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Practice Management Guidelines for Nutritional Support of the Trauma Patient

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Nutritional support is an integral, though often neglected, component of the care of the critically injured patient. Our understanding of the metabolic changes associated with starvation, stress, and sepsis has deepened over the past 20 to 30 years, and along with this has come a greater appreciation for the importance of the timing, composition, and route of administration of nutritional support to the trauma patient. Although supportive data exist for many of our current nutritional practices, the trauma surgeon cannot assume that interventions that are successful in laboratory animals or even in the critically ill nontrauma patient will produce the same results in critically ill trauma patients. Stanley J. Dudrick, MD, one of the forefathers of surgical nutrition in this country, put it this way: ". . .we do get ourselves into an awful lot of trouble and lack of consensus as a result of mixing in animal data together with normal, starved man data when we are talking about trauma, especially in burns."[1] For this reason, the recommendations provided in this guideline are based, when at all possible, on studies using trauma or burn patients. Nevertheless, a brief discussion of some of the basic science principles of nutritional support is provided in the following section as a backdrop for the clinical studies presented in this guideline.

This practice management guideline is a compilation of six separate guidelines; each addresses a specific aspect of the nutritional support of the trauma patient. These topics are presented in the following order:

A. Route of nutritional support (total parenteral nutrition vs. total enteral nutrition).
B. Timing of nutritional support (early vs. late).
C. Site of nutritional support (gastric vs. jejunal).
D. Macronutrient formulation (how many calories and what proportion of protein, carbohydrate, and fat?).
E. Monitoring of nutritional support (which tests and how often?).
F. Type of nutritional support (standard vs. enhanced).

Each subguideline is a separate and free-standing document, with its own recommendations, evidentiary tables, and references. Where possible, we have attempted to eliminate redundancy and ensure consistency among the guidelines. Yet, because of substantial differences in both the quantity as well as the quality of supporting scientific data for each topic, and the fact that certain clinical circumstances are not conducive to a single guideline, concise and consistent recommendations were not always possible. Even when Class I (prospective, randomized, controlled) studies were available, limited patient numbers and inconsistent definitions rendered study conclusions less authoritative that they might have otherwise been. Recognizing the need to incorporate the major recommendations from the subguidelines into a logical overall approach to the nutritional support of the trauma patient, a summary algorithm is provided at the conclusion of the guideline (Fig. 1). Because of the scope of this document, many of the recommendations from the subguidelines could not be included in the algorithm. In addition, distinguishing between the various levels of recommendations (I, II, and III) within the algorithm was not practical. Nevertheless, the algorithm provides a safe, reasonable, and literature-supported approach to nutritional support and, we hope, will provoke constructive discussion and stimulate further investigation.

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References and evidentiary tables referenced in this article are located on the EAST Web site: www.east.org.

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EXPERIMENTAL BACKGROUND

The first suggestion that route and type of nutrition influence clinical outcome was made in a study by Alexander and others, which included severely burned patients randomized to a standard enteral diet or a protein-supplemented diet.[2] Children receiving the high-protein enteral diet had a higher

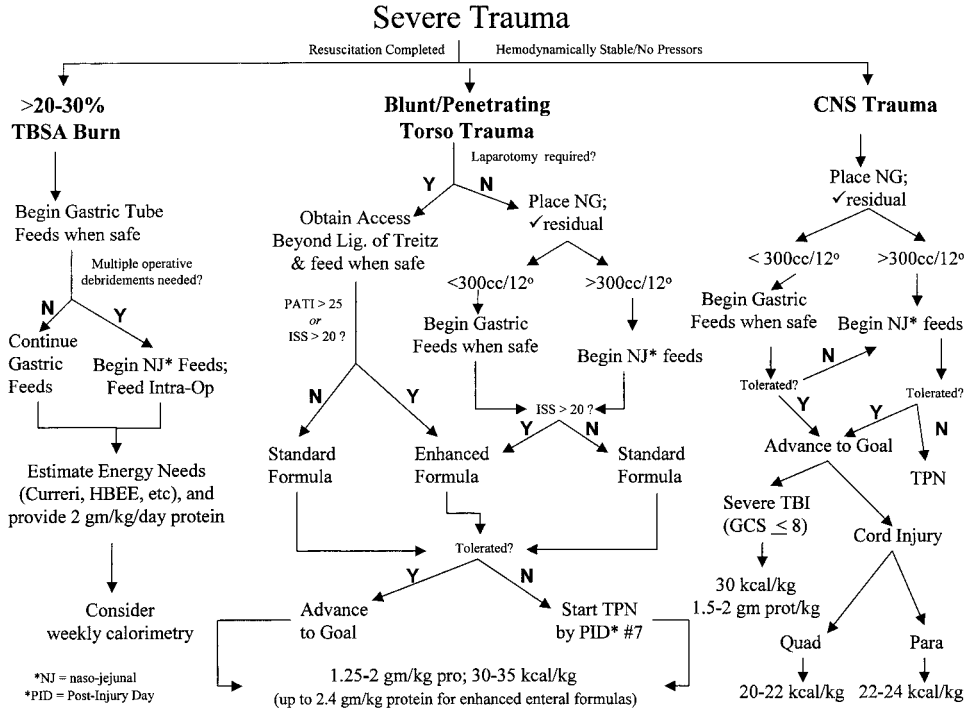

Fig. 1. *Summary algorithm for nutritional support of the trauma patient.*

survival rate and fewer septic complications than children receiving the standard enteral diet. Although not discussed at the time, patients receiving the high-protein diet were administered significantly less parenteral nutrition than the standard diet group. During the same time period, experimental observations depicted differences between enteral and parenteral feeding. In a model of septic peritonitis, both malnourished and well-nourished animals administered the total parenteral nutrition (TPN) solution enterally survived peritonitis significantly better than animals fed the TPN solution intravenously.[3,4] Since these initial studies, many clinical trials have studied the impact of route and type of nutrition comparing enterally fed patients (receiving a variety of enteral products) with (1) unfed trauma patients[5,6] and (2) trauma[7–9] or burn patients[10] given intravenous TPN. In addition, burn patients have been studied after receiving a variety of enteral formulas (high vs. standard protein,[2] enhanced vs. standard diet[11]), whereas patients sustaining severe head injury have been randomized to intravenous nutrition versus intragastric feeding[12,13] or intragastric versus postpyloric feeding.[14,15]

Although the preponderance of these studies show benefits of the enteral route with additional improvement with various specialty substrates in select patient populations, investigators have searched for mechanisms to explain improved infectious rates with enteral feeding. Intravenous feeding increases gut permeability[16,17] and increases bacterial translocation to mesenteric lymph nodes,[18,19] connoting a breakdown in the gut mucosal barrier that allows passage of small and large molecules from the intestinal lumen. Experimentally, bacterial translocation increases with intravenous nutrition, an enteral elemental diet, burns, hemorrhage, and shock, but not with starvation alone unless a simultaneous inflammatory focus is created.[20] Inflammatory molecules, such as zymosan, also increase gut permeability to bacteria.[21] Reduction in immunoglobulin (Ig) A and increases in bacterial translocation occur with bacterial overgrowth within the gastrointestinal tract (primarily aerobic bacteria).[19] These permeability increases to macromolecules have been noted in burn patients[22,23] and patients sustaining blunt and penetrating trauma to the torso.[24,25] Numerous investigations into the significance of bacterial translocation have engendered a hypothesis that the permeable gut allows systemic entry of toxic substances with deleterious end organ effects, but this work has not shown a relationship between increased permeability and the development of intra-abdominal or pulmonary infectious complications. Recently, the gastrointestinal tract has been defined as a site for leukocyte "priming" after initial injury which up-regulates the inflammatory response in the lungs after a secondary hit.[26–28] Manipulation of this initial priming via the gastrointestinal tract is a current focus of investigation.

Investigations into the nutrient manipulation of the mucosal immune system also provide an intriguing insight into the host defenses at mucosal surfaces. Mucosal associated lymphoid tissue, which originated from gut-associated lymphoid tissue (GALT), accounts for approximately 50% of the body's total immunity and 70% to 80% of immunoglobulin production by the body, primarily in the form of IgA.[29] Experimentally, dietary conditions that increase bacterial translocation (intravenous TPN or an elemental diet) are

associated with significant reductions in GALT cells within the Peyer's patches, lamina propria, and intraepithelial space in association with decreases in intestinal and respiratory IgA levels.[30] Functionally, the hypoplasia of this GALT system induced by inadequate nutrient regimens impair IgA-mediated antiviral mucosal immunity[31] and resistance to established immunity against intratracheal *Pseudomonas*.[32] This deterioration may be associated with loss of systemic immunity with impaired function of polymorphonuclear cells and monocytes. Experimentally, reduction in IgA levels in vitro increases the virulence of intraluminal bacteria, improving bacterial ability to attach, and potentially invade, mucosal surfaces.[33] These experimental manipulations serve as a backdrop for our understanding of the clinical studies of route and type of nutrition in patients sustaining severe trauma, burns, or head injury.

A. ROUTE OF NUTRITIONAL SUPPORT

I. Statement of the Problem

The metabolic response to injury mobilizes amino acids from lean tissues to support wound healing, immunologic response, and accelerated protein synthesis. The goal of aggressive early nutrition is to maintain host defenses by supporting this hypermetabolism and preserve lean body mass. The route of nutrient administration affects these responses, and the benefits of early enteral feeding have been clearly shown. Laboratory and clinical studies reveal beneficial affects of early nutrition on the gut mucosa, immunologic integrity, survival of septic peritonitis, pneumonia, and abscess formation.

Therefore, the question arises as to the route by which to deliver nutrition to the traumatized hypermetabolic patient with multisystem injuries including severe head injuries, burns, and blunt and penetrating injuries. There are certainly risks and benefits to enteral and parenteral nutrition in this complicated patient population. The purpose of this review is to determine the benefits and the risks of the route of nutrition in the severely injured patient through peer-reviewed publications over the past 25 years and to develop recommendations and guidelines from the conclusions of these studies on the basis of the scientific methodology of these studies.

II. Process

A. Identification of References

References were identified from a computerized search of the National Library of Medicine for English language citations between 1976 and 2000. Keywords included nutrition, enteral, parenteral, trauma, injury, and burn. The bibliographies of the selected references were reviewed for relevant articles not found in the computerized search. Literature reviews, case reports, and editorials were excluded. Twenty-eight articles were identified.

