Chapter 33. Nutritional Support

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Background

There is a consensus that nutritional support should be routinely provided to intensive care unit (ICU) patients.[1] Hospitalized patients with malnutrition (macronutrient and/or micronutrient deficiency) suffer from increased infectious morbidity, prolonged hospital stays, and increased mortality.[2] Moreover, even those hospitalized medical and surgical patients without antecedent malnutrition are typically subjected to stress, infection and impaired organ function, resulting in a hypercatabolic state. Often these patients are unable to meet their caloric needs, as they are either too sick or physically unable to ingest food. Although strong evidence demonstrates that providing nutritional support for such patients results in improved clinical outcomes, the optimal method of delivery, timing of administration, and specific formulation requires further research.

Practice Description

There are several ways to provide nutritional support to patients in the ICU. Enteral nutrition (EN) can be administered via transoral, transnasal, or percutaneous transgastric routes, or by surgical jejunostomy. Total parental nutrition (TPN) is generally used when the enteral route is either inaccessible or its use is contraindicated. It is also used as a supplement to enteral feeding if adequate nutrition is not possible via the enteral route alone.

The total caloric requirement of critically ill patients can be estimated or directly measured. Calorimetry, although accurate, is not practical in the clinical setting as it is costly, time consuming, and requires technical skill. It is also unclear that exactly matching energy input with energy expenditures improves patient outcomes. Therefore, a pragmatic approach is to attempt administration of 25 kilocalories per kilogram ideal body weight per day for most patients.[3] The total caloric daily requirement should be administered in a fluid volume consistent with the patient's needs (usually 1mL/kcal). Protein sources should comprise 15-20% of the total daily calorie requirement. The generally accepted amount of protein is between 1.2 and 1.5 g/kg per day, except in severe losses such as burns. Glucose should comprise 30-70% of the total calories and fats 15-30%.[1]

Prevalence and Severity of the Target Safety Problem

Malnutrition in hospitalized patients often goes unrecognized.[4,5] Early studies reported a prevalence of malnutrition in 30-50% of hospitalized patients.[6] A later study revealed that up to 40% of patients were malnourished at the time of their admission.[7] The majority of these patients continued to be nutritionally depleted throughout their hospital course. These patients are also at a greater risk for the development of severe malnutrition than those patients whose nutritional status was adequate at the time of admission.

Unfortunately, there is no single, readily available measure of malnutrition that is both sensitive and specific in critically ill patients.[1] Most studies have used body mass index (BMI=weight (kg)/height (m)) and/or anthropometry (measuring skin fold thickness) to assess patients' nutritional status.[7] BMI alone is not a sensitive indicator of protein-energy malnutrition as it does not distinguish between depletion of fat or muscle.[4] In a large number of studies,

malnutrition has been defined as a BMI ≤20 kg/m and a triceps skin fold thickness (TSF) or mid-arm muscle circumference (MAMC) <15th percentile.[7] Patients with a BMI of ≤18 and ≤16 kg/m with anthropometric measurements below the 5th percentile were considered to have moderate and severe malnutrition respectively.[7] Weight loss exceeding 10% of ideal body weight (IBW) also suggests malnutrition.[1]

Opportunities for Impact

Providing nutritional support has the potential to significantly reduce several clinically relevant endpoints (eg, infectious complications, hospital stay, mortality). However, even when malnutrition is recognized, adequate nutrition is often not delivered. Prescription of optimal enteral nutrition to meet energy requirements ranged from 76% to 100% in a prospective survey of 5 ICUs in the United Kingdom.[8] Another study of enteral nutrition among patients receiving no oral nutrition in medical and coronary care units at 2 US university-based hospitals, documented that physicians ordered only 65.6% of daily goal requirements and only 78.1% of this was actually delivered.[9] A recent prospective study of both enteral and parenteral nutrition in a French university-affiliated ICU found that physicians prescribed only 78% of the mean caloric amount needed by patients, and only 71% of this was effectively delivered.[10] Efforts targeted at increasing physician awareness of the problem and early delivery of appropriate nutrition may improve patient outcomes.

