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Nutritional Support in Critical Illness

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INTRODUCTION

Critically ill patients, almost by definition, are catabolic and often hypermetabolic. Although it is generally accepted that such patients would benefit from nutritional support, there are remarkably little data to support this premise.

Several experts believe that prospective, randomized, controlled studies to document the efficacy of nutrition support in improving outcome in critically ill patients are unlikely to occur for a variety of reasons. It is difficult to recruit acceptable (large) numbers of patients that can be matched in terms of diagnosis, severity of illness and nutritional status prior to intensive care unit (ICU)[b] admission. With the broad acceptance of early nutritional support amongst physicians, ethical dilemmas are created in proceeding with trials in which control groups receive no nutritional support. Finally, as Soeters et al. [1] point out, it is likely that those patients who are most severely ill will receive the least benefit in terms of outcome because of overwhelming illness. Nevertheless, nutritional depletion is generally associated with increased morbidity and mortality, and intuitively the correction of these deficiencies should minimize the component of the adverse outcome attributable to malnutrition.

THE METABOLIC RESPONSE TO INJURY

The situation frequently confronted in the critically ill is not simply that nutrient supply is less than nutrient demand as in starvation. Critically ill patients have a state of hypermetabolism [1, 2] initiated by a variety of causes such as shock, sepsis, thermal injury, trauma, etc. This hypermetabolism is secondary to a number of events initiated in large part by the same mediators seen in the systemic inflammatory response syndrome (SIRS). There are marked increases in sympathetic activity; elevations of glucocorticoids, glucagon, and insulin; as well as cytokine release (tumor necrosis factor, interleukin-1, interleukin-2); lipid-related mediators such as platelet activating factor; and a variety of leukotrienes and prostaglandins [3-5]. Additionally, though poorly studied, it seems certain that a number of described growth factors will be shown to play an active role in the metabolic response to injury.

The net result is dramatic as the body mobilizes substrates to meet energy requirements and for the hepatic production of acute phase reactants. The latter are important in healing wounds and modulating the inflammatory response. The expense is in lean body mass—patients often losing 10 to 20 gm of nitrogen per day (Table 1).

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[b] *Abbreviations:* ICU, intensive care unit; SIRS, systemic inflammatory response system; TPN, total parenteral nutrition; BCAA, branched-chain amino acid.

Table 1. Metabolic response to injury and inflammation.

- Increased resting energy expenditure
- Increased respiratory quotient
- Markedly increased proteolysis, ureagenesis, urinary nitrogen loss
- Increased gluconeogenesis

NUTRITIONAL ASSESSMENT IN THE INTENSIVE CARE UNIT

Most measurement tools for nutritional assessment for critically ill patients are at best only estimates of the need for nutritional support. Virtually all of the current assessment methods are impacted by serious illness. There is no consensus on appropriate assessment, and there are little comparative data between assessment methodologies. If we cannot agree on nutritional assessment, how can we agree on whether to feed, when to feed and how to feed?

Subjective global assessment

Probably the best of the current assessment tools is the subjective global assessment [6, 7], which involves an assessment of nutritional restriction, metabolic and nutritional influence of the patient's disease, and effects upon organ function or composition. It uses a variety of means including history, symptomatology and physical assessment. As the title suggests, some elements are influenced by subjective weighting, yet there is a good reproducibility, and it is a better prediction of postoperative complications than most other objective tests. It has not been well tested in critically ill patients.

Muscle function

Changes in skeletal muscle function in response to hypocaloric diets and fasting occur rapidly, prior to detectable changes in nitrogen or protein homeostasis. Tests of adductor pollicis function, in response to electric stimulation, appear to be both sensitive and specific compared to more common assessments [8]. Reciprocal changes in function can be detected during refeeding. There is a wide variation amongst patients, however, potentially making standardization difficult.

Blood tests

The measurements of serum albumin, transferrin or retinol-binding-prealbumin serum complex are commonly utilized in nutritional assessments [6, 9-11]. All have potential error introduced in critical illness as they can be influenced by events such as infection, liver dysfunction, renal dysfunction and other processes not related to nutritional status. Having said that, a decreased serum albumin is clearly associated with increased morbidity and mortality.

Other assessment tests, such as measurement of serum fibronectin [12, 13] and insulin-like growth factor [12, 14], have been suggested particularly for patients with renal failure, but these studies are rarely available and their reliability not yet proven.

Anthropometry

The use of these standard measurements in the critically ill patient is limited because of variability between observers and difficulty with reproducibility, compounded in critically ill patients because of changes in volume state, i.e., subcutaneous edema.

Body weight

Body weight is a poor assessment tool in the ICU for nutrition because total body water changes such as edema, ascites, effusions and dehydration are frequent occurrences in the ICU. Derived indices such as body mass index are subject to similar errors.

Delayed cutaneous hypersensitivity

Delayed cutaneous hypersensitivity is a poor choice of nutritional assessment in critically ill patients as it is altered in many conditions and by many medications commonly seen in the ICU in the absence of malnutrition [15].