B. Quality of the References

The quality assessment instrument applied to the references was developed by the Brain Trauma Foundation and subsequently adopted by the Eastern Association for the Surgery of Trauma (EAST) Practice Management Guidelines Committee. Articles were classified as Class I, II, or III according to the following definitions:

Class I: A prospective, randomized clinical trial. Fourteen articles were chosen and analyzed.

Class II: A prospective, noncomparative clinical study or a retrospective analysis based on reliable data. Ten articles were chosen and analyzed.

Class III: A retrospective case series or database review. Four articles were chosen and analyzed.

III. Recommendations

A. Level I

Patients with blunt and penetrating abdominal injuries should, when feasible, be fed enterally because of the lower incidence of septic complications compared with parenterally fed patients.

B. Level II

Patients with severe head injuries should preferentially receive early enteral feeding, because outcomes are similar compared with parenterally fed patients, and the cost and complications associated with enteral feedings are lower than with parenteral feeding. If early enteral feeding is not feasible or not tolerated, parenteral feedings should be instituted.

C. Level III

1. In severely injured patients, TPN should be started by day 7 if enteral feeding is not successful.
2. Patients who fail to tolerate at least 50% of their goal rate of enteral feedings by postinjury day 7 should have TPN instituted but should be weaned when $>$ 50% of enteral feedings are tolerated.

IV. Scientific Foundation

Moore and Jones[1] reported the benefits of enteral feedings using immediate jejunal feedings in 1986. The patients in this study had laparotomy for severe abdominal injuries (abdominal trauma index [ATI] $>$ 15). Nutritional parameters and overall complications were not different between the enterally and parenterally fed groups; the septic morbidity was higher in the parenterally fed group ($p < 0.025$). Peterson et al.[2] further evaluated this effect and reported that acute-phase proteins increased from baseline to a higher extent in the TPN group compared with total enteral nutrition in patients suffering abdominal trauma with an ATI $>$ 15, $<$ 40. The TPN group reached a nadir in constitutive proteins at day 10, whereas the total enteral nutrition group had an increase in serum albumin and retinol-binding protein ($p < 0.05$). In 1989, Moore et al.[3] reported further evidence of the reduced septic complications in patients (ATI $>$ 15, $<$ 40) fed enterally versus parenterally. A

meta-analysis of eight prospective, randomized trials attests to the feasibility of early postoperative enteral feedings in high-risk surgical patients. These patients had reduced septic morbidity rates compared with patients fed parenterally.[4] In 1992 and 1994, Kudsk et al.[5,6] showed further evidence of the effectiveness of enteral nutrition over parenteral nutrition. In the earlier study, the rate of septic complications including pneumonia, intra-abdominal abscess, and line sepsis were significantly reduced in the enterally fed group of patients with an ATI $>$ 15. Furthermore, the sicker patient (ATI $>$ 24, Injury Severity Score [ISS] $>$ 20, transfusions $>$ 20 units, and reoperation) had significantly fewer infections. The latter study confirmed the previous report of Peterson et al.[2] concluding that enteral feeding produces greater increases in constitutive proteins and greater decreases in acute-phase proteins after severe trauma. This is primarily caused by reduced septic morbidity with enteral feeding. Other factors involved in the reduced septic complications include bacterial translocation; endotoxin; interleukin (IL)-1, IL-2, IL-6, IL-11, and IL-12; and macrophage stimulation. These effects are beyond the scope of this review.

One potential disadvantage regarding the enteral approach to nutrition of the trauma patient is the concern that adequate amounts of protein and calories cannot be delivered via this route, because of frequent interruptions in feeding resulting from multiple operative procedures. Moncure et al. have recently shown that, in selected patients, enteral feedings can be safely administered up to the time of transport to the operating room. This approach facilitated delivery of greater amounts of protein and calories without an increase in perioperative aspiration events.[7]

In the head-injured patient, the optimal route of administration remains controversial, as both routes are effective and each has advantages and disadvantages. One of the earliest studies to show a benefit to the early use of parenteral feedings was by Rapp et al.[8] in 1983. Patients with severe head injury were randomly assigned to receive enteral or parenteral nutrition. Patients receiving TPN within 72 hours of admission had a lower mortality rate ($p < 0.0001$). Haussman and colleagues[9] found that combined parenteral and enteral feeding was comparable to parenteral feeding alone with regard to mortality, nitrogen balance, creatinine, and 3-methylhistidine excretions, but noted that brain-injured patients with impaired gastric function (as evidenced by high gastric residuals) were better treated with parenteral nutrition. Hadley and others[10] further demonstrated the equal effectiveness of each route. Although the parenteral nutrition group had higher mean daily nitrogen intakes ($p < 0.01$) and mean daily nitrogen losses ($p < 0.001$), there were no significant differences in serum albumin levels, weight loss, incidence of infection, nitrogen balance, and final outcome. A series of studies performed by Young and others[11,12] and Ott and colleagues[13] further defined nutritional support in the head-injured patient. In the laboratory, intravenous hyperosmolar solutions were found to potentiate cerebral edema after head injury. In 1987, Young et al.[11] reported no significant difference in peak intracranial pressure, failed therapy of intracranial pressure, serum osmolality, morbidity or mortality, and patient outcome in patients receiving parenteral compared with enteral nutrition. Young et al.[12] then reported on 51 brain-injured patients in a prospective, randomized trial of parenteral versus enteral nutrition. Not only did the parenteral support patients have better outcomes at 3, 6, and 12 months, but the enteral group had a higher septic complication rate ($p < 0.008$), believed to be attributable to lower total protein intake, cumulative caloric balance, and negative nitrogen balance. The enterally fed group did not tolerate feedings until a mean of 9 days and received fewer calories and less protein. Ott et al.[13] studied enteral feeding intolerance in head-injured patients. They noted that gastric emptying was biphasic and that a majority of brain-injured patients displayed delayed gastric emptying during postinjury week 1. This delayed and biphasic response persisted through the second week in more than 50% of the patients. By week 3, most patients exhibited rapid gastric emptying, and all patients tolerated full-volume enteral feedings by day 16. Borzotta and colleagues[14] confirmed the efficacy of enteral and parenteral support using early jejunal feedings in the enteral group and delayed gastric feeding (days 5–9) in the parenteral group. No difference was found regarding measured energy expenditure, protein intake, albumin, transferrin, nitrogen balance, infectious rates, or hospital costs. Thus, it appears that, in the head-injured patient, establishment of early and consistent enteral feeding may obviate the need for parenteral nutrition in this patient population. These related issues of timing (early vs. late) and site (gastric vs. jejunal) of enteral feeding are discussed in greater detail later in this report. Much of this information has been summarized recently in an excellent review published by the Cochrane Library.[15]

The relative superiority of enteral over parenteral nutrition in the trauma patient should not be used as an excuse for delaying appropriate nutritional support. Total starvation for less than 2 to 3 days in healthy adults causes only glycogen and water losses and minor functional consequences. Functional deficits are evident in healthy normal weight adults who voluntarily restrict food intake after approximately 15 days of semi-starvation. Many trauma patients are hypermetabolic, and depletion of nutrient stores proceeds more rapidly in the case of total starvation than it does in healthy adults. The functional consequences of total or partial starvation thus evolve more rapidly in the stressed and catabolic patient than in healthy individuals. For these reasons, most investigators recommend achievement of the severely injured patient's nutritional support goals by postinjury day 7, whether by enteral or parenteral means, or some combination of the two.[16]

V. Summary

Although the evidence is not abundant, there is scientific support that patients with blunt and penetrating abdominal injuries sustain fewer septic complications when fed enterally as opposed to parenterally. The surgeon must be aware of the

potential benefits of enteral feedings in these severely injured patients. The trauma surgeon caring for patients with head injury must weigh the benefits and the risks of the route of nutrient administration, as patients with severe head injuries have similar outcomes whether fed enterally or parenterally. As determined in studies of malnutrition and starvation, the hypermetabolic state of the severely injured patient requires that calorie and protein goals should be achieved by day 7. Patients who fail to tolerate at least 50% of their goal rate of enteral feedings by this time should have TPN instituted.

VI. Future Investigation

Many of the issues related to the route of nutrition in the trauma patient are far from settled. Although the benefits of enteral nutrition in the severely injured patient with abdominal trauma are well documented, the mechanisms (immunologic and physiologic) remain unclear. The route of administration of enteral feedings, the nutrient composition, and the long-term outcome of trauma patients are still areas for future evaluation by clinicians and scientists. The effectiveness of nutritional support in the severely head-injured patient remains a difficult area to evaluate, as the injury itself remains the most significant factor in the outcome of the patient. Prospective studies of nutritional support evaluating long-term outcomes are still required. Previous work has demonstrated the safety and efficacy of enteral and parenteral nutrition in head-injured patients, but their exact roles or the preference of either route has not been demonstrated. Further study is required to determine a cost-effective approach to nutritional support that may improve outcome in severely head-injured patients.

B. EARLY VERSUS DELAYED ENTERAL FEEDINGS

I. Statement of the Problem

Over the past two decades, the impact of nutrition support on critically injured patients has received significant attention, with research focusing on the importance of route and type of nutrition, timing of nutrition, severity of injury, and clinical outcome. Comparative studies in laboratory animals have documented improved outcomes associated with early enteral feeding (2 hours postinjury) compared with feedings initiated at 72 hours postinjury. With the diverse patient populations of blunt and penetrating torso trauma, severe burns, and head injuries, the metabolic and clinical effects of nutritional support are significantly different. This document summarizes published data and makes recommendations regarding the relative advantages and disadvantages of early enteral feeding in these diverse populations.

II. Process

A. Identification of References

References were identified from a computerized search of the National Library of Medicine for English language citations between 1983 and 2000. We reviewed only articles that attempted to use specialized nutritional support as early as possible after injury and analyzed the data for clinical success with the therapies. The bibliographies of the selected references were reviewed for relevant articles not found in the computerized search. Literature reviews, case reports, and editorials were excluded. Twenty-five articles were identified.

B. Quality of the References

The quality assessment instrument applied to the references was developed by the Brain Trauma Foundation and subsequently adopted by the EAST Practice Management Guidelines Committee. Articles were classified as Class I, II, or III according to the following definitions:

Class I: A prospective, randomized clinical trial. Thirteen articles were chosen and analyzed.