Study Design

The field of nutritional support can be divided into several basic areas of investigation. First, research has evaluated whether nutritional support is of benefit to malnourished critically ill patients. Second, studies have compared the impact of EN versus TPN on patient outcomes. Further investigations have looked at the timing of administering nutritional support. Lastly, recent research has focused on the type of EN, specifically considering whether immune-enhancing formulas (immunonutrition) improve outcomes.

At least 26 randomized controlled trials (RCTs) have compared the use of TPN to standard care (usual oral diet plus intravenous dextrose), and one meta-analysis reviewed these studies.[11] A different meta-analysis specifically reviewed the use of TPN in surgical patients.[12] A systematic review with meta-analysis (duplicated in the other publications[11,12]) included evaluation of 6 randomized trials in surgical patients that compared the benefits of early enteral nutrition with standard care.[2] Numerous randomized controlled trials have compared EN to TPN. Three RCTs of surgical patients evaluated the merits of early enteral feeding postoperatively. A few studies have compared EN delivered into the stomach versus into the small bowel (jejunum). Several randomized controlled trials have studied the effects of using immunonutrition and we found 2 meta-analyses of immune-enhancing enteral supplementation in critically ill patients after trauma, sepsis or major surgery.

Study Outcomes

The majority of studies reported Level 1 outcomes including infectious complications and mortality. Some measured hospital length of stay (Level 3) as well. Several studies evaluating immunonutrition reported its effects on surrogate outcomes such as wound healing. Studies evaluating immediate enteral nutrition in burn patients have also used surrogate markers. Animal studies have assessed the effects of immunonutrition on gastrointestinal physiology as well as wound strength.

Evidence for Effectiveness of the Practice

Nutritional supplementation in hospitalized patients may reduce mortality and is associated with weight gain (see Table 33.1).[13] However, there are no randomized controlled trials comparing supplemental nutrition to starvation in critically ill patients. Research does show that patients not receiving any nutritional support for more than 2 weeks postoperatively have a much higher complication and mortality rate than patients receiving TPN or some short-term glucose administration.[14] A large body of research in the past 2 decades has focused on determining the ideal type and method of delivery of nutritional support.

A meta-analysis comparing supplemental TPN to standard care (oral diet as tolerated and intravenous dextrose) found no effect on mortality (relative risk (RR) 1.03, 95% CI: 0.81-1.31).[11] There was a trend toward a lower complication rate among those receiving TPN (RR 0.84, 95% CI: 0.64-1.09), but this is due mainly to benefit among malnourished patients.[11] There are no data from randomized controlled trials to support the use of supplemental TPN among patients with an intact gastrointestinal tract ("If the gut works, use it").

Several studies have evaluated the use of supplemental EN in surgical patients. These studies often used surrogate outcomes, but one randomized double-blind trial of early EN versus standard diet as tolerated following surgery found fewer total complications (26.7% vs. 63.3%, p=0.009), fewer infectious complications (6.7% vs. 46.7%, p<0.001) and a trend towards a reduction in hospital length of stay (8 vs. 11.5 days, p=0.08) with early EN.[15] Based on this evidence, early EN is recommended in critically ill surgical patients. There is no specific research evaluating the benefits of supplemental EN in critically ill medical patients, but results from research in surgical patients appear to be applicable.[2] In animal studies, EN promotes gut motility, reduces bacterial translocation, prevents mucosal atrophy and stimulates the secretion of IgA that helps to reduce infectious complications.[3] There is also evidence that EN improves nutritional outcomes and results in greater wound healing.[2] A review of 5 trials studying postoperative EN found no significant reduction in morbidity or mortality.[6] However, a recent study of patients with non-traumatic intestinal perforation and peritonitis found there to be a total of 8 septic complications in the early EN group versus 22 in the control group (p<0.05).[16]

