Recent investigations of nutrition support in the intensive care unit (ICU) have revived discussion of optimal strategies for tight glucose control and the administration of total parenteral nutrition. Mode, timing, and adequacy of nutritional support affect glycemic control and outcomes in critically ill patients. The delivery of correctly formulated and safely administered nutritional and metabolic support is a matter of life or death in surgical and critical care units. High-quality research, adequately powered to detect differences in clinically meaningful outcomes, is needed to inform the delivery of nutrition support and serve as the foundation for future clinical trials. These are issues that will need to be addressed in the months and years ahead. Today, the field is in the midst of challenges and change, and though much has been accomplished, much remains to be done. The last 30 years have seen radical changes in the rates of severe obesity, metabolic syndrome, and weight loss surgery. Obese patients heighten surgical risk and require extra caution by ICU nutrition support specialists. This commentary will address the direction of nutrition support services by covering the history, progress, and potential of the field. It will review parenteral nutrition from its inception to its current standing in ICU patient care and discuss the future role of parenteral nutrition in a rapidly changing and increasingly diverse population.

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Nutrition support has a rich past and a promising future, but it will face many challenges and opportunities in the years ahead. Since Stanley J. Dudrick pioneered parenteral nutrition (PN) in the late 1960s, advances in the field have been grounded in a growing body of scientific research. These studies provide a methodologically sound precedent for future investigations and the development of evidence-based guidelines for nutrition support therapy.

This commentary will address the direction of nutrition support services in the hospitalized patient by covering the history, progress, and potential of the field. It will review PN from its inception to its current standing in intensive care unit (ICU) patient care and discuss its future role in a rapidly changing and increasingly diverse patient population.

Although enteral nutrition is the preferred route of feeding for critically ill patients who require nutrition support therapy, this article will focus on the use of total parenteral nutrition (TPN) in those who are malnourished and unable to be fed through enteral means. It will also discuss the importance of early and adequate feeding and tight glucose control (TGC) regardless of the method used to provide alimentation.

HYPERALIMENTATION

A seminal 1968 article by Dudrick et al introduced the medical world to the science of TPN, an alternative means of alimentation when the gastrointestinal tract was precluded for prolonged periods. His research—first in 6 beagle puppies and then in a clinical trial of 30 patients with chronic
gastrointestinal disease—established TPN as a valuable way to address malnutrition in hospitalized patients.

The second advance came from Bistrian et al in a 1974 article showing that approximately 50% of surgical patients in an urban hospital had protein-calorie malnutrition. This high prevalence spurred the development of dedicated nutrition support services to prevent malnutrition in critically ill patients. In those with baseline malnutrition, the stress response to injury and infection was of particular concern. Rapid deterioration due to the metabolic consequences of injury and infection (ie, the release of counterregulatory hormones and proinflammatory cytokines) made protein-sparing TPN technology a lifesaving component of perioperative care for these and other malnourished patients.

In 1975, 35 health care professionals gathered in Chicago, Illinois, to create the American Society for Parenteral and Enteral Nutrition (ASPEN). The group’s mission focused on an interdisciplinary approach to nutrition support therapy based on the importance of research, clinical practice, advocacy, and education. As a fitting tribute to his role in the development of TPN, Dudrick became the first president of ASPEN. In 1977, the society began publishing the Journal of Parenteral and Enteral Nutrition. It also held its first clinical congress in Boston, Massachusetts. The keynote speaker was Sen George McGovern, the political leader most clearly identified with the role of nutrition in health. With the guidance of ASPEN and the evolving technology of TPN, nutrition support services were better equipped than ever to address the issue of malnutrition in the ICU.

OVERFEEDING AND HYPERGLYCEMIA

Findings from the 1991 Veterans Affairs TPN Cooperative Study challenged nutrition support experts to consider the effects of hyperalimentation. Based on initial findings that preoperative TPN could significantly reduce the rate of complications and mortality in intermediate- and high-risk patients, Buzby et al assessed the efficacy of 10 days of perioperative TPN in a cohort of mild to severely malnourished patients who required laparotomy or noncardiac thoracotomy. In the randomized, multicenter trial, TPN was used to deliver a hypercaloric diet (44 kcal/kg) that provided 550 kcal from lipids and the remainder from dextrose. The daily caloric goal was 1000 kcal higher than resting metabolic expenditure.