Class II: A prospective, noncomparative clinical study or a retrospective analysis based on reliable data. Eight articles were chosen and analyzed.

Class III: A retrospective case series or database review. Two articles were chosen and analyzed.

III. Recommendations

A. Level I

In severely injured blunt/penetrating trauma patients, there appears to be no outcome advantage to initiating enteral feedings within 24 hours of admission as compared with 72 hours after admission.

B. Level II

1. In burn patients, intragastric feedings should be started as soon after admission as possible, because delayed enteral feeding (>18 hours) results in a high rate of gastroparesis and need for intravenous nutrition.
2. Patients with severe head injury who do not tolerate gastric feedings within 48 hours of injury should be switched to postpyloric feedings, ideally beyond the ligament of Treitz, if feasible and safe for the patient.

C. Level III

1. Patients who are incompletely resuscitated should not have direct small bowel feedings instituted because of the risk of gastrointestinal intolerance and possible intestinal necrosis.
2. In severely injured patients undergoing laparotomy for blunt and penetrating abdominal injuries, direct small bowel access should be obtained (via nasojejunal feeding tube, gastrojejunal feeding tube, or feeding jejunostomy) and enteral feedings begun as soon as is feasible after resuscitation from shock.

IV. Scientific Foundation

Several clinical trials have attempted to examine whether the benefit of "early" enteral feeding documented in the research laboratory extends into the clinical arena. Unfortunately, as is seen in the accompanying evidentiary tables, there is no consensus as to what is meant by early, ranging

between 4 and 72 hours after admission. In contrast, animal data demonstrating the superiority of an early enteral strategy initiated feeding within 2 hours of injury.[1] Furthermore, very few of the clinical trials actually compare early enteral with late enteral feeding, the majority comparing early enteral feeding and TPN. Because the impact of an early enteral strategy may vary depending on the specific injury type, three specific trauma patient subsets (blunt/penetrating torso, burn, head injury) are examined in this section.

Only one prospective, randomized study in blunt/penetrating trauma patients has actually compared early and late enteral feeding, finding no metabolic or clinical advantage to early enteral feeding.[2] However, as the authors acknowledge, it may be that initiating enteral feeding at 39 hours postinjury was not early enough to demonstrate this advantage, or perhaps the metabolic advantages are not demonstrable until after the 10-day study period used in this study. Regardless, the findings from this report are important for two reasons. First, it is unlikely, in this patient population, that enteral feeding can be consistently initiated much earlier than the 39 hours postinjury achieved by these authors, given their very aggressive approach to postpyloric enteral access. Second, despite the small number of patients in this study, no clinical outcome advantage could be ascribed to initiating enteral feeding within 30 hours of admission compared with 80 hours from admission. Thus, in this particular patient population, there is no literature support for early enteral feeding, at least as defined by these authors.

One recent study[3] randomized multisystem trauma patients (ISS $>$ 25, Glasgow Coma Scale [GCS] score $\geq$ 12) to early ($<$6 hours after resuscitation from shock) or late ($\geq$24 hours after resuscitation from shock) gastric feeding using the same enteral diet for both groups. Parenteral feeding was provided to both groups to meet caloric demands. Within 4 days, the early-fed group tolerated significantly more enteral feeding than the late-fed group, and by the end of 1 week, they were receiving 80% of their enteral feeding compared with 61% in the late-fed group ($p < 0.025$). The early-fed group sustained significantly fewer incidents of late multiple organ dysfunction, but intensive care unit (ICU) length of stay and duration of mechanical ventilation were similar between the two groups. The use of TPN in this study, and the use of shock resolution as a criterion for initiation of enteral feeding, makes the results of this trial difficult to compare to those of Eyer referred to above.[2] However, the two studies considered together would seem to raise serious questions regarding the significance of early enteral feeding, even if feedings are initiated as early as 6 hours after resuscitation.

The remainder of the prospective, randomized trials of blunt and penetrating trauma have been limited to patients with direct small bowel access obtained at the time of surgery. Moore et al.[4] randomized patients to either needle catheter jejunostomy feedings with a chemically defined diet started 18 to 24 hours postoperatively or to no early enteral nutrition and demonstrated a significant reduction in septic complications, primarily intra-abdominal abscesses. Patients were limited to an ATI between 15 and 40 because of previous work[5,6] that demonstrated decreased gastrointestinal tolerance in patients with an ATI $>$ 40 or direct viscus injury. In this study, enteral feedings were administered to a goal rate within 72 hours, which limited successful advancement in the more severely injured. A second study of early enteral feeding versus TPN[7] confirmed a reduction in septic complications (primarily pneumonia, with a trend toward reduced intra-abdominal abscesses) in a similar population with mild to moderately severe injuries. In another study recruiting patients with moderately severe injuries (i.e., ATI of 18–40 or ISS of 16–45),[8] diets were started within 24 hours and advanced to goal by 72 hours, with gastrointestinal intolerance in approximately 26% of patients but interruption or discontinuation in only 13.5% of study patients.

A randomized, prospective study of enteral feeding via jejunostomy versus parenteral feeding demonstrated a significant reduction in intra-abdominal abscesses and pneumonia in moderate to very severely injured patients receiving enteral nutrition.[9] Four percent of enterally fed patients failed enteral feedings (defined as 50% of nutrient goal by 1 week) because of severity of injury. As a result, parenterally fed patients received more nutrition than the enterally fed population. Benefits of enteral feeding were only noted in patients sustaining an ATI $>$ 24 or an ISS $>$ 20. Feedings were successfully started within 24 hours in both groups. A subsequent study randomized severely injured patients with an ATI $>$ 24 or an ISS $>$ 20 to one of two enteral diets.[10] Diets were started 1.5 to 2 days after surgery because of early hemodynamic instability in many of the patients. Gastrointestinal symptoms were common and occurred in 88% of enterally fed patients, which required slowing the feedings in 45%. The more severe the blunt and penetrating trauma to the torso in patients requiring laparotomy, the greater the intolerance to feeding, the longer the delay before institution of feeding, and the slower the rate of progression necessary to improve tolerance.

Intragastric feedings have been studied most closely in burn patients. In a population of pediatric patients with greater than 40% total body surface area (TBSA) burns, early intragastric feeding started soon after admission was highly successful.[11] This was duplicated in a larger population of pediatric patients with burns greater than 10%[12] TBSA and confirmed again in a group sustaining 25% to 60% TBSA burn.[13] Although diarrhea occurred in 40%, early intragastric feeding after burn was well tolerated. In a population of patients with burns of 40% to 70% TBSA,[14] intraduodenal feeding was started within 48 hours and was well tolerated. Fifty-five intubated, ventilated patients with burns of approximately 45% were started on intragastric feedings with gastric stimulatory agents.[15] When diets were started within 15 hours, goals were reached in 82% of patients within 72 hours, but when feedings were delayed to 18 hours or greater, the majority of patients failed. A study in patients with 35%

TBSA burn of intraduodenal feeding started within 48 hours also was well tolerated, with rare episodes of distension, reflux, or diarrhea.[16] In a retrospective study of 106 patients with burns of 20% TBSA or greater,[17] tolerance of intragastric feedings was greater than 90% in patients started within 6 hours of burn.

Success with enteral feeding of patients with severe head injuries is less encouraging. In two studies of patients with GCS scores between 4 and 10,[18,19] patients randomized to intragastric feeding received less than 500 to 600 kcal/d over the first 2 days, less than 800 kcal/d on days 3 to 5, and <1,500 kcal/d on days 6 to 8 because of gastroparesis. However, no attempts were made to feed patients until nasogastric drainage had dropped below 100 mL. Similar results were noted in 23 patients sustaining blunt and penetrating trauma to the head with GCS scores between 4 and 10.[20] Although feedings were not initiated unless nasogastric drainage was less than 200 mL/d and bowel sounds were present, only one third of patients tolerated feedings within 7 days of injury, and 12 never tolerated feedings. Resolution of gastroparesis occurs on days 3 to 4 in many patients, although it may occur sooner than the studies above because gastric emptying may occur despite higher nasogastric drainage and before return of bowel sounds.[21] In another study,[22] nasojejunal feedings approached nutrient needs within 3 days but did not approach nutrient goals until day 5 to day 7 in patients receiving intragastric feeding because of high gastric residuals. Similar delays were noted in a study of 48 evaluable head-injured patients.[23] Recently, 82 patients sustaining head injury were randomized to either intragastric feeding or to intestinal feeding using a pH sensor tube. All patients required mechanical ventilation on the first day of hospitalization, had a GCS score > 3, and had at least one reactive pupil. Intestinal tube placement was confirmed by abdominal radiography. Patients receiving the small intestinal tube had a higher percentage of energy and nitrogen administration during the study. Within 3 days of injury, the intestinal-fed patients achieved 70% of their nutrient goal and by 6 days achieved 90% of their nutrient requirements. Intragastric-fed patients achieved 30% of nutrient goals by day 3 and 55% by day 6. The intestinally fed patients sustained fewer complications and had an associated reduction in acute-phase protein production.[24] The Cochrane Library has recently summarized the available data concerning the timing of nutritional support in head-injured patients.

V. Summary

Direct small bowel access is necessary to successfully feed patients via the gastrointestinal tract who have sustained severe blunt and penetrating torso and abdominal injuries as well as severe head injuries. Intragastric feeding becomes successful in the majority of head-injured patients at approximately day 3 or 4, at the earliest, because of gastroparesis. Small bowel feedings are tolerated in this patient population with small bowel access. In patients with penetrating and blunt injuries to the abdomen who have small bowel access, enteral feeding can be instituted in most patients after resuscitation is complete and hemodynamic stability has been gained. Advancement to goal rate is slower in patients with higher ATI scores, in particular if ATI > 40. In addition, gastrointestinal injury below the site of access may slow advancement of tube feedings but is not a contraindication to direct small bowel feedings. Intragastric feeding in patients with severe burns should be instituted as soon as possible during resuscitation to prevent or minimize the onset of gastroparesis that appears to occur with increasing incidence if feedings are delayed, particularly if delayed beyond 18 hours. In all patient populations, total parenteral nutrition can be instituted soon after injury, ideally after hemodynamic stability has been gained and resuscitation is complete.