Multiple studies comparing use of EN to TPN in critically ill medical and surgical patients demonstrate that EN is safe, less expensive, and results in similar or better outcomes.[2] Among patients with acute severe pancreatitis, those fed enterally had fewer total complications (44% vs. 75%, p<0.05) and fewer septic complications (25% vs. 50%, p<0.01).[17] In numerous studies of surgical patients, EN also appears to be more effective than TPN. A study of patients undergoing total laryngectomy revealed no difference in mortality or infectious complications. However, the patients who received TPN had a longer length of stay (34 days vs. 11 days, p<0.05).[18] In another study of patients with abdominal trauma, those fed enterally had significantly fewer septic complications (15.7% vs. 40%, p<0.02).[19] A meta-analysis combining data from 8 prospective randomized trials found that 18% of patients receiving EN developed infectious complications compared with 35% in the TPN group (p=0.01).[20] Of note, EN may not be preferred to TPN in head-injured patients.[2] In a study of patients with head trauma there appeared to be no significant difference in relation to infectious outcomes and mortality between EN and TPN. However, patients fed enterally had a trend toward a higher incidence of aspiration pneumonia (32% vs. 13%, p=0.11), though no difference in overall infections and mortality.[21]

The effects of preoperative TPN have been evaluated in 13 prospective randomized controlled trials of patients undergoing surgical resection of a gastrointestinal tumor. Combining the data from these studies reveals a modest reduction in surgical complications (approximately

10%) in those patients receiving TPN.[6] This benefit appears to be due entirely to significant reduction in surgical morbidity among patients who are severely malnourished.[22] Therefore, <u>preoperative</u> TPN may be of benefit in severely malnourished patients undergoing major gastrointestinal surgery, but EN should be used instead, if possible. The use of postoperative TPN has been evaluated in 8 prospective randomized trials of patients undergoing gastrointestinal surgery. Patients in the combined TPN group experienced an increased rate of complications (27.3% vs. 16.0%; p<0.05). Thus, routine use of <u>postoperative</u> TPN in this setting is not recommended.[6]

Since enteral administration is the preferred method of nutritional support, additional research has focused on the utility of early administration of EN to severely ill surgical patients. In animal studies early EN is associated with greater wound strength after abdominal surgery.[23] In burn patients immediate EN was associated with a decrease in catecholamines and glucagons, and improved nitrogen balance compared to delayed EN.[24] A prospective randomized controlled study evaluated the effect of immediate jejunal feeds in patients with major abdominal trauma. The overall complication rate was similar in both groups, but 9 patients in the control group developed postoperative infections versus 3 in the EN group (p<0.025).[25] Although other studies do not show a change in outcomes, based upon this data it is reasonable to begin EN as soon as possible in surgical patients. More research is needed to evaluate the necessity of administering EN into the jejunum.[2]

Recently, intense study has focused on use of immunomodulating enteral formulations (containing arginine, glutamine, omega-3 fatty acids, and nucleotides). In animal and human studies, specific immunonutrients have had favorable effects such as promotion of T-cell blastogenesis, enhancement of cellular immunity and increased concentration of trienoic eicosanoids.[2] The largest (n=390) prospective, double-blinded RCT comparing enteral immunonutrition (IMPACT™, Novartis Nutrition, Bern, Switzerland) to isocaloric, isonitrogenous control enteral feed revealed no significant difference in hospital mortality rate in the intention-to-treat analysis (48% vs. 44%, p=0.36).[26] This study, conducted in a 13-bed adult general ICU in a London teaching hospital, resulted in randomization of patients with higher Acute Physiologic and Chronic Health Evaluation (APACHE) II scores (p=0.07, ie, they were "sicker") to the immunonutrition group, with this possibly accounting for the slightly higher mortality rate. Subgroup analyses of patients who received some enteral nutrition (n=369) and therapeutic levels of enteral feeding (>2.5 L within 72 hours of ICU admission, n=101) also showed non-significant higher mortality rates in the group receiving IMPACT. However, the subgroup analyses also showed significant reductions in days of mechanical ventilation, length of ICU stay, and overall hospital length of stay (LOS) in the group receiving immunonutrition compared to the control group (see Table 33.1). Of note, the reductions in length of stay may be attributable to the higher mortality rates in the group receiving immunonutrition, as more patients died sooner in the immunonutrition group than the control group (ie, LOS reduced by early death).[27]