After stratifying for nutritional status, data showed that TPN put mildly and moderately malnourished patients at greater risk for hyperglycemia, infections, and subsequent complications that would increase morbidity and mortality. In severely malnourished patients, who only accounted for 5% of the cohort, the frequency of infections did not increase and there was a significant reduction in noninfective sequelae. Based on these outcomes, the authors concluded that TPN should be limited to severely malnourished patients.

Subsequent studies compared enteral nutrition and PN with little regard for overfeeding, Large quantities of dextrose, easily and continuously administered via TPN, put critically ill, insulin-resistant patients at high risk for life-threatening hyperglycemia. While many studies compared enteral nutrition with TPN, few included any discussion of the greater risk of overfeeding when using TPN. This oversight led to widespread confounding, with differences in infective complications affected by varying rates of hyperglycemia.

To address the risk of overfeeding, the American College of Chest Physicians released a consensus statement that established a standard weight-based regimen for caloric intake in ICU patients requiring nutrition support. The new standard for TPN dosage—20 to 25 kcal/kg and 1.5 g of protein/kg—delivered a eucaloric infusion based on ideal body mass. McCowen et al used these guidelines to study the effects of a hypocaloric diet (1000 kcal/d and 70 g of protein/d) on hyperglycemia and complications from infections. While outcomes showed no difference in hyperglycemia rates between the treated subjects and controls on a 25–kcal/kg diet, there were fewer infections in the hypocaloric group. These findings warrant a larger intervention (n > 175) to investigate the possible associations between decreased infection rates and the hypocaloric diet.

TGC AND EARLY NUTRITION SUPPORT

The McCowen et al study underscored the need for more aggressive glucose control in the ICU. Hyperglycemia, which induces a state of oxidative stress and cytokine activation, is a risk factor for adverse outcomes in acutely ill patients. Close attention to glucose control as well as early and adequate feeding are critical factors in ICU nutrition support. In a landmark study, Van den Berghe et al found that TGC treatment to true normoglycemia (glucose level, 80–110 mg/dL; to convert to micromoles per liter, multiply by 0.0555), and early and aggressive feeding decreased hospital mortality by 33% in surgical ICU patients, especially those with sepsis and multisystem organ failure.

Subsequent trials have produced conflicting and contrary data about the benefits of TGC, spurring controversy as to whether it is warranted in all critically ill adults. However, nutritional support in these reports varied widely, as did the range of kilocalories provided. In addition, many of the studies did not provide adequate early feeding. These differences in feeding strategies necessitate clarification on the impact of feeding route on insulin therapy and TGC. (Table 1)

Both the 2001 Van den Berghe study and high-quality data from a meta-analysis of all intention-to-treat comparisons of enteral nutrition and PN in ICU patients show a significant reduction in mortality with early and adequate feeding, with no difference in mortality related to the route of feeding. Such evidence indicates that early feeding should be the norm in critically ill patients and an essential component of any evaluation of TGC control in those patients. A potential increase in the risk of infection notwithstanding, PN with TGC should be considered the desirable alternative to late enteral nutrition or no feeding.

In Van den Berghe et al, all ICU patients received relatively high-dose intravenous dextrose on admission and were maintained on nutritional support throughout their stay in the ICU, with the majority receiving parenteral nutrition. The initial level of feeding approximated 8 kcal/kg on average and approached 24 kcal/kg by day 5, with an eventual goal of 20 to 30 nonprotein kcal/kg/24 hours with.
Table 1. Comparison of 5 Key Studies on TPN and TGC

<table>
<thead>
<tr>
<th>Source, Year</th>
<th>Early Feeding With Standard Weight-Based Formula</th>
<th>Glucose Control</th>
<th>Experimental Group Compared With Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Veterans Affairs Total Parenteral Nutrition Cooperative Study Group, 1991</td>
<td>Yesañ</td>
<td>No</td>
<td>Increased mortality/morbidity from overfeeding</td>
</tr>
<tr>
<td>Van den Bergh et al, 2001</td>
<td>Yes (TPN)</td>
<td>Yes (glucose level 80-101 mg/dL)</td>
<td>Decreased mortality with TGC and early feeding</td>
</tr>
<tr>
<td>Van den Bergh et al, 2006</td>
<td>No</td>
<td>Yes (glucose level 80-101 mg/dL)</td>
<td>Increased risk of hypoglycemia in the absence of early and adequate feeding</td>
</tr>
<tr>
<td>Treggiari et al, 2008</td>
<td>No</td>
<td>Yes (glucose level 80-110 mg/dL)</td>
<td>No mortality benefit, increased risk of mortality in patients with ICU LOS &lt; 3 associated with hypoglycemia</td>
</tr>
<tr>
<td>Finner et al, 2009</td>
<td>No</td>
<td>Yes (glucose level 80-108 mg/dL)</td>
<td>Increased risk of mortality due to hypoglycemia</td>
</tr>
</tbody>
</table>

