed or activated, with protein kinase C-d essential for this effect.
Studies of hypoxia support the concept that depletion of cellular ATP increases paracellular permeability. Stimulation of cells by pro-inflammatory cytokines amplifies cellular elaboration of other cytokines and the combined effects result in an increased mucosal permeability via NO synthase mRNA induction. Anti-inflammatory cytokines have the opposite effect. IL-6 appears necessary for the effect of sepsis on intestinal permeability in mice. NO can be both protective and damaging. Toxic effects are thought to be mediated via the peroxynitrite anion, with permeability effects mediated via Na-K ATPase inhibition.
An overall picture emerges of a large and cellular organ responding to stress and in doing so altering its interaction with the lumen contents, with the potential for huge and harmful amplification of the inflammatory response not just in the intestine but throughout the rest of the body. (5)

8. GENERAL NUTRITION SUPPORT

Timing of intervention

The optimal time to initiate nutrition support in critically ill patients is unknown. The American Society for Parenteral and Enteral Nutrition recommends that beginning nutrition Support within 5–10 days is reasonable in critically ill patients. (7)
Many studies have examined the utility of early initiation of EN in critically ill patients. Initiation of EN within 36 hours of admission to the hospital or within 36 hours after surgery is associated with a decrease in infectious Macronutrients complications and a reduction in length of hospital stay. However, these data should be interpreted carefully because of significant heterogeneity in results among studies. Similar analyses have shown that EN started within 24–48 hours results in a trend toward decreased mortality when compared to delayed nutrient intake (3, 7). Similarly, a trend toward a reduction in infectious complications has been observed in patients randomized to early EN when compared to delayed nutrient intake. In studies reporting nutritional indices, such as calorie intake, protein intake, percentage of goal feeding achieved, and improvement in nitrogen balance, early EN is associated with improved results relative to control groups. Therefore, it is recommended that critically ill adults be initiated on EN within 24–48 hours, assuming that they are adequately resuscitated and hemodynamically stable (3). In cases where enteral nutrition is not an option then parenteral nutrition can be given. Preoperative PN is beneficial for malnourished patients undergoing surgery who cannot be fed enterally. Recent studies have shown parenteral nutrition reduces mortality compared with delay. (3)

Route of Intervention

During the past 10–15 years, many studies have been conducted to determine the optimal route of nutrient administration in critically ill patients. These studies have resulted in a major push toward the use of EN whenever possible. (1, 2, 3)

Physiology

Numerous studies in animals, and a small number in humans, have shown the detrimental effects of prolonged disuse of the gut that occurs in patients fed parenterally. The gut is a major immune organ, and dysfunction and disuse increase the incidence of numerous complications. Disuse of the gut results in atrophy of the villi lining the intestines, a decrease in gut motility, and decreased secretion of bile salts and secretory immunoglobulin A. These changes are associated with decreased barrier function and a greater degree of bacterial translocation from the gut to the systemic circulation. In addition, hypoperfusion injury to the gut as a result of disuse leads to increased antigen exposure and gut macrophage activation. This priming of the immune system has been hypothesized as a means to increase the production of inflammatory mediators that are associated with sepsis and multiorgan failure. (1, 2, 3, 6)

Clinical studies comparing EN to PN

Studies noting clinical differences between critically treatments of patients who are hypermetabolic for extended periods should in all likelihood include nutrient supplementation.

The fundamental objectives of nutrition support of the hypermetabolic patient are to provide sufficient nonprotein energy sources and sufficient protein substrate to alleviate or at least minimize catabolism of endogenous energy and protein sources.

Enteral and parenteral nutritional support in metabolically depleted patients often improves nitrogen balance during the catabolic phase of injury. Enteral nutrient provision is clearly the preferred route of feeding in the presence of a functional intestinal tract.