A meta-analysis of 12 randomized controlled trials (including the aforementioned study) comparing use of one of two commercially available enteral feeding preparations (IMPACT™ or Immun-Aid™, McGaw, Irvine, CA) to standard enteral nutrition did not find any effect on mortality (RR 1.05, 95% CI: 0.78-1.41).[28] However, patients receiving enteral immunonutrition had significant reductions in infection rate (RR 0.67, 95% CI: 0.50-0.89), ventilator days (reduced 2.6 days, 95% CI: 0.1-5.1) and hospital length of stay (reduced 2.9 days, 95% CI: 1.4-4.4).[28] The benefits were most pronounced in surgical patients. Another meta-analysis of 11 prospective RCTs (not including the aforementioned RCT) also found reductions in the odds of

developing major infectious complications (odss ratio 0.47, 95% CI: 0.32-0.70), and hospital length of stay (reduced 2.5 days, 95% CI: 1.0-4.0).[29] Though there was no "significant" difference in mortality between patients receiving immune-enhanced versus standard nutritional support, there was a trend toward increased mortality (odds ratio 1.77, 95% CI: 1.00-3.12).[29]

Potential for Harm

TPN has been associated with an increase in septic complications. Patients may also be placed at increased risk from attempts to obtain central venous access. While EN decreases the overall rate of infectious complications when compared to TPN, it may place patients, especially those with head injuries, at greater risk of aspiration pneumonia. Use of a promotility agent, such as metoclopramide, has reduced this risk in one study.[30]

Costs and Implementation

TPN is itself expensive. Moreover, hospital costs can climb dramatically if patients who receive TPN suffer infectious complications that prolong their hospital stay. Obtaining central venous access also increases the costs of administration. Nutritional support teams (NSTs) can help ensure that patients are receiving adequate nutrition while at the same time reducing the rate of line complications.[28] However, the use of NSTs is expensive and has not been subject to a cost analysis.[28] The economics of early postoperative enteral nutrition was studied in a recent nonrandomized, prospective, clinical trial of patients undergoing bowel resections. There was a reduction in variable cost of $1531 per success in the treatment group (p=0.02) and $4450 total cost savings per success in the treatment group (p=0.04).[31] Immunonutrition is significantly more expensive than standard enteral formulas but in 2 prospective randomized controlled trials of patients undergoing upper gastrointestinal surgery it has been shown to be cost-effective. In one study, the cost per patient for nutrition and complications in the control group was $1633 compared to $783 in the immunonutrition group.[32] In another study the cost per patient for nutrition and complications in the control group was $1107 compared with $755 in the treatment group.[33]

Comment

The literature on appropriate nutritional support for critically ill patients is complex to analyze. A wide variety of treatment modalities have been evaluated in a fairly heterogeneous patient population, making interpretation of the various studies difficult.

Nonetheless, there are several general recommendations that can be made. First, malnutrition leads to poor outcomes and should be avoided or treated if present. Patients who have prolonged starvation for more than 2 weeks are at a significantly increased risk for complications. EN in these patients decreases this risk, and should be administered to all critically ill medical and surgical patients who can tolerate it. There are no data to support the use of TPN in critically ill patients who have a functional gastrointestinal tract. However, TPN may be of benefit preoperatively when given electively to severely malnourished patients undergoing gastrointestinal resection. Postoperative administration of TPN worsens outcomes. There is no evidence to suggest that postoperative enteral nutrition is superior to advancing a patient's oral diet, as tolerated, if they are capable of eating, but research into early administration of EN via the jejunum is ongoing.