Abbreviations: ICU, intensive care unit; LOS, length of stay; TGC, tight glucose control; TPN, total parenteral nutrition.

añ Early feeding as defined by Martin et al: feeding within 24 hours of ICU admission or initial injury. Standard weight-based formula as defined by McCowen et al: 25 kcal/kg of body weight (goal, 20-25 kcal/kg), 1.5 g/kg of protein adjusted by ideal body weight and administered continuously over 24 hours.

0.13 to 0.26 g of nitrogen per kilogram—a nearly optimal energy intake. Subsequent studies, in which enteral nutrition was administered to most patients, were characterized by an increased rate of hypoglycemia, an outcome that leaves the ideal combination of feeding and glucose control protocols open to further debate. Even small increases in plasma glucose concentrations are known to have deleterious effects, yet threshold values for hyperglycemic complications have yet to be established. The most recent evidence from the NICE-SUGAR trial found no additional benefit from the lowering of blood glucose levels below the range of 140-180 mg/dL. Until optimal blood glucose levels are better defined in future studies, it is prudent to maintain values as close to normoglycemia as possible in surgical patients receiving 200 to 300 g of dextrose per day. Therefore, when administered in conjunction with early and adequate feeding, it is reasonable to provide exogenous insulin to achieve glucose values of less than 150 mg/dL for at least the first 3 days in critically ill ICU populations followed by tighter control if critical illness persists.

FUTURE OF NUTRITION SUPPORT SERVICES

Changing Patient Demographics

The last 30 years have seen radical changes in the levels of severe obesity, metabolic syndrome, and weight loss surgery. The prevalence of class III obesity has increased nearly 10-fold since the late 1960s and doubled since the early 1990s. As of 2002, an estimated 22% of US adults had metabolic syndrome. Between 1996 and 2002, population-adjusted rates of weight loss surgery increased more than 7-fold, with an estimated 220,000 Americans undergoing weight loss procedures in 2008.

These patients heighten surgical risk and require extra caution by ICU nutrition support specialists. Greater abdominal fat deposits are linked with insulin resistance, hyperglycemia, and increased risk of death. Abdominal adiposity is also the form of obesity most strongly associated with metabolic syndrome. In 2002, the National Cholesterol Education Program’s Adult Treatment Panel III report first defined metabolic syndrome as a clustering of risk factors with primary clinical outcomes of cardiovascular disease and insulin resistance. Metabolic syndrome may, therefore, be a cause for hospitalization as well as a risk factor for further complications in the ICU.

Because of a baseline dysmetabolic state and hyperglycemia, extremely obese trauma patients may benefit from a protein-sparing hypocaloric formula and TGC. A recent 2-center, randomized study in general adult ICUs demonstrated a significant reduction in mortality for obese patients treated with TGC compared with a conventional glycemic control group (16.7% vs 51.4%, respectively; P < .01). Other earlier studies found that insulin secreted in response to continuous infusion of glucose during TPN reduced lipolysis as well as the favorable effects of starvation ketosis during trauma-induced negative calorie balance.

Because TPN should be administered in hypocaloric dosages to overweight and obese patients, it is recommended that they receive ample nitrogen to promote wound healing and fight infection. The protein dosage can be administered in levels of up to 2 g/kg of ideal body weight in these patients. This could help preserve lean body mass and reduce adipose tissue. Prior to major elective surgery, class III obese patients may also benefit from progressive resistance training. By increasing lean body mass and improving skeletal muscle insulin sensitivity and general fitness, a preoperative progressive resistance training protocol might reduce perioperative risk and recovery time.

Status of Nutrition Support Services

With the advent of new therapies for gastrointestinal disease and minimally invasive surgery, the number of patients requiring greater than 2 days of nutrition support has decreased markedly in recent years. These trends, along with data showing increased complications with TPN in trauma patients, have contributed to steep declines in the use of TPN. Between 2000 and 2003, its use in surgical ICU trauma patients fell significantly from 26% to 3%. Such reductions pose a challenge to current investigations.