There is also evidence to suggest that some nutrients may become conditionally essential during catabolic illness. Among these is the amino acid glutamine, which is a major component of the tissue free amino acid pool and appears to be rapidly depleted in periods of stress. It is also essential for nucleotide and glutathione synthesis, as well as for gluconeogenesis. Other studies suggest that other amino acids, such as arginine, may also be limiting to the maintenance of lymphocyte function and wound healing. (1, 2, 3, 6)

Enteral Feeding

Enteral feeding is a method of provision of nutrients into the gastrointestinal (GI) tract through a tube. This method is used for nutritional support in patients who cannot ingest or digest sufficient amounts of food but have adequate intestinal functional capacity.

Enteral feeding is clearly a major advance in the ability to provide nutrients to patients with various illnesses and thus potentially to affect morbidity, mortality and quality of life. Severe dysphagia from obstruction or dysfunction of the oropharynx or esophagus.

- Coma or delirious state.
- Persistent anorexia
- Nausea or vomiting. Patients who suffer from nausea and vomiting arising from a gastric disorder (gastroparesis, gastritis, gastric outlet obstruction) can be safely fed into the jejunum. If these symptoms are the result of intestinal obstruction, however, enteral feeding is contraindicated.
- Fistulas of the distal small bowel or colon.

- Severe malabsorption secondary to decreased absorption capacity of the GI tract, such as a short bowel or inflammatory disease. In these conditions, a pump-controlled slow drip of enteral formula can maximize utilization of the limited absorption capacity, which may be overwhelmed by the large volume of food and fluids delivered to the intestines from oral or bolus feeding.
- Recurrent aspiration. In this condition, formulas should be delivered through a jejunostomy .
- Diseases or disorders that require administration of specific formulas that cannot be taken orally for prolonged periods.
- Increased nutritional requirements that cannot be met by oral intake. This indication applies mostly to patients with burn injury, who have high nutritional requirements.
- Growth induction in children with Crohn disease and other diseases.

Enteral feeding is contraindicated in patients with complete intestinal obstruction, paralytic ileus, severe pseudointestinal obstruction, severe diarrhea, or extreme malabsorption. In patients with a proximal intestinal fistula, enteral feeding can be attempted only if the tip of the feeding tube is distal to the fistula.(2)

ENTERAL FEEDING FORMULAS

More than 100 commercial formulas are available for enteral feeding. The composition of different products varies greatly, with some intended for general nutrition and others designed for specific metabolic or clinical conditions. Enteral feeding formulas have been classified according to various criteria. (2)
The following is a classification based on practical considerations according to clinical indications:

1. Polymeric formulas: These contain macronutrients in the form of isolates of intact protein, triglycerides, and carbohydrate polymers. They can be used orally or through a tube and provide complete nutrition. They also contain vitamins, minerals, trace elements, and, in some cases, fiber. These are the most commonly used formulas for enteral feeding.

2. Monomeric formulas: These usually contain proteins as peptides and/or amino acids, fat as long-chain triglycerides (LCTs) or a mixture of LCTs and medium-chain triglycerides (MCTs), and carbohydrates as partially hydrolyzed starch maltodextrins and glucose oligosaccharides. They also contain vitamins, minerals, and trace elements. These formulas are often used for patients with impaired digestion or absorption; however, it is questionable whether they are more advantageous than polymeric formulas

3. Blenderized foods: These are natural foods, semiliquified in a blender that can be used for the provision of nutrition by the oral route or through a tube. Currently, these foods are rarely used.

4. Formulas for specific metabolic needs: These are intended for patients who have unique metabolic requirements: inborn errors of metabolism, renal failure, diabetes, and other illnesses presenting specific needs.

5. Immune-enhancing formulas: These formulas contain specific nutrients thought to improve the immune response. In spite of extensive research, no clear evidence of clinical advantages exists, although some studies identified specific patients in whom these formulas offer benefits.

6. Modular formulas: These are single nutritional components that can be given by themselves or mixed with other enteral products to provide formulas that meet special nutritional or metabolic needs (i.e., increased calories, protein, and minerals

7. Hydration solutions: These provide minerals, water, and small amounts of carbohydrates. Hydration solutions have been designed mostly to provide fluid and minerals to children and adults with acute diarrhea to prevent dehydration. The solutions contain sodium and glucose. Osmolarity varies between 224 and 311 mmol/L (2). Glucose facilitates sodium absorption in the small bowel. Hydration solutions have been used successfully in developing countries during epidemics of infectious diarrhea to treat or to prevent dehydration. These solutions can be taken orally or administered through tubes to patients with excessive fluid and mineral requirements.