Use of immune-enhanced EN appears to significantly reduce infectious complications, number of days of mechanical ventilation, and overall hospital length of stay, though it does not appear to affect overall mortality (and may increase it). Of note, study groups with increased

mortality rates may also have a diminished incidence of infectious complications and decreased length of stay artifactually due to patients dying early in the study. One expert interpreted the published research as strongly suggesting that immune-enhancing formulas should be used in critically ill patients, especially surgical patients, despite their high cost.[34] Nonetheless, a large multicenter RCT is needed to resolve with certainty whether or not use of these expensive formulas is safe and improves outcomes in critically ill patients before formally recommending their widespread use.[29]

Table 33.1. Studies evaluating nutritional support*

Study	Study Design, Outcomes	Results (95% Confidence Interval)

Routine protein energy supplementation in adults; systematic review[13]	Level 1A, Level 1	Reduced mortality: OR 0.66 (0.48 to 0.91)
		Increased body weight gain (%):
		    Oral Sip Feeds: 2.39 (1.80 to 2.96)
		    Oral natural feeds: 5.36 (1.73 to 8.99)
		    Nasogastric feeding: 4.04 (3.15 to 4.94)
		    Percutaneous or enteral feeding, enterostomy:
		            -1.38 (-2.35 to -0.41)

TPN in critically ill patients; meta-analysis[11]	Level 1A, Level 1	No effect on mortality: RR 1.03 (0.81 to 1.31) Complication rate: RR 0.84 (0.64 to 1.09) Complication rate (malnourished subgroup): RR 0.52 (0.30 to 0.91)

TPN in surgical patients; meta-analysis[12]	Level 1A, Level 1	No effect on mortality: RR 0.97 (0.76 to 1.24)
		No effect on mortality (malnourished subgroup):
		    RR 1.13 (0.75 to 1.71)
		Major complication rate (malnourished subgroup):
		    RR 0.52 (0.30 to 0.91)

Immunonutrition in critically ill patients; systematic review and meta-analysis[28]	Level 1A, Level 1	No effect on mortality: RR 1.05 (0.78 to 1.41) Reduction in infection rate: RR 0.67 (0.50 to 0.89) Reduction in days of mechanical ventilation: 2.6 days (0.1 to 5.1) Reduction in hospital LOS: 2.9 days (1.4 to 4.4)

Immunonutrition in patients with critical illness and cancer; meta-analysis[29]	Level 1A, Level 1	Trend toward increased mortality:
		    OR 1.77 (1.00 to 3.12)
		Reduction in infectious complications:
		    OR 0.47 (0.32 to 0.70)
		No reduction in pneumonia risk: OR 0.91 (0.53 to 1.56)
		Reduction in hospital LOS: 2.5 days (4.0 to 1.0)

EN vs. TPN in seriously ill hospitalized patients; systematic review and meta-analysis[2]	Level 1A, Level 1	Reduction in septic complications:
		    EN 18% vs. TPN 35% (p=0.01)
		Reduction in infectious complications:
		    EN 16% vs. TPN 35% (p=0.01)

Enteral immunonutrition in the critically ill; double-blind randomized controlled trial[26]	Level 1, Level 1	<u>Overall analysis</u> (immunonutrition vs. control formula)
		Mortality: 48% vs. 44% (p=0.36)
		Total days of mechanical ventilation (median):
		    4 vs. 4 days (p=NS)
		Hospital LOS (median): 12 vs. 13 days (p=NS)
		<u>Early enteral feeding subgroup</u>
		Total days of mechanical ventilation (median):
		    6 vs. 10.5 days (p=0.007)
		Hospital LOS (median): 15.5 vs. 20 days (p=0.03)

* LOS indicates length of stay; NS, not statistically significant; OR, odds ratio; and RR, relative risk.

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