A 2008 study by Doig et al required 27 ICUs and 6 months to accumulate enough patients for a retrospective analysis of feeding guidelines and mortality in critically ill
adults. Ultimately, the study identified many barriers to effective implementation of nutrition guidelines in the critical care setting, an outcome consistent with the finding of Blaha et al\textsuperscript{47} of a need for computerized algorithms to simplify protocols and assure proper administration of insulin therapy.

Although Doig et al reported significant overall improvements in patient care, nutrition support guidelines
had little effect on mortality and length of stay compared with control hospitals that did not use feeding guidelines. This evidence suggests suboptimal use of nutrition support in ICUs as hospitals struggle to meet unique challenges of developing effective nutrition support teams.48

Mode, timing, and adequacy of nutritional support affect glycemic control and outcomes in critically ill patients. The delivery of correctly formulated and safely administered nutritional and metabolic support is a matter of life or death in surgical and critical care units (Figure). Yet increasingly, this essential service is supplied without appropriate staffing, oversight, or financial compensation. Implementing clinical practice guidelines for proper nutrition support has proven to be a complex process. Future research will need to address a wide range of variables (Table 2).

The traditional nutrition support services model, a multidisciplinary team headed by highly skilled internists or general surgeons, has given way to a hodgepodge version of care delivered under the guidance of diverse specialists working with pharmacists and, at times, dietitians.39 This trend, fueled by insurance changes that sharply limit financial support for nutrition support services teams, especially physicians and nurse specialists, exposes patients to unacceptable levels of risk.

Physician-directed teams deliver the highest level of enteral and parenteral support, with the lowest level of TPN-related complications, especially infectious morbidity. These groups also provide the impetus for randomized clinical trials on the value of new techniques and novel compounds, as well as the benefits of nutrition support services and specialists. Without the specialized knowledge of nutrition experts, patient safety in clinical trials that use nutritional means to achieve medical ends, such as TGC, can be compromised. Lack of financial reward also stifles innovation by draining the field of bright recruits and reducing opportunities for specialized training and fellowships.

High-quality research, adequately powered to detect differences in clinically meaningful outcomes, is needed to inform the delivery of nutrition support and serve as the foundation for future clinical trials (Table 2). Recent investigations of nutrition support in the ICU have made claims about feeding routes and glucose control without full attention to their combined effect on patient outcomes (Table 1). These are issues that will need to be addressed in the months and years ahead. Today, the field is in the midst of challenges and change, and though much has been accomplished, much remains to be done.

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REFERENCES

Parenteral Nutrition: Future Directions

In this article, Blackburn and coauthors examine the direction of nutrition support in the ICU with particular emphasis on the current and future role of PN support for critically ill and surgical patients. Blackburn and coauthors suggest that (1) nutrition support in the ICU is a challenging and complex endeavor that requires a coordinated team of physicians, nurses, diabetics, physicians’ assistants, and pharmacists and (2) PN provides an important option in critically ill patients who cannot be fed by other means. Blackburn and colleagues provide a nice history of PN and the issues surrounding its use and application. They hypothesized that TGC might improve morbidity and mortality in parenterally fed patients.

Blackburn et al note that PN is restricted to critically ill patients and some surgical patients who cannot be fed enterally for 7 days or who present with evidence of malnutrition. The detailed indications for PN support are defined in the 2009 Executive Summary Guidelines of the Society of Critical Care Medicine and the American Society for Parenteral and Enteral Nutrition. While the indication for PN is limited by these guidelines, it is clear that PN continues to offer an important option for nutrition care in critically ill patients when it is properly applied and steps are taken to maximize efficiency and minimize potential complications.

There appears to be little doubt that early enteral nutrition, when possible, is superior to PN. The benefits of early enteral nutrition are thought to be significant and numerous. They include a decrease in the incidence of mortality and infection, diminished stress-induced metabolic response, improved wound healing including gut anastomoses, restoration of positive nitrogen balance, stimulation of gut motility and fecal transit, enhanced gut immunity via direct support of gut-associated lymphoid tissue and/or mucosal-associated lymphoid tissue (GALT/MALT), and augmented control of blood glucose levels. The postulated mechanisms for the beneficial effects of enteral feeding are numerous and include direct nutrient delivery to the gastrointestinal system and GALT/MALT, and indirect benefits, such as enhanced gastrointestinal blood flow during postprandial hyperemia.