Enteral Formula Selection

Most critically ill patients can be fed formulas with intact polymeric protein. Studies conducted comparing polymeric protein formulas with more elemental peptide-based formulas have failed to show a difference in clinical outcomes. No differences in caloric delivery have been observed with peptide-based formulas compared to polymeric EN. Although a meta-analysis of available studies revealed no difference in the incidence of diarrhea with peptide-based formulas, individual study results have noted a decrease in stool frequency with these more elemental products. Some authors advocate the use of peptide-based or semielemental formulas in patients who develop refractory diarrhea while receiving polymeric EN.

Critically ill geriatric patients, who are at a greater nutritional risk, as indicated by an albumin concentration less than 2.5 g/dl, tolerate a semielemental formula with fiber better than a polymeric formula.
There is also a potential benefit for peptide-based formulas in patients with gastrointestinal complications, such as short bowel syndrome or pancreatitis. When considering the paucity of documented benefit in light of the increased cost of elemental or semielemental formulas, polymeric formulas should be used as long as they are tolerated. (2)

COMPLICATIONS OF ENTERAL FEEDING

Enteral feeding can be a safe and effective nutritional support method. Its safety depends on (a) the choice of the appropriate formula and infusion method, (b) delivery of the formula into the appropriate part of the GI tract, and (c) the clinical and metabolic evaluation of the patient before and during enteral feeding.
The most severe complication of enteral feeding is aspiration. Numerous factors may predispose a patient to aspiration: location of the tip of the feeding tube in the esophagous or upper stomach impaired gastric emptying, decreased lower esophageal sphincter pressure, large volume of feeding, patient's position during feeding, and various medications that decrease GI peristalsis. The risk of aspiration can be reduced by appropriate positioning of the feeding tube, elevating the patient's upper body to 45 degrees, and avoiding enteral feeding when contraindicated.
Determination of residual volume in the stomach during enteral feeding is widely used to assess tolerance to feeding and aspiration risk, but this practice has not been assessed adequately. Postpyloric feeding may reduce aspiration risk. (3)
Bacterial contamination of enteral feeding formulas can occur because the formulas are an ideal growth medium for bacteria. Occasional case reports of sepsis associated with feeding of contaminated enteral feedings have been published.
Nonspecific symptoms of abdominal cramps, distention, and bloating can occur and are usually caused by too rapid an infusion or by an underlying intestinal disorder.
Diarrhoea during enteral feeding remains a common problem whose causes include infected diets, lactose intolerance, concomitant administration of medications particularly antibiotics and laxatives. Furthermore continuous infusion of enteral diets causes alterations in colonic stimulation and significant colonic secretion of water, sodium and chloride which contribute to diarrhea. (1, 2)
Constipation occurs commonly in patients receiving long-term enteral feedings. This condition may be alleviated by administering formulas with insoluble fiber or giving fiber separately from the feedings. (1)
The frequency and severity of metabolic abnormalities in patients receiving enteral feeding depend mostly on the general medical condition of the patient. Thus, patients with renal failure are at risk of developing increased azotemia, hyperkalemia, hypermagnesemia, and hyperphosphatemia, whereas the diabetic patient is at risk of hyperglycemia. These potential complications are not inherent to enteral feeding and can be avoided by careful monitoring of the patient. Dehydration is a potential complication in patients given formulas with high calorie and nitrogen content. Patients receiving such products must be monitored closely to prevent dehydration and metabolic complications. (1)
Case reports have described small bowel necrosis associated with jejunal feeding inserted by modified Witzels technique (1).