VI. Future Investigation

Several obstacles limit the successful use of early enteral nutrition. First, access to suitable sites in the gastrointestinal tract for the delivery of nutrition support requires clinical vigilance and planning. Although many patients can be successfully fed intragastrically, critical illness and critical injury often mandate placement of the tube beyond the ligament of Treitz. Unless access is obtained at the time of celiotomy, methods to successfully advance tubes beyond the ligament of Treitz are limited, and further research for solutions to this problem is warranted. Methods are needed to recognize dislodgment into the stomach and to keep the tube beyond the ligament of Treitz, particularly those advanced through the stomach. Second, protocols or markers that promote successful, safe advancement of feeding rate are needed, especially markers that identify patients who will be intolerant of enteral feeding because of distension, bloating, diarrhea, and the rare complication of intestinal necrosis. Third, development of pharmacologic or nonpharmacologic means to reverse or eliminate gastroparesis or ileus may minimize progressive calorie deficits and maximize the benefits of early enteral delivery of nutrients. Finally, authors do not agree about what constitutes early or delayed enteral feeding. In some studies, early is defined in hours, and in others, it is defined in terms of days. Until there is consensus regarding these definitions, it is impossible to determine whether the theoretic benefits ascribed to early enteral feeding truly outweigh the additional effort and potential complications associated with this approach to nutritional support. Well-designed, prospective, randomized studies, using a precise definition of early feeding, together with clinically relevant outcome parameters (e.g., morbidity, infectious morbidity, neurologic outcome) in a well-defined patient population (burns, head injury, or torso trauma), are needed to adequately resolve this important issue.

C. SITE OF ENTERAL SUPPORT: GASTRIC VERSUS JEJUNAL

I. Statement of the Problem

Enteral nutrition is preferable to parenteral nutrition, and feeding into the stomach is convenient. Delayed gastric emptying may reduce the effectiveness and safety of gastric feedings compared with feeding into the small intestine.

II. Process

A. Identification of References

References were identified from a computerized search of the National Library of Medicine for English language citations between 1973 and 2000. Keywords included enteral nutrition, trauma, gastrostomy, and jejunostomy. The bibliographies of the selected references were reviewed for relevant articles not found in the computerized search. Literature reviews, case reports, and editorials were excluded. Twenty articles were identified.

B. Quality of the References

The quality assessment instrument applied to the references was that developed by the Brain Trauma Foundation and subsequently adopted by the EAST Practice Management Guidelines Committee. Articles were classified as Class I, II, or III according to the following definitions:

Class I: A prospective, randomized clinical trial. One article was chosen and analyzed.

Class II: A prospective, noncomparative clinical study or a retrospective analysis based on reliable data. Five articles were chosen and analyzed.

Class III: A retrospective case series or database review. Fourteen articles were chosen and analyzed.

III. Recommendations

A. Level I

No recommendations.

B. Level II

In critically injured patients, enteral feeding should not be delayed for lack of postpyloric access. Because early gastric feeding is feasible, clinical outcome is equivalent to patients fed via the duodenum, and because access to the stomach can be obtained more quickly and easily than the duodenum, an initial attempt at gastric feedings appears warranted.

C. Level III

Patients at high risk for pulmonary aspiration because of gastric retention or gastroesophageal reflux should receive enteral feedings into the jejunum.

IV. Scientific Foundation

Since Moore and Jones[1] and Adams and colleagues[2] reported simultaneously that enteral nutritional support was feasible and possibly associated with fewer complications than parenteral nutrition in the metabolic support of the trauma patient, feeding into the gut has become the preferred technique for nutrition after major injury. Access to the gut can be obtained by a variety of devices: surgically placed gastrostomy or jejunostomy tubes if the patient has to undergo a laparotomy for abdominal injuries; nasogastric or nasoenteric tubes; and endoscopically or radiologically placed gastric or gastrojejunal tubes.

Patients with brain injuries often require early and prolonged nutritional support. Early experience with such patients suggested that parenteral nutrition was preferable to enteral feeding in patients with moderate to severe brain injury.[3–5] Support for this conclusion was obtained from studies in brain-injured patients that identified physiologic derangements such as delayed gastric emptying[6,7] and lower esophageal sphincter dysfunction.[8] Even when gastric feedings were given, they did not meet the increased metabolic requirements of the neurotrauma patient.[9] Feeding into the jejunum has been proposed to avoid some of the problems with gastric feeding and has been shown to provide adequate calorie and nitrogen intake.[10] One recent study, however, demonstrated that gastric feeding can be accomplished relatively soon (3.6 days in this series) after head injury without incurring significant complications.[11] Evidence regarding the optimal site of enteral nutrition in trauma patients is woefully inadequate. Although several studies have examined complication rates of gastric versus jejunal feeding in nontrauma patients, these studies tend to be retrospective,[12–16] have small numbers of subjects in each group,[12,15,17,18] or compare nonequivalent procedures such as percutaneous gastrojejunostomy with surgical gastrostomy.[13] Percutaneous endoscopic gastrostomy has recently been compared with percutaneous endoscopic gastrojejunostomy in a consecutive group of severely injured patients, finding more rapid attainment of feeding goals in the percutaneous endoscopic gastrojejunostomy group but no differences in outcomes.[14] A recently published randomized trial comparing gastric with duodenal feeding demonstrated equivalent outcomes but slightly earlier achievement of protein and calorie goals with duodenal feedings.[15] On balance, there seems to be no superiority of jejunal feeding over gastric feeding, but more prospective, randomized studies with larger numbers of patients are needed to make a scientifically supported decision.

V. Summary

The need for nutrition after severe injury is intuitively apparent, especially in patients who cannot resume oral intake within a few days after injury. Enteral feeding is more physiologic and less expensive than parenteral feeding. Whether it is preferable to feed into the stomach or into the jejunum is not clear, but care must be taken in all patients to ensure that feedings are tolerated, and that aspiration is avoided. Patients with moderate to severe brain injury demonstrate delayed gastric emptying and dysfunction of the lower esophageal sphincter. These abnormalities may limit

nutritional delivery of calories and protein for the first 2 weeks after injury. Nasojejunal feedings provide earlier success attaining nutritional goals compared with intragastric feedings, which are limited by high gastric residuals.

VI. Future Investigation

A multicenter, randomized, prospective trial is needed to evaluate the safety, efficacy, and cost of gastric feeding compared with postpyloric enteral feeding in trauma patients. Patients with brain injury should be evaluated as a separate subgroup to avoid confounding issues.

D. ASSESSMENT OF ENERGY AND SUBSTRATE REQUIREMENTS FOR THE TRAUMA PATIENT

I. Statement of the Problem

Provision of adequate calories and protein to the hypermetabolic injured patient is of paramount importance in achieving optimal outcomes for these patients. Failure to meet caloric requirements leads to erosion of lean body mass and subsequent negative nitrogen balance as the body attempts to provide sufficient energy and nitrogen to carry out vital functions. Conversely, overzealous nutritional support is associated with derangements in hepatic, pulmonary, and immunologic function and may lead to outcomes nearly as detrimental to the injured patient as malnutrition.

II. Process

A. Identification of References

References were identified from a computerized search of the National Library of Medicine for English language citations between 1973 and 2000. Keywords included nutritional support, trauma, critically injured, head injury, spinal cord injury, paraplegia, quadriplegia, burns, energy expenditure, energy intake, enteral, parenteral, dietary proteins, dietary fats, dietary carbohydrates, protein, carbohydrate, fat, lipid, requirements, and nutrition. Studies involving laboratory animals were excluded from our review, as were studies where the patient population was exclusively or predominantly pediatric so as to avoid the effect of growth and maturation of the patient on energy and substrate requirements. The bibliographies of the selected references were reviewed for relevant articles not found in the computerized search. Literature reviews, case reports, and editorials were excluded. Seventy-three articles were identified.

B. Quality of the References

The quality assessment instrument applied to the references was developed by the Brain Trauma Foundation and subsequently adopted by the EAST Practice Management Guidelines Committee. Articles were classified as Class I, II, or III according to the following definitions (one article was classified as Class I and Class II):

Class I: A prospective, randomized clinical trial. Eighteen articles were chosen and analyzed.

Class II: A prospective, noncomparative clinical study or a retrospective analysis based on reliable data. Forty-two articles were chosen and analyzed.

Class III: A retrospective case series or database review. Thirteen articles were chosen and analyzed.

III. Recommendations

A. Level I

No recommendations.

B. Level II

1. Moderately to severely injured patients (ISS of 25–30) should be provided 25 to 30 total kcal/kg/d or 120% to 140% of predicted basal energy expenditure (BEE), as measured by the Harris-Benedict equation.
2. Patients with severe head injury (GCS score $<$ 8) should be provided approximately 30 total kcal/kg/d ($\sim$140% of measured resting energy expenditure [MREE]) in nonpharmacologically paralyzed patients, and approximately 25 total kcal/kg/d ($\sim$100% of MREE) in paralyzed patients.
3. Within the first 2 weeks after spinal cord injury, nutritional support should be delivered at 20 to 22 total kcal/kg/d (55–90% of predicted BEE by the Harris-Benedict equation) for quadriplegics and 22 to 24 total kcal/kg/d (80–90% of predicted BEE by the Harris-Benedict equation) for paraplegics.
4. Patients with burns exceeding 50% TBSA should not receive TPN supplementation of enteral feedings to achieve Curreri-predicted caloric requirements, as this is associated with higher mortality and aberrations in T-cell function.
5. Once- or twice-weekly determination of energy expenditure via calorimetry may be of benefit in avoiding over- and underfeeding in patients with severe burns.
6. Burn patients that require frequent burn wound debridement should have their enteral feedings continued intraoperatively, as this practice is safe and leads to more successful attainment of calorie and protein goals.
7. Approximately 1.25 g of protein per kilogram of body weight per day should suffice for most injured patients, whereas up to 2 g of protein per kilogram of body weight per day is appropriate for severely burned patients.
8. Carbohydrate administration should not exceed 5 mg/kg/min ($\sim$25 kcal/kg/d) for burn patients, and even less for nonburn trauma patients. Exceeding these limits may predispose patients to the metabolic complications associated with overfeeding.
9. Intravenous lipid or fat intake should be carefully monitored and maintained at less than 30% of total calories. Zero fat or minimal fat administration to

burned or traumatically injured patients during the acute phase of injury may minimize the susceptibility to infection and decrease length of stay.

C. Level III

Patients with less than 20% to 30% TBSA burns do not require caloric supplementation beyond that required for patients without burns.