Body composition analysis

Technology now exists to measure a variety of tissue components, but they are expensive and not readily available. Examples are dual energy x-ray absorptiometry, *in vivo* neutron activation analysis and bioelectrical impedance. Data have not allowed an accurate prediction of outcome as yet, but these technologies have the potential to overcome many of the obstacles inherent in other methods of nutritional assessment.

PHYSIOLOGICAL CONSIDERATIONS IN NUTRITION

Shock, severe illness, starvation, trauma and possibly total parenteral nutrition (TPN) [16, 17] are associated with changes in the small intestine resulting in villous and mucosal atrophy and concomitant changes in permeability. These findings have led to the theory that translocation of bacteria and endotoxin occurs as a result of these intestinal changes which, in turn, leads to inflammatory and/or infectious events [18, 19]. Enteral nutrition has been shown to improve mucosal mass, integrity, absorptive capacity and barrier function [20]. Animal studies suggest that these improvements in the gut provide an advantageous outcome in terms of sepsis [21, 22]. Human data are not quite as conclusive, but the available evidence suggests that early enteral nutrition is superior to TPN [23, 24].

There are other physiologic implications associated with the delivery route for nutrition. TPN can induce cholestasis and fatty infiltration of the liver. Enteral feeding releases cholecystokinin, which stimulates bile flow and decreases the incidence of cholehepatic complications. Early enteral feeding has also been shown to attenuate the hormonal response to inflammation [25]. Despite early aggressive nutrition, acute phase reactants (proteins) are synthesized at the expense of visceral protein, and current therapy cannot reverse the decrease in lean mass (protein wasting) that occurs in catabolic critically ill patients.

Early enteral feeding may also have a protective effect on the gut by restoring gastrointestinal blood flow often compromised in critical illness. Trace elements are regulated via the gastrointestinal tract, but it is not known if regulation continues when trace elements are given parenterally. TPN requires central venous access, which has its own mechanical and infectious hazards. Intravenous lipid emulsions have been associated with immunosuppression. TPN is also associated with frequent severe metabolic changes such as hyperglycemia, acid-base disturbances and electrolyte abnormalities.

Generally, the majority of clinical evidence supports improved outcomes in patients fed enterally as opposed to parenterally [23, 24]. Though the benefit to enteral nutrition is thought by many to relate to its physiologic effect on the gastrointestinal tract, it makes little difference whether it is the avoidance of problems associated with TPN, as opposed to any physiologic benefit of enteral nutrition. The adage "if the gut works, use it" still holds.

ECONOMIC CONSIDERATIONS

In this time of fiscal scrutiny, the mention of economics to physicians results in immediate dysphoria. In terms of nutritional support, however, it appears the right thing economically is the right thing for most patients. The cost implications of using TPN when the gastrointestinal tract is functional are enormous and probably unconscionable, given the compelling data that enteral nutrition is more cost effective for a variety of reasons [26].

TIMING: WHEN DO WE FEED?

Critically ill patients are often not previously-well patients who have reverted to starvation metabolism. The patients we are primarily concerned with are those that are hypermetabolic/hypercatabolic, with large (10 to 20 gm nitrogen per day) losses of protein in the urine.

There remain surprisingly little firm data available to help one select the time when nutrition should begin. Consensus at a recent conference sponsored by the National Institutes of Health (NIH), the American Society for Clinical Nutrition (ASCN) and the American Society for Parenteral and Enteral Nutrition (ASPEN) concluded that critical depletion of lean tissues would occur by 14 days and that nutrition should be instituted in those who cannot feed by seven to 10 days [27].

Limited, and controversial, evidence exists that early feeding may be beneficial and ameliorate the inflammatory response. Early feeding is most beneficial when given enterally, decreasing infections, morbidity, and mortality [23, 24]. In general, patients with critical illness (hypermetabolic and hypercatabolic) should be fed if they will not be able to nourish themselves within five to seven days. Some centers opt for more aggressive feeding, proceeding as early as is practical with supplemental nutrition. With the lack of firm evidence, it is difficult to argue with that approach.

PRACTICAL POINTS AND COMPLICATIONS

"If the gut works, use it"—and use it maybe even if it seems not to work! Most critically ill patients will have relatively normal small bowel motility. Even those patients with gastric and/or colonic dysmotility can tolerate small bowel feedings in the vast majority of instances whether bowel sounds are present or not. Indeed, even patients with bowel anastamosis can frequently be fed early via the enteral route [28]. A recent study showed that upwards of 90 percent of all patients in need of nutrition therapy could be fed via the gastrointestinal tract when prokinetic agents such as erythromycin or cisapride were used when indicated [29]. In those patients with some element of malabsorption, elemental as opposed to polymeric diets may benefit. In general, one should fail enteral nutrition before beginning on TPN.