DRUGS IN ENTERAL FEEDING

The absorption, activity, toxicity, and disposal of medications may be altered by the site in the GI tract into which they are delivered. Therefore, each drug administered through a feeding tube must be evaluated for potential changes in absorption and activity. The rate-limiting step to oral drug absorption is dissolution. The crushing of tablets and preparation of slurries often used for administration through a tube modify this process and can alter the drug kinetics and activity. The crushing of tablets may result in quicker absorption and higher maximal concentration in the blood, with an increase in dose-related toxicity. Faster absorption may also result in enhanced clearance and reduced duration of effect. Depending on gastric emptying times, the increased or decreased exposure to gastric acid can also significantly alter the amount of drug available for intestinal absorption.

Postpyloric administration may have a major impact on drug activity by skipping the acid milieu of the stomach and the regulated passage through the pylorus. Drugs are absorbed more quickly when they are un-ionized. Gastric acidity enhances drug un-ionization and absorption. Skipping the stomach, as in jejunal feeding, will thus render the drug less absorbable in the intestinal tract. Drugs such as ketocanazole will be poorly absorbed when delivered directly in the less acid millieu of the intestines.

Little research has been done to document drug activities when drugs are administered with enteral feeding. Nevertheless, guidelines regarding specific drugs have been published, based mostly on physiologic considerations rather than actual clinical observations.

When administering drugs through tubes, it is advisable to do it separately from the feeding formula and to monitor the patient carefully with regard to the drug effect, toxicity, and plasma levels when feasible. (2, 1)

PARENTERAL NUTRITION.

Indications:

The primary objective of PN is maintaining or improving the nutritional and metabolic status of patients who, for a critical period of time, cannot be adequately nourished by oral or tube feeding. The decision to undertake PN requires weighing various factors and considering the patient's diagnosis and prognosis. It is not a defensible substitute for oral or tube feeding when adequate provision by either of these methods is feasible. (1)

Parenteral access

Parenteral nutrition may be delivered through either central or peripheral intravenous access. Because of the nature of critical illness, patients in the ICU typically receive PN through central venous access. Numerous types of intravenous access devices and sites of insertion may be considered for central administration of PN. Common sites of insertion include the subclavian, internal jugular, and femoral veins. Each is associated with different levels of technical difficulty, patient discomfort, risk of infection, and risk of noninfectious complications.

Peripheral PN is less frequently used in the ICU, despite recommendations from some advocating the use of peripheral PN using rotating sites. To date, no evidence has been published to support an advantage to this method of administration.

Administering PN No definitive evidence exists to guide clinicians in the best way to administer PN, or how to advance PN to reach feeding goals.

It has been recommended that no more than 150–200 g of carbohydrate should be given in the first day, and that this may be advanced as patients demonstrate metabolic tolerance.
It is further recommended that, in patients with preexisting hyperglycemia, the initial PN not provide more than 100 g of carbohydrate in the first 24 hours, and that adding a basal amount of insulin therapy is reasonable. The amount of carbohydrate should not be advanced until blood glucose concentrations are consistently controlled for 24 hours. (7)

Complications of PN

Administering PN through central venous access is associated with several mechanical and procedural complications. These include catheter obstruction, venous thromboembolism because of the presence of the venous access device (more common with femoral placement), and pneumothorax.
Catheter-related infection is a commonly encountered problem in patients receiving central PN. The size, type of material, and position of the catheter influence the probability of blood stream infection. Controversy exists about whether the use of single versus multiple lumen venous access devices results in different rates of infection.
Strict aseptic technique is essential to minimize catheter infection, as is fastidious care of catheters already in place. Another practice aimed at decreasing bloodstream infection is the use of dedicated ports for PN administration, which is done to minimize the disruption of the intravenous line, which may allow a greater opportunity for bacterial contamination and growth. (1, 2)

Metabolic complications
Overfeeding

Overfeeding, which may occur with any form of nutrition support, is a distinct risk in patients receiving PN.
Excessive protein administration is associated with azotemia and elevations in blood urea nitrogen. Patients with preexisting renal insufficiency, hepatic dysfunction, or hypovolemia are particularly at risk. The response to these changes is addressing the primary disease process if possible, but moderation of protein provision may be necessary. Periodic assessment of serum prealbumin concentration and nitrogen balance are recommended to help monitor the appropriateness of protein delivery.