IV. Scientific Foundation

Calorie requirements of trauma patients have been debated for years. The "gold standard" for determining the caloric needs of patients with traumatic injuries is to measure their energy expenditure with indirect calorimetry. By measuring oxygen consumption (V_{O_2}) and carbon dioxide production (V_{CO_2}) via indirect calorimetry, resting energy expenditure (REE) can be calculated using the abbreviated Weir equation: $REE = [3.9\ (V_{O_2}) + 1.1\ (V_{CO_2})] \times 1.44$. Despite the availability of this technology, there have been few prospective, randomized clinical trials conducted specifically to determine the optimal number of calories for this patient population. The best study to date that has addressed this issue with Class I evidence compared the effect of three different parenteral nutrition regimens (hypercaloric, isocaloric, and hypocaloric) on protein catabolism and nitrogen loss when protein administration was fixed at 1.7 g/kg/d.[1] Caloric needs were provided at 125% of MREE in the hypercaloric group, 100% of MREE in the isocaloric group, and 75% of MREE in the hypocaloric group. The mean ISS was 27 for all three groups, and patients with burn, spinal cord, or isolated head injuries were excluded from study enrollment. Despite significant differences in caloric provision, no significant differences were observed in nitrogen balance, 3-methylhistidine excretion, or visceral protein status among the groups. The mean MREE was approximately 28 kcal/kg/d for all patients on day 4 of the study. However, 80% (24 of 30) of the patients were sedated with fentanyl, and 7% (2 of 30) of the patients were pharmacologically paralyzed. Both of these treatment interventions have been associated with a hypometabolic response in neurologically injured patients. The only additional Class I evidence available is derived from a trial comparing the metabolic effects of a carbohydrate-based diet with a fat-based diet in critically ill patients with infections or trauma.[2] Only 2 of 12 patients were identified as having traumatic injuries. The mean MREE was approximately 26 kcal/kg/d for patients while receiving the different nutritional regimens. Demographic data describing the severity of illness or injury of the patients were not provided in the study.

Several methods have been used to estimate energy requirements of patients with traumatic injuries as an alternative to measuring actual energy requirements with indirect calorimetry. These include calculating basal energy expenditure with the Harris-Benedict energy equation (HBEE), multiplying the HBEE by an activity factor and a stress factor depending on the type of injury (i.e., blunt trauma, skeletal trauma, head trauma) and using 25 kcal/kg/d. A number of clinical trials have evaluated the accuracy of these predictive methods for estimating MREE in trauma patients. The MREE of trauma patients has been variously reported to be approximately 26 kcal/kg/d (range, 21–32 kcal/kg/d), 33 kcal/kg/d (postabsorptive state [range, 25–41 kcal/kg/d]), 37 kcal/kg/d (while receiving parenteral nutrition [range, 29–46 kcal/kg/d]), 38 to 48 kcal/kg/d (requiring insulin in TPN), and HBEE $\times$ 1.2 (activity factor) $\times$ 1.75 (stress factor).[3–6] One recent study noted a biphasic metabolic response to injury, with total energy expenditure (TEE) peaking during the second postinjury week at 59 kcal/kg/d, compared with only 31 kcal/kg/d during the first postinjury week.[7] Furthermore, these studies have attempted to identify a relationship between MREE and scoring systems used to evaluate the severity of disease and injury. Although some investigators[8,9] have found no correlation ($r = -0.042$) between MREE and ISS, others[4] have reported a relatively high correlation between ISS and MREE per kilogram ($r = 0.84$).

Head and spinal cord injury patients represent a subset of trauma patients with unique metabolic requirements. Most clinical trials report hypermetabolism in head-injured patients, with an average increase of 40% above that predicted with REE.[10] The increases in energy expenditure are related to the increased oxygen consumption caused by the stress hormone flow in response to brain injury and may further be increased by hyperventilation, fever, seizures, and posturing. Patients with decerebrate or decorticate posturing have demonstrated elevations in energy expenditure at 200% to 250% of predicted energy expenditure.[11] Pharmacologic treatments have also been shown to dramatically impact energy expenditure.[10] High-dose barbiturates have been used to control increased intracranial pressures refractory to standard therapy. However, barbiturate therapy can decrease energy expenditure by as much as 40% below that predicted with HBEE.[12] Other pharmacologic interventions, such as neuromuscular blockade with pancuronium bromide, have reduced energy expenditure by 42% below predicted energy expenditure with HBEE.[11]

In contrast to trauma and head injury patients, spinal cord injury patients exhibit a decrease in energy expenditure. Within the first 3 weeks after spinal cord injury, metabolic rates 94% (range, 55–129%) of those predicted by HBEE have been observed.[13] An inverse relationship has been identified between the location of injury and energy expenditure. Thus, the higher the lesion, the lower the energy expenditure measurement. Nutrition support recommendations for quadriplegics are 20% to 40% below HBEE (20–22 kcal/kg/d) and 10% to 20% below HBEE for paraplegics. Recognizing the hypometabolic response in spinal cord injury patients is important because overfeeding can have adverse effects. Providing calories in excess of energy expenditure in any patient can cause impaired glucose control, suppression of chemotactic/phagocytic actions of monocytes because of hypergly-

cemia, respiratory dysfunction from excessive carbon dioxide production, lipogenesis, and hepatic steatosis.

Energy requirements in the burn patient are difficult to determine because many factors impact this calculation. Early studies demonstrated a relationship between the percentage of TBSA burned and energy requirements in these patients as determined by indirect or direct calorimetry. Wilmore[14] was the first to document this relationship in his study of 20 patients with burns ranging from 7% to 84% TBSA. He further noted that this hypermetabolism appeared to be mediated by catecholamines and appeared to plateau at 60% TBSA. During that same year Curreri,[15] in a prospective study of nine patients, derived a formula, now bearing his name, relating energy expenditure to preburn weight and the percentage TBSA burned. Although subsequent studies have shown that this formula frequently overestimates actual energy requirements, it remains one of the most, if not the most, commonly used method to determine energy requirements of patients in burn centers in the United States today.[16]

Since the Curreri study, many formulas have been proposed as more accurate predictors of caloric requirements of the burned patient. The formulas tend to fall into two broad categories, formulas that include a factor for TBSA burned and those that do not. The majority of formulas in this latter category are based on calculations of basal energy expenditure as determined by the Harris-Benedict equation, which takes into account patient age, sex, height, and weight. To the BEE are multiplied factors for the degree of stress (injury) and for the level of patient activity to arrive at an estimate for the patient's overall caloric requirement. Many studies have compared the Curreri formula with formulas based on the Harris-Benedict–derived BEE. Turner and colleagues[17] completed such a prospective study in 35 patients with second- and third-degree burns ranging between 10% and 75% TBSA and concluded that the Harris-Benedict–derived BEE underestimated actual energy expenditure by 23%, whereas the Curreri formula overestimated energy expenditure by 58%. Long et al.[18] measured energy expenditure in 39 critically ill patients and in 20 normal volunteers, finding that energy expenditure in burned patients exceeded that predicted by the Harris-Benedict equation by 132%. They suggested that the Harris-Benedict equation be multiplied by a stress factor as well as an activity factor to arrive at a more accurate estimation of caloric requirements. In fact, the values for stress and activity factors, which he proposed nearly 20 years ago, are still widely used today.

However, even with these correction factors, Harris-Benedict predictions seem to perform no better than the Curreri formula. In a prospective study of 21 patients with between 21% and 81% TBSA burns, the Curreri formula overestimated actual energy expenditure by 25% to 36%, whereas the Harris-Benedict predictions modified by stress and activity factors overestimated actual energy expenditure by 32% to 39%.[19] Other Harris-Benedict–derived formulas have attempted to simplify matters by simply multiplying the Harris-Benedict–derived BEE by either 1.5[20] or by a factor of 2.[21] Each of these authors claim superiority over Curreri-based predictions which, as indicated above, seem to consistently overestimate actual energy expenditure as determined by indirect calorimetry.

The other major category of energy-predicting formulas in burn patients includes those which, like the Curreri formula, are based on the patient's TBSA and/or TBSA burned. Both Xie[22] and Allard[23] have compared their TBSA-based formulas with the Curreri formula and claim superior results, though the overall number of patients studied is quite small.

Despite the many published studies that claim superiority of a particular formula over the Curreri formula in the prediction of energy requirements in burn patients, the Curreri formula remains the most commonly used despite its well-documented propensity to overestimate energy requirements.[16] One would suspect, therefore, that actual determination of energy expenditure by indirect calorimetry might be the most accurate and commonly used method of determining caloric requirements of burned patients. However, in an interesting study documenting actual burn practices in North American burn centers, Williamson[16] noted that indirect calorimetry is infrequently carried out on a routine basis, being used only occasionally or for research purposes only. More importantly, there appear to be no differences in patient outcome when calories are provided on the basis of direct measurement of energy expenditure or on the basis of a mathematical formula. In a prospective randomized study of 49 patients, patients received feedings based on the Curreri formula or on indirect calorimetry-determined energy expenditure. Despite the significant difference in the number of calories prescribed to each group, the actual number of calories received by each group was the same, and there were no differences in clinical outcomes or complications.[24] An important finding in this study was the discrepancy between the number of calories prescribed and the number of calories delivered to these burn patients. Regardless of whether the Curreri formula is used or the BEE is multiplied by an activity factor and/or a stress factor, it is frequently difficult, if not impossible, for a patient to ingest this number of calories. Indeed, in Ireton's study mentioned above,[20] patients received a caloric intake of only 81% of the calculated Curreri-predicted caloric requirement. Thus, it is perhaps advantageous that many of these formulas overestimate caloric need to compensate for the less-than-prescribed caloric load that these patients actually receive.

At the same time, however, it seems unwise to attempt to achieve these high caloric loads by supplementing enteral nutrition with TPN. In a prospective, randomized study of 39 patients with TBSA burns exceeding 50%, Herndon et al.[25] demonstrated a significantly higher mortality and greater depressions in T-helper/suppressor ratios in patients receiving TPN.