ENTERAL COMPLICATIONS

Gastrointestinal problems, chiefly diarrhea, are frequent in the enterally-fed ICU patient. It is more common in patients with low serum albumin and those on prolonged antibiotic therapy. Diarrhea is more common when patients are fed in bolus fashion rather than by continuous delivery. Diarrhea is often caused by a variety of etiologies other than tube feedings, e.g., *C. difficile* or sorbitol-containing medications. Diarrhea may also result from malabsorption, lactose intolerance, intestinal atrophy or bacterial contamination of the enteral feeding itself.

Depending upon the type of access, multiple potential problems exist including endotracheal placement (with potential for disaster) or dislodgment of jejunal tubes into the peritoneum. Other problems include nasopharyngeal irritation or infection, dysphagia and esophageal reflux.

Potential metabolic problems are not different with enteral versus parenteral feeding and include overfeeding; hypo- and hyperglycemia; uremia; vitamin, trace mineral and essential fatty acid deficiencies; abnormalities of fluid and electrolyte status; and elevation of liver function tests. Enteral feeding compared to parenteral feeding, however, is probably associated with a decreased incidence of metabolic problems and of lesser severity when they do occur.

The most common concern with the enteral approach revolves around aspiration. The incidence of aspiration varies widely, depending upon the definition and type of patient population. With proper selection, monitoring, and management, serious morbidity or mortality from aspiration is remarkably rare [30].

COMPLICATIONS OF PARENTERAL THERAPY

The most feared complications of parenteral therapy stem from the need for central venous access. Rates of complications of catheter insertion are somewhat operator-dependent and range up to about six percent [31], including all types of injuries from pneumothorax to thoracic duct injury. In addition, there is a complication rate for maintaining catheters in place including infections, venous thrombosis, arrhythmias, cardiac perforation with tamponade, catheter occlusion and air embolism. Other than sepsis and venous thrombosis, the others are fortunately uncommon.

Gastrointestinal complications include cholestasis, steatosis and acalculous cholecystitis. The enteral advantages of maintaining gut integrity is also lost. Potential metabolic complications of parenteral feeding are similar, but probably on whole more frequent and severe compared to enteral nutrition.

DIETARY ADJUVANTS AND ADDITIVES

Arginine

Arginine, an amino acid, stimulates the release of a variety of hormones including prolactin, insulin and growth hormone. It is also a precursor for nitric oxide. It reputedly enhances both wound healing and immune function. There are no studies, however, that examine outcome with arginine supplementation in critical illness.

Antioxidants

As injury from oxidation is a prominent process in inflammatory states that often accompany critical illness, it is natural to assume that inhibiting oxygen radicals would be beneficial. There is evidence that antioxidants, such as vitamin E, may lower risk in more chronic inflammatory conditions (i.e., coronary artery disease), but there is as yet no evidence to support antioxidant therapy in critically ill patients.

Omega-3 Fatty Acids

Many of the harmful mediators of SIRS are metabolites of omega-6 fatty acids, and it has been theorized that the substitution of omega-3 fatty acids would be beneficial in inflammatory states. Indeed, there are both animal and human data to support this [32-34]. In critical illness, the data are difficult to interpret because of study design but suggest some benefit.

Glutamine

Glutamine, an amino acid, serves a number of physiologic functions, most notably as a precursor for glutathione (antioxidant) and as fuel for the gastrointestinal tract endothelium and some blood elements. Although there are several studies that suggest benefit, the salutary effect of glutamine remains controversial and poorly examined in terms of randomized, prospective studies.

Branched-chain amino acids

Branched-chain amino acids (BCAA), particularly leucine, can stimulate protein synthesis and impede degradation *in vitro*. This finding has led to advocating BCAA as a mechanism to spare protein loss in critical illness. There is little or no evidence to demonstrate clinical benefit from this approach. BCAA have been used in the treatment of patients with hepatic encephalopathy with good results (in terms of encephalopathy).

Growth factors

In recent years, a multitude of growth factors (neurotensin, epidermal growth factor, insulin-like growth factor and others) have been discovered. Large, prospective, randomized studies will be required to determine if any positive role exists for these substances in nutrition support for the critically ill.

SPECIFIC CRITICAL ILLNESS

A recent intersociety conference reviewed the available published data in reference to critical illness (trauma, sepsis, SIRS, multiple organ dysfunction syndrome, burns, acute lung injury, acute renal failure) [24]. Despite the large volume of material reviewed, the nature of the majority of nutritional data led to remarkably scant conclusions:

- Critically ill patients have increased nutrient requirement and are hypermetabolic.
- Improved clinical outcomes as a result of nutritional support have been inadequately studied.
- Begin nutrition in patients not expected to resume oral feeding for seven to 10 days.
- Trauma patients enterally fed have fewer complications than those parenterally fed.
- No conclusions can be reached regarding the efficiency of specialized substances and formulas.

CONCLUSIONS

Because of the basic nature nutrition plays in supportive care, it is unlikely that appropriate adequate studies will answer these questions soon. In the meantime, the choice of enteral nutrition in critical illness, when feasible, has advantages in terms of theory, economics, preponderance of clinical opinion, and possibly outcome that make enteral nutrition the route of choice when alimenting critically ill patients.

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