Overfeeding Carbohydrates and Hyperglycemia

Carbohydrate intolerance can manifest in numerous complications in patients in the ICU. The liver may be affected, manifesting as hepatic steatosis or cholestasis. Lipogenesis and excessive carbon dioxide production also may result, which may lead to difficulty discontinuing mechanical ventilation.
Hyperglycemia is the most common complication of carbohydrate administration in the ICU, especially when rates of carbohydrate infusion exceed 5 mg/kg/minute. The occurrence of hyperglycemia has had great impact outcome in the past several years. In the past, glucose concentrations typically were tolerated until they reached 180–220 mg/dl, where osmotic diuresis and volume depletion are likely to occur.
However, intensive insulin therapy to maintain blood glucose between 80 mg/dl and 110 mg/dl has been associated with decreases in mortality, the percentage of patients requiring more than 10 days of antibiotic therapy,

transfusion requirements, the length of ICU stay, and mechanical ventilation when compared with standard therapy.
It is recommended that intensive insulin to maintain blood glucose between 80 mg/dl and 110 mg/dl be considered in critically ill surgery patients, particularly after cardiovascular surgery. Although the results with intensive insulin therapy to maintain tight glucose control have not yet been replicated in other critically ill populations, they emphasize the importance of good glycemic control. It is recommended that a reasonable goal in these populations is to maintain blood glucose between 100 mg/dl and 150 mg/dl until further data are available.

Overfeeding lipid

Overfeeding of fat calories is associated with dysfunction of the reticuloendothelial system, leading to the development of hypertriglyceridemia. Other potential complications include immunosuppression and hepatic steatosis. Some elevation in triglyceride concentrations is to be expected with nutrition support, especially PN, but excessive elevation requires moderation of fat delivery. Although the exact concentration requiring intervention has not been defined, the American College of Chest Physicians recommends that serum triglyceride concentrations be maintained at 500 mg/dl or less. The rate, and not just total daily dose, is associated with symptoms of lipid intolerance. It is recommended that the rate of lipid infusion not exceed 0.1 g/kg/hour. If significant hypertriglyceridemia occurs, lipid-free PN can be given or limiting the administration of lipids to 1–2 days/week may be appropriate. It also is important to evaluate whether other sources of lipid administration are present, such as propofol.
Refeeding Syndrome
Refeeding syndrome is another complication observed when severely malnourished patients or patients with cardiac or pulmonary failure receive nutrition support. The response to aggressive feeding in these populations is increased insulin release, leading to acute sodium and fluid retention; cellular uptake of glucose; and rapid intracellular movement of phosphorus, potassium, magnesium, and thiamine. Hypophosphatemia and hypokalemia often result, which may cause cardiac arrhythmias, neuromuscular abnormalities, and respiratory failure. Management of refeeding syndrome begins with identification and conservative initiation of nutrition support in patients at risk. Close monitoring of phosphorus, potassium, magnesium, and glucose are imperative in patients in the ICU being started on nutrition support.

9. IMMUNE-ENHANCING NUTRITION.

Throughout the past several years, many enteral feeding formulas have been developed that include ingredients that enhance immune function. These include the amino acids arginine and glutamine, nucleotides, such as antioxidants, fish or borage oils, and omega-3 fatty acids.

Arginine

The most commonly studied of these immune-enhancing products in ICU population are those enriched with arginine. Arginine is a nonessential amino acid that may become conditionally essential during periods of severe physiological stress.
It also is a precursor to the production of nitric oxide, which is important for gastrointestinal function, vascular tone, and immune function. Arginine is a C5 basic amino acid that plays a central role in the immune system. It is a principal precursor for NO synthesis (with the formation of citrulline) and functions as a secretagogue for a number of hormones including growth hormone and prolactin.