Thus, the available data support the use of some formula to determine the initial caloric requirements of burned pa-

tients, recognizing that formulas may overestimate a patient's actual caloric need and that it is unlikely that the entire caloric load can be delivered. One common reason for the inability to deliver the prescribed caloric load in burn patients is the need to interrupt the tube feeding regimen for frequent debridement and grafting in the operating room. The Williamson survey[16] documents that most patients in North American burn centers are given nothing by mouth for at least 6 to 8 hours before surgery. Jenkins,[26] however, demonstrated the feasibility and safety of continuing enteral feedings throughout operative procedures in a very select group of burn patients with enteral access established beyond the pylorus and airway access established via an endotracheal tube or tracheostomy. These investigators demonstrated significant caloric deficits and an increased incidence of wound infection in the unfed group compared with the group that underwent intraoperative enteral feeding.

Finally, it should be mentioned that the caloric requirements of the burn patient fluctuate over the course of burn wound healing because of closure of the burn wound and other undetermined factors. Saffle and colleagues[27] demonstrated the biphasic character of measured energy expenditures in burn patients. Energy expenditures actually rise from the time of admission through the 10th to 20th postburn day and then decline thereafter but remain elevated at the time of discharge. This observation was confirmed by Cunningham[21] as well as by Ruten,[28] who noted a trend toward decreased energy expenditures with excision and coverage of the burn wound. Ireton-Jones,[29] however, was unable to identify a relationship between the percentage of burn wound remaining open and the measured energy expenditure. Even in the absence of a demonstrated relationship between the percentage of burn wound remaining open and energy expenditure, the caloric needs of the burn patient fluctuate from day to day depending on other factors such as temperature, activity level, degree of anxiety, pain control, ventilator dependency, caloric intake, the presence or absence of sepsis, and other yet-to-be defined factors. Therefore, providing the same caloric requirement over time runs the risk of overfeeding or underfeeding the burned patient. This has led some authors to recommend the use of indirect calorimetry to determine actual caloric requirements on a weekly or twice-weekly basis.[19,30,31]

At this time, there are insufficient data on protein, fat, and carbohydrate requirements in traumatically injured or burned patients to provide any Level I recommendations. One major problem is the difficulty in identifying specific groups of patients for study. For this reason, guidelines can only be applied broadly to patients within these two general categories. Another issue is that the current focus of nutrition and metabolic support has necessarily changed. The state of the art is such that we are less concerned with how to provide adequate quantities of macronutrients. The bulk of available evidence suggests that, with the exception of the risk of overfeeding, we currently provide patients with sufficient calories and protein to avoid the detrimental effects of malnutrition. Our attention has shifted toward manipulating a patient's physiologic and biochemical environment to his or her advantage through the administration of specific nutrients, growth factors, or other agents, often in pharmacologic doses.

A few Class I reports, randomized, prospective, and adequately controlled trials, have presented "convincingly justifiable" data. However, in these instances, either the number of patients studied was too small or the particular population investigated was too specialized to warrant inclusion in this practice management guideline.

Protein requirements were largely established by reports from the early 1980s that presented dose ranges believed to be appropriate. Most of these reports are Class II studies.[6,32–35] More recent publications have confirmed these dose ranges on the basis of extensive research conducted by a leading investigator,[36,37] studies of protein requirements using state-of-the-art measurements of body composition,[38] measurements of substrate metabolism and energy requirements,[39] or expert opinions based on reviews of available literature.[40,41]

The focus of other investigations has not been on specific protein requirements, but these studies provide a reference point for the range of protein intake that appears to be efficacious.[2,42–45] Variations in protein requirements as a function of time after burn or injury have been acknowledged, illustrating that current recommendations are only estimates of average need.[46]

The question of whether the contribution from protein should or should not be included in calculations of total caloric intake has not been specifically addressed. However, the preponderance of evidence available from detailed studies of actual energy expenditure[21,47] or nutrient utilization,[48,49] reviews of published reports,[50] or prospective trials[51,52] suggest that the majority of calories should be administered as carbohydrate. Although the exact percentage of total calories needed as fat is unknown, consensus opinion suggests that 30% or less is sufficient under most circumstances. This conclusion does not obviate the need to modify carbohydrate administration to minimize carbon dioxide production in selected instances,[47,49,50] but the specific range under which these modifications should occur has not been established. Some reports, though not all,[53] especially the Class I report by Battistella,[54] suggest that minimizing fat intake or altering the type of fat administered[55–57] may decrease morbidity and improve outcome or favorably alter metabolic profiles.

A few reports suggest that the specific macronutrients administered[56,58] or the use of growth factors[45,59–61] may favorably influence metabolic responses. However, recent preliminary reports suggest that the use of growth hormone for this purpose in critically ill patients may be associated with deleterious outcomes.

V. Summary

Multiple formulas provide an estimate of an individual patient's energy and substrate needs. Although many of these provide accurate estimates, many do not and can lead to overfeeding, with all of its inherent complications. It is best to remember that these formulas provide at best only an estimate of an individual patient's initial energy and substrate needs, and that these requirements will vary throughout the course of illness and recovery. Ongoing assessment of the appropriateness of nutritional support is crucial in avoiding under- and overfeeding.

VI. Future Investigation

It is unlikely that there is an ideal energy or substrate formula that will perform better than those currently in use. However, more reliable and easier-to-use means of measuring energy expenditure and substrate use would have significant advantages over the current state of technology with indirect calorimetry. Identification of these markers of metabolism will help in assessing a patient's initial requirements and will help the clinician modify nutritional support throughout the course of illness and recovery. It is unlikely that prospective, randomized, double-blind, controlled trials will study the effects of the administration of different quantities of protein, fat, or carbohydrate. Our present health care environment requires a clearer delineation of the indications for nutritional or metabolic support and for unequivocal demonstrations of efficacy with regard to decreasing costs and improving outcomes. Important issues that should be examined include: (1) the nature of injury and its time course, with the goal of minimizing the effects of nutritional, especially parenteral, interventions; (2) the effects of macronutrient administration on cellular biology and organ function during critical illness; and (3) the identification of groups of patients who will benefit from the administration of specific nutrients or growth factors, who needs them, what kind, and when.

E. MONITORING NUTRITIONAL SUPPORT IN THE TRAUMA PATIENT

I. Statement of the Problem

Previous sections of these guidelines contain recommendations regarding the quantity of calories and protein required by the trauma patient (see Section D, Assessment of Energy and Substrate Requirements for the Trauma Patient). The majority of these recommendations are based on formulas that provide, at best, only a rough estimate of the patient's nutritional needs, and thus the potential exists to either over- or underfeed any given patient. Therefore, some form of nutritional monitoring is essential to assess the adequacy of the initial nutritional prescription. There are a myriad of monitoring tests available, highlighting the fact that no single test can accurately assess the appropriateness of the nutritional support provided to the patient. Furthermore, any test used to monitor nutritional support must take into account the unique hypermetabolic response of the injured patient and the massive fluid shifts that occur in this patient population. Accordingly, nutritional monitoring tests that are reliable in the cancer or chronically malnourished patient may not be valid in the trauma patient. This section of the nutritional support of the trauma patient guidelines reviews the available scientific literature to determine answers to the following questions:

1. Which nutrition monitoring tests best reflect the appropriateness of nutritional support in the trauma patient?
2. How often should nutritional monitoring be performed in the trauma patient?
3. Is there evidence to support improved outcomes when nutritional support is modified as a result of nutrition monitoring?

II. Process

A. Identification of References

References were identified from a computerized search of the National Library of Medicine for English language citations between 1974 and 2001. Keywords included nutrition, monitoring, enteral nutrition, parenteral nutrition, albumin, nitrogen balance, indirect calorimetry, injury, and trauma. The bibliographies of the selected references were reviewed for relevant articles not found by the computerized search. Literature reviews, case reports, and editorials were excluded. Eighteen articles were identified.

B. Quality of the References

The quality assessment instrument applied to the references was developed by the Brain Trauma Foundation and subsequently adopted by the EAST Practice Management Guidelines Committee. Articles were classified as Class I, II, or III according to the following definitions:

Class I: A prospective, randomized clinical trial. No Class I articles were identified.

Class II: A prospective, noncomparative clinical study or a retrospective analysis based on reliable data. Fourteen articles were identified and analyzed.

Class III: A retrospective case series or database review. Four articles were identified and analyzed.

III. Recommendations

A. Level I

No recommendations.

B. Level II

1. In head-injured patients, and in trauma patients with multiple injuries, serum prealbumin is the most reliable serum indicator of the adequacy of nutritional support. There is insufficient scientific support to indicate the frequency with which this nutritional parameter should be determined.

2. Albumin levels correlate poorly with nutritional status and should not be used to determine the adequacy of nutritional support.

C. Level III

Serial determinations of serum levels of acute-phase reactants (e.g., C-reactive protein, fibrinogen, alpha-1-glycoprotein), along with constituent proteins (e.g., prealbumin, retinol-binding protein, transferrin) may improve the latter's value as a nutritional monitoring tool.

IV. Scientific Foundation

In an excellent review of nutritional monitoring in critically ill patients, Manning recommends that "nutritional assessment should be repeated frequently in patients requiring prolonged nutritional support, to assess the adequacy of the support provided and to guide adjustments to the nutritional regimen."[1] Unfortunately, in the case of the trauma patient, the scientific evidence to support this recommendation is weak overall, and in some instances, nonexistent. Although a recommendation can be made for the relative superiority of prealbumin as a marker for the adequacy of nutritional support, there certainly are no data to suggest how often this laboratory parameter should be repeated. Nor is there evidence to suggest that adjustments to the nutritional regimen based on the prealbumin level or any other monitoring tool will improve patient outcome. As Manning states, "whether improved nutritional state is directly responsible for the improvement in the condition of a sick patient or whether the patient's recovery leads to improvement in these measures of nutritional status is unclear."[1]

Although firm scientific evidence is lacking, it seems intuitive that, in the catabolic trauma patient, nitrogen balance studies would provide the best evidence of adequacy of the nutritional support prescription. According to Manning, "improvement in nitrogen balance is a single nutritional parameter most consistently associated with improved outcomes, and the primary goal of nutritional support should be the attainment of nitrogen balance."[1] Winkler agrees: "Because nitrogen balance measures the net effect of protein synthesis and degradation, it should be the standard against which other tests are compared."[2] Thus, there appears to be adequate scientific support for a Level III recommendation establishing nitrogen balance as the gold standard for nutritional monitoring.

However, the accurate determination of nitrogen balance is fraught with difficulty, both in terms of ensuring complete collection of nitrogenous waste (e.g., urine, feces, wound exudate) and in the mathematical calculation of nitrogen balance itself. Specifically, the use of the urinary urea nitrogen (UUN) in the calculation of nitrogen balance, as opposed to the total urea nitrogen (TUN), can possibly lead to a significant overestimation in nitrogen balance in burn patients.[3] Iapichino, in a series of patients with multiple injuries receiving parenteral nutrition, demonstrated that nitrogen output was remarkably constant during the first 6 days after trauma and that nitrogen balance was primarily determined by the nitrogen intake.[4] Thus, nitrogen output, if properly determined, might not need to be repeated frequently, at least early on after trauma. Given the theoretical as well as the practical concerns associated with nitrogen balance determinations in trauma patients, additional monitoring tools are needed that correlate well with nitrogen balance. Thus, for this section of the guidelines, particular emphasis was placed on studies that used nitrogen balance as the gold standard. Only one study cited in the evidentiary table claims a monitoring tool to be superior to nitrogen balance. However, this study contained a small number of subjects, and the criteria used for "successful" nutritional outcomes included gains in body weight and serum albumin, parameters widely accepted as unreliable in burn and trauma patients.[5]

Multiple diagnostic tests have been proposed to monitor the response to nutritional support. For classification purposes, these tests can be placed into one of the following categories: body measurements (e.g., weight change, anthropometric determinations), body composition studies (e.g., determinations of body fat, lean body mass, total body water), urine analyses for metabolic byproducts (e.g., urea, creatinine), immunologic tests (e.g., antibody production, delayed hypersensitivity skin tests), functional tests (e.g., handgrip strength), and serum chemistry analyses (e.g., albumin, prealbumin).[6] The interested reader is referred to the excellent review by Manning for a more thorough listing and discussion of these particular tests.[1] Many of these tests are insufficiently sensitive or specific for clinical use in any patient population, whereas others have been used primarily in research settings. For the trauma patient in particular, there is insufficient literature support for the use of any of these tests for nutritional monitoring purposes with the exception of serum chemistry assays and calorimetric studies. Recommendations provided within this guideline, therefore, are limited to these two categories of monitoring tests.

Spiekerman has outlined the requirements for the ideal serum protein to be used for nutritional assessment purposes. These requirements include a short biologic half-life, a relatively small body pool, a rapid rate of synthesis, and a constant catabolic rate. In addition, the protein marker to be followed should reflect the entire protein compartment status by measurable concentration changes in the serum levels of the protein and should be responsive only to protein and energy restrictions.[7] By far, the most commonly assayed serum proteins used in nutritional monitoring are albumin, prealbumin, transferrin, and retinol-binding protein. Other proteins that have been used for monitoring purposes include somatomedin C (insulin-like growth factor-1) and fibronectin. These six serum proteins are compared as to their suitability for nutritional monitoring purposes in Table 1.[2,7–9]

Despite being easy to measure on a serial basis and relatively inexpensive, the measurement of serum protein levels in trauma patients may not accurately reflect nutritional

status for several reasons. First, capillary permeability is increased in critical illness, causing a loss of protein from the intravascular compartment. Second, the massive fluid shifts that occur in trauma patients may compound the apparent hypoproteinemia via a hemodilution mechanism. Finally, trauma is associated with a profound up-regulation in the acute-phase response, resulting in a shift in protein synthesis toward acute-phase proteins, such as C-reactive protein and others, and a net decrease in synthesis of constitutive proteins, including albumin and prealbumin. Thus, it has been suggested that the increase in serum levels of the short-lived constitutive proteins (prealbumin, transferrin, retinol-binding protein) may not, in fact, be a reflection of appropriate nutritional support but rather a reflection of resolution of the acute-phase response, with restoration of constitutive protein synthesis.[1,7] These authors have therefore recommended simultaneous measurement of the levels of acute-phase proteins along with constitutive proteins, to better identify this reprioritization in protein synthesis. It may be that the impact of appropriate nutritional support, as reflected in increasing levels of short-lived constitutive proteins, may only be evident after resolution of the acute-phase response.

As shown in Table 1, albumin is unsuitable as a marker of the acute efficacy of nutritional support. This appears to be attributable primarily to its long half-life and its high exchange rate between the intravascular and extravascular fluid compartments, which is 10 times higher than its synthetic rate.[1] Consequently, changes in serum albumin level lag significantly behind those seen with nitrogen balance. Boosalis documented this phenomenon in 20 burn patients and 27 patients with head injuries. In this series, prealbumin levels reflected changes in nitrogen balance much more quickly than did serum albumin levels.[10] Similar observations were made by Vehe and Erstad in trauma patients[11,12] and by Brose in burn patients.[9] An ancillary observation in the latter study was that serum levels of both albumin and prealbumin appeared to be affected not only by nutritional status but also by the extent of the burn injury; albumin and prealbumin levels were lower in patients with total body surface area burns exceeding 40%.[9] Carlson, in a small series of thermally injured patients, noted similar findings, concluding that serum levels of prealbumin, transferrin, and retinol-binding protein, although reflective of nutritional status, also appeared to be affected by the extent of the burn injury, patient age, postburn day, and nitrogen intake. Serum albumin levels correlated poorly with nitrogen balance.[13] Finally, the improved performance of prealbumin relative to albumin was also demonstrated in a prospective study of elderly women undergoing hip fracture repair, although no comparison with the nitrogen balance studies was made.[14] These studies, considered together, reveal a pattern of improved performance of prealbumin as a monitoring tool for nutritional support relative to serum albumin levels. Design of the various studies, however, precludes a recommendation regarding the frequency of serum prealbumin determinations, with some authors making these determinations on a daily basis and others only on a weekly basis.

In addition to serum prealbumin, other serum markers have been investigated as nutritional monitoring tools. In a relatively large study of 45 head-injured patients, only prealbumin and retinol-binding protein were found to correlate with nitrogen balance, with prealbumin performing better than retinol-binding protein. Serum transferrin and albumin levels did not correlate with nitrogen balance.[15] These same four serum proteins were used to monitor the response to two parenteral diets that differed only in their nitrogen content. Although nitrogen balance was better in the high-nitrogen group, no difference was noted between the two groups with respect to any of the serum protein levels. However, it is important to note that positive nitrogen balance was never achieved in either of the two groups, nor was there even a trend of improving nitrogen balance.[16]

Several authors have questioned the monitoring capabilities of these serum proteins. Lown was unable to document an increase in transferrin or prealbumin level despite providing 3 weeks of nutritional support. However, only six patients were included in this study, and nitrogen balance studies were not performed.[17] Clark attempted to correlate prealbumin and transferrin levels, not with nitrogen balance but with measurements of total body protein. No correlation was noted between total body protein, which fell significantly through study day 15, and serum levels of prealbumin, transferrin, or

Table 1 A Comparison of the Nutritional Monitoring Suitability of Six Serum Proteins

	Half-Life	Body Pool Size	Levels Increased by:	Levels Decreased by:
ALB	20 d	Large	Dehydration, insulin, infection, anabolic steroids	CHF, edema, cirrhosis, renal failure, burns, overhydration
PA	2 d	Small	Renal failure (minor impact)	Cirrhosis, hepatitis, inflammation, stress
TFN	8–10 d	Medium	Iron deficiency, chronic blood loss, pregnancy, estrogens, hepatitis	Renal failure, cirrhosis, cancer, aminoglycosides, tetracycline
RBP	12–24 h	Very small	Renal failure	Cirrhosis, stress, vitamin A and zinc deficiency, hyperthyroidism
SMC	2–4 h	Minute	Growth hormone, refeeding	Protein deprivation
FN	15 h	Small	—	Shock, burns, infection

ALB, albumin; PA, prealbumin; TFN, transferrin; RBP, retinal-binding protein; SMC, somatomedin C; FN, fibronectin; CHF, congestive heart failure.

insulin-like growth factor-1, which showed significant increases throughout the same time period. Once again, no nitrogen balance studies were performed, and it was suggested that these increases in serum protein levels may be related more to restoration of hepatic constitutive protein synthesis than they are markers of nutritional progress.[18] Rettmer performed a comparison of serum protein levels against functional tests of nutritional status as measured against nitrogen balance. Although there was poor correlation between serum protein levels and positive nitrogen balance, serum protein levels were determined only once during the study, on postburn day 15, thus precluding any possibility of detecting a trend of improvement in these serum markers. Furthermore, the authors acknowledged the possibility that their nitrogen determinations might not have been accurate because of inability to measure nitrogen losses from the burn wound.[19] This inability to quantitate protein loss from burn wounds is a major obstacle in performing accurate nitrogen balance studies in this patient population. Waxman attempted to quantitate this protein loss through the use of occlusive wound sponges, the effluent from which was then analyzed for total protein, albumin, and globulin content. Protein losses were found to fluctuate throughout the postburn course and were affected by dressing type as well as wound care.[20] Thus, it seems that protein loss via burn wounds will continue to be a source of potential error, both in the clinical environment and the research environment in this patient group.

Two studies have evaluated the potential of fibronectin and somatomedin C to serve as markers of nutritional progress in patients receiving enteral feedings. One study demonstrated significant correlations between fibronectin levels and nitrogen balance,[21] whereas the other study demonstrated significant correlations between somatomedin C and nitrogen balance.[22] Both of these serum markers have demonstrated promise as nutritional monitoring tools in other patient populations;[23–27] however, their use in trauma patients cannot be recommended at this time on the basis of the available scientific literature. Similarly, the use of indirect calorimetry as a monitoring tool for patients with thermal injury cannot be recommended on the basis of the existing literature. In the single prospective study evaluating this technology in burn patients, there were significant variations in resting energy expenditure observed, both within the entire patient group over the course of burn wound closure, and also in individual patients, with daily fluctuations as large as 100%. Although adjustments in nutritional support were made on the basis of data derived from indirect calorimetry, there is no evidence to suggest that this improved patient outcome.[28] A small retrospective study in burn patients compared caloric balance (using indirect calorimetry) with nitrogen balance as nutritional monitoring tools, concluding that the former correlated better with good nutritional outcomes. However, the criteria used by the authors for "good" nutritional outcomes included gains in body weight and serum albumin, parameters widely accepted as unreliable in burn and trauma patients.[5]

V. Summary

Serial monitoring of the response to nutritional support can be performed, although there is no evidence to suggest that this practice improves clinical outcomes. Nitrogen balance determination, if performed correctly, is likely the best currently available means of assessing the adequacy of nutritional support and is the standard to which all other monitoring tests should be compared. However, difficulties in specimen collection and mathematical computation may result in significant overestimation in nitrogen balance, particularly in burn patients. Serial determination of serum prealbumin levels seem to correlate reasonably well with nitrogen balance determinations in trauma and burn patients, although there is no evidence available to recommend how often monitoring should be carried out.