Arginine can participate in a systemic inflammatory response, first through the production of NO and second through utilization for T lymphocyte and macrophage function and proliferation. A recent review has compared the initial systemic inflammatory response signaled by cytokines IL-1, IL-2, g-interferon and TNF with the subsequent down-regulation of the immune response (compensatory anti-inflammatory response) signalled by IL-4, -10 and -13. In inflammatory response syndrome inducible NO synthase increases NO production from arginine in macrophages, and arginine is used for T-cell function and proliferation. In compensatory anti-inflammatory response syndrome one or both arginase isoforms are up regulated in macrophages, which can modulate the inflammatory response by: (1) producing ornithine, thus enhancing wound healing; (2) producing polyamines from ornithine that support macrophage function;(3) metabolic redirection, reducing arginine availability for NO synthesis (3). Trials of the effect of free arginine on clinical outcome are lacking; clinical controlled trials have used 'immune enhancing' enteral feeds that combine arginine with other immune-nutrient such as antioxidants, glutamine, anti-inflammatory fatty acids and nucleotides. Most of the clinical trials have employed mixtures of these nutrients in enteral feeds. Since these mixtures vary, results can be difficult to analyse. Meta-analyses have been performed but provide different interpretations dependent on which trials are included and which trials are taken together. 'Immunonutrition' feeds tend to be associated with a lower number of infectious complications and a shorter length of hospital stay, most notably in interventions that used a high content of arginine. However, the same meta-analysis drew attention to the higher mortality associated with immunonutrition in trials with high (good) methodological scores. At present, routine use cannot be recommended in critical ill patients (3)

Gluamine.

Glutamine is the most abundant amino acid in healthy patients, but rapid depletion occurs during periods of physiological stress. Glutamine may become conditionally essential in critically ill patients. It functions by serving as a source of energy for enterocytes and colonocytes. It further enhances immune competence by promoting lymphocyte trophism. Finally, glutamine is involved in glutathione function as an antioxidant.
Plasma and intramuscular glutamine concentrations drop during metabolic stress such as surgery, trauma, infection and sepsis to levels of approximately 300–500 mmol/l and 15 mmol/l respectively (3). It remains unclear to what extent this drop in concentration affects the metabolism and function of the intestinal mucosa, particularly in the presence of an existing inflammatory response. Glutamine has been shown previously to maintain intestinal cell layer barrier function, suppress an acetaldehyde- induced increase in paracellular permeability in cell monolayers, down regulate cell line CXC chemokines, down regulate cytokine production and enhance haemoxygenase-1 expression in the duodenal mucosa (1, 3).
Glutamine through glutamate is a glutathione precursor. Glutathione is an important intracellular antioxidant. Glutamine infusion can result in enhanced tissue glutathione levels and enhanced antioxidant capacity. (1, 3)
Glutamine has been used in both enteral and parenteral feeds, and parenteral glutamine has emerged in metaanalysis in critical illness as possibly the most effective in reducing mortality.

Antioxidants.

Oxidant stress is increased in critical illness and can be assessed by measuring a number of markers. A commonly employed technique is to measure byproducts of oxidative damage of lipids (thiobarbituricreacting substances) by the malondialdehyde assay. High oxidant stress is associated with poor outcome. As discussed earlier such oxidant stress can be viewed as pivotal to a gradual amplification of the generalized immune response to the point where it becomes harmful and progresses to multiple organ failure. The use of large doses of antioxidants might prevent this outcome. In critically-ill patients who have undergone surgery a combination of a-tocopherol and ascorbic acid reduces the risk of developing multiple organ failure. Other antioxidants that have been employed include N-acetylcysteine, vitamin A and Selenium. Recent studies have shown a reduction in mortality but not infectious complications when antioxidants are used in critical illness. High dose parenteral Selenium appears to emerge as the most effective. Se could, through glutathione peroxidase activation, enhance the clinical effect of glutamine. Enzymes such as superoxide dismutase, catalase and gluthathione peroxidase protect against reactive oxygen species. (1, 2, 3)

Selenium.

Se is a critical cofactor in the activity of gluthathione peroxidase, and is also important in the management of peroxynitrite. The acute-phase response can reduce circulating levels of Se via redistribution out of the bloodstream. Although acutely-ill patients are presumed to be free of previous deficiency at the time of presentation, studies have shown that the Se status is suboptimal in a large portion of the population in various European countries. The current WHO recommendation for the safe maximum long-term intake of Se is 400 mg/d, which is applicable to healthy individuals who have no symptoms of Se deficiency and are not under conditions of increased stress. In individuals with disorders associated with excessive free radical production such as trauma, higher intakes may be beneficial. Various doses of Se have been prescribed in clinical trials. A dose of 500 mg/d has been shown to reduce the need for haemodialysis in patients with systemic inflammatory response syndrome and reduce pulmonary infections in patients with burns. Studies of patients with burns and systemic inflammatory response syndrome have shown that without supplementation Se levels can be depleted for a period of 10–14 d. (3, 7)

10. MONITORING NUTRITION SUPPORT.

Monitoring for Effectiveness to adequately monitor nutrition support in the ICU, patient-specific goals of therapy must be developed and frequently reviewed. Once nutrition support has been initiated, the trend in visceral protein markers may be followed as part of the assessment of nutritional maintenance or repletion. C-reactive protein concentrations may be collected to associate this with an increase in physiological stress. Many clinicians combine protein assessment with baseline urinary urea nitrogen and routine nitrogen balance assessment to monitor the appropriateness of nutritional intervention. Clinical markers of nutritional status, such as wound healing and respiratory function, also should be used to determine the effectiveness of the nutrition support regimen. Patients in whom nutritional goals are not being met may benefit from indirect calorimetry and/or nitrogen balance studies to better define nutritional needs.

Monitoring for Complications

Fluid and electrolyte status should be monitored closely, with the frequency determined by the severity of patient illness and risk factors for abnormalities. Daily weight measurement is an important marker for fluid status, as rapid changes likely reflect changes in total body water. More invasive measures, such as central venous pressure monitoring and pulmonary artery catheterization, should be used as appropriate.

Complete blood cell counts with white cell differentials and international normalized ratio should be monitored frequently to monitor for infectious complications, hematopoietic function, and coagulopathy.

Electrolyte concentrations should be monitored at least daily in critically ill patients and maintained within normal ranges. Particular attention should be paid to potassium, phosphorus, magnesium, and ionized calcium. Similarly, arterial blood gases should be used as necessary to monitor acid/base status.

Baseline and weekly monitoring of triglyceride concentrations and liver function tests also are important to avoid adverse outcomes. Routine monitoring of trace element concentrations are not normally necessary, but should be evaluated in patients with, or at risk for, specific deficiencies.

Blood glucose monitoring should be conducted frequently with initiation of nutrition support in the ICU. Frequency of monitoring should be based on severity of illness, presence of drugs, such as corticosteroids, which can cause hyperglycemia, and prior history of diabetes or hyperglycemia. In a typical patient being fed parenterally, it is reasonable to begin monitoring glucose every 6 hours to allow for corrective insulin therapy and determination of baseline insulin needs. When the glucose concentration stabilizes, glucose monitoring may be done less frequently, but changes in the clinical status of the patient may necessitate reassessment of the monitoring plan.

Gastric residual volumes should be collected every 6 hours in patients being fed intragastrically. This should be done in conjunction with evaluation of the patient's respiratory and abdominal examination and frequency of gas or stool passage. These assessments may need to be conducted every 4 hours in patients with a history of EN intolerance.

11. CONCLUSION.

Nutrition management is a vital part of the care of critically ill patients. The changes in metabolic state that occur to patients in the ICU put them at risk for morbidity and mortality. Patients should receive appropriate amount of nutrition hat prevents an accelerated depletion. The enteral route of nutrition support should be used whenever possible, and feeding should typically begin within the first 24–48 hours after resuscitation after hemodynamic stability is achieved. Complications related to overfeeding should be avoided, and close metabolic monitoring is vital. The use or immunonutrition in parenteral and enteral feed has shown to improve clinical outcomes. Its important to consider critical ill patients as a very heterogeneous group, and the provision of nutrition should be tailored according to the individual patient.

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