VI. Future Investigation

Much work remains to be done in the field of nutrition monitoring. Serum protein markers, because of their simplicity, ready availability, and relatively low cost, will likely remain the mainstay of nutritional monitoring tests in the future. Prospective, randomized studies are needed to identify the optimal serum protein marker and the frequency with which it should be assayed. Most importantly, prospective studies are needed to determine whether changes in the nutritional prescription based on routine nutritional monitoring actually improve patient outcomes.

F. STANDARD VERSUS ENHANCED NUTRITIONAL SUPPORT

I. Statement of the Problem

An accumulating body of evidence in animal models suggests that the addition of specific micronutrients to enteral formulations can improve outcomes with regard to immune function, septic morbidity, and overall mortality. Although a host of these additives have been examined, glutamine (GLN), arginine (ARG), omega-3 fatty acids (ω-3 FAs), and nucleotides (RNA) have received the greatest attention. Whether the enhancement of standard enteral formulas with any of these micronutrients is beneficial in humans, and if so, in which patient populations, remains unclear. This document examines the existing literature, focusing specifically on clinically relevant endpoints in trauma (including burn) patients.

II. Process

A. Identification of References

References were identified from a computerized search of the National Library of Medicine for English language citations between 1980 and 2000. Keywords included enhanced nutrition, nutrition support, trauma, burn, enteral, parenteral, and micronutrients. The bibliographies of the selected references were reviewed for relevant articles not

found in the computerized search. Literature reviews, case reports, and editorials were excluded. Ten articles were identified.

B. Quality of the References

The quality assessment instrument applied to the references was developed by the Brain Trauma Foundation and subsequently adopted by the EAST Practice Management Guidelines Committee. Articles were classified as Class I, II, or III according to the following definitions:

Class I: A prospective, randomized clinical trial. Ten articles were chosen and analyzed.

Class II: A prospective, noncomparative clinical study or a retrospective analysis based on reliable data. No Class II articles were identified.

Class III: A retrospective case series or database review. No Class III articles were identified.

III. Recommendations

A. Level I

No recommendations.

B. Level II

No recommendations.

C. Level III

The use of enteral formulations enhanced with "adequate" doses of arginine and glutamine appears to reduce length of stay and septic morbidity in severely injured trauma patients (ISS $>$ 20, ATI $>$ 25). The precise doses of and lengths of treatment with ARG and GLN required to obtain this effect have not yet been determined. Whether an additional benefit is gained from further supplementation with ω-3 FAs, nucleotides, and trace elements is unclear.

IV. Scientific Foundation

The concept of "immunonutrition," wherein the addition of specific micronutrients to standard enteral or parenteral formulations enhances host immunologic function, is well supported by many animal studies dating back to the mid-1980s.[1–11] Although the roles of several of these additives have been examined, including branched chain amino acids, selenium, and zinc, the best studied (and most commercially available) micronutrients are GLN, ARG, nucleotides, and the ω-3 FAs.

Glutamine, despite being the most abundant amino acid in the body, appears to become conditionally essential in various critical care states. It is the major fuel source for enterocytes, lymphocytes, and macrophages, and thus its deficiency can cause not only compromise of the barrier function of the intestinal epithelium but also impaired immunologic function.[12] Arginine is another nonessential amino acid that can become conditionally essential under conditions of stress and sepsis. Administration of pharmacologic doses of arginine has been shown to enhance secretion of many hormones including growth hormone, insulin-like growth factor, pituitary growth hormone, prolactin, and others. It is also a precursor for synthesis of nitrates, nitrites, and nitric oxide, which seems to play an important role in macrophage killing capacity.[13,14] The omega-3 fatty acids (the so-called fish oils) have a number of advantageous properties compared with the more commonly used omega-6 fatty acids (vegetable oils). The latter are generally considered immunosuppressive (inhibit antibody formation, lymphocyte and macrophage activity, and T-suppressor cell proliferation), whereas the former are less inflammatory and more immunostimulatory.[12,15] Finally, the purine and pyrimidine nucleotides (adenine, guanine, thymidine, and uracil), being precursors for DNA and RNA, appear to be essential for cell energetics (adenosine triphosphate) and may also play a role as physiologic mediators (cyclic adenosine monophosphate). Administration of these agents improves natural killer cell activity and enhances resistance to infection.[16]

Many prospective, randomized trials in many different patient populations have evaluated the impact of these immunologically enhanced nutritional formulations. However, because of differences in the patient populations studied, the composition of the diets, and the clinical and laboratory outcomes measured, it has been extremely difficult to gain consensus regarding the proper role for these expensive formulations. Several recent evidence-based reviews[17–19] and the recently published consensus statement from the American Society for Parenteral and Enteral Nutrition[20] reflect the limitations of the currently available literature and the need for additional scientific study in specific patient populations. Our purpose in performing this review was to examine the role of enterally enhanced formulas in the trauma patient, to determine whether distinct recommendations could be made regarding this patient population that might not have been evident in the reviews of less specifically defined patient groups. Unfortunately, the same shortcomings that plague the immunonutrition literature as a whole apply to the currently available studies of trauma patients. Despite our review comprising 10 Class I (prospective, randomized, controlled) studies (see evidentiary table that follows), small patient numbers in the individual studies and methodological differences between the studies prevent us from making Level I recommendations. Future studies need to address the following limitations in the immunonutrition in trauma literature.

Lack of Uniformity in the Study Population

Of the 10 studies included in this review, only 6 focus specifically on trauma patients,[11,21–25] and 2 are limited to burn patients.[26,27] The final two studies, in ICU patients, were included because they clearly specified the percentage of trauma patients in their ICU patient population.[28,29] In one of these studies, however, only 13% of the patients were trauma patients,[29] and in neither study is the severity of injury for the trauma patient subset provided. The inclusion criteria for both

burn studies are relatively broad, and the resulting differences in mean age (20 years vs. 35 years) make it difficult to justify the conflicting outcomes. Furthermore, the inclusion of pediatric patients in both studies adds yet another variable that must be taken into account when interpreting these results. Even the six studies in trauma patients may not necessarily be comparable given the rather wide variations in mean ATI (20–34) and mean GCS score (8.6–14) in the studies reporting these scores. In contrast, age, ISS, and APACHE II scores (for the three studies reporting this score) are similar.

Lack of Uniformity in Composition of Enhanced Formulations

The evidentiary table shows a lack of uniformity concerning the additives constituting the enhanced diets. Although most recent enhanced formulas contain arginine, glutamine, omega-3 fatty acids, and nucleotides, one study compares two formulas that differ only in their glutamine concentrations.[25] Another study features an enhanced formula that contains no glutamine but instead has added zinc, cysteine, and histidine to the arginine/glutamine/omega-3 fatty acid/nucleotide mix.[26] Similarly, there is inconsistency in the composition of the control enteral formulation. In the study by Saffle et al., the control formula actually contains more glutamine, total protein, and omega-3 fatty acids than does the enhanced formula.[27]

Lack of Consistent Outcome Parameters

Despite the fact that we confined our analysis to studies with clinically relevant endpoints, the existing literature demonstrates a fairly broad array of outcome parameters. Recognizing that none of the 10 prospective, randomized studies demonstrated a reduction in mortality associated with enhanced enteral formulations, various secondary outcome parameters were examined by the various authors. Although there was consistency regarding some endpoints (hospital length of stay, ICU length of stay, ventilator days, and overall septic morbidity), there was significant variability in others, particularly those involving sepsis (pneumonia rates, intra-abdominal abscess rates, major infection rates, bacteremia rates, antibiotic use). Some studies compare overall complication rates in addition to the more commonly reported septic morbidity rates. The use of the multisystem organ failure syndrome and acute respiratory distress syndrome as clinical endpoints was also inconsistent.

Lack of Consistent Time of Initiation of Enteral Feeding

The time of initiation of enteral feeding varied from as early as 24 hours after admission to as late as 7 days, although 48 hours was the most frequently used deadline (6 of 10 studies). One study did not specify a deadline for initiation of feedings but stated an attempt to institute early feeding.[26] Atkinson et al. not only specified a 48-hour deadline for initiation but also limited their analysis to patients who received more than 2.5 L of formula within 72 hours of ICU admission.[29] Although there appears to be no consensus regarding a specific absolute deadline for institution of enteral feedings, the concept of early enteral feeding is generally accepted, and therefore attempts should be made to standardize this variable in future studies.

Lack of Consistent Duration of Enhanced Feeding

Similarly, the duration of administration of enhanced formula feeding varies considerably in the selected studies. Although most studies required a minimum of 5 to 7 days of assigned product infusion, one study required only 72 hours.[22] Several studies did not specify a minimum or maximum duration of enteral feeding but simply continued feedings until oral intake was adequate.[23,26,27,30] Others mandated that feedings be continued for a prescribed period of time[21] or until ICU discharge.[29] Given these observations, it is not surprising that the average number of days spent receiving the study formulations also varied considerably from a low of approximately 7 days[22] to almost 4 weeks.[26] Despite the fact that a minimum effective infusion volume or infusion duration for these enhanced enteral formulations has not been determined, future investigators should consider adopting a uniform prescribed course of therapy to facilitate data interpretation.

Inconsistency Regarding Supplemental Use of Parenteral Nutrition

Two of the 10 studies included in this section's evidentiary table use TPN in addition to the studied enteral formulations.[26,30] In one study, 10 of 50 patients (20%) were provided TPN during approximately 50% of their study time, although the exact caloric and protein contribution of the TPN to the patient's overall nutritional support is not stated.[26] In the other study, TPN was provided to all patients in significant amounts. Although patients received their enteral formulations for an average of approximately 22 days, TPN accounted for the majority of protein and calorie intake for the first 6 days.[30] Clearly, the use of TPN to these extents at best clouds the discernment of a potential benefit of enhanced enteral formulations.

Inconsistent Use of Isocaloric, Isonitrogenous Formulations

Of the 10 prospective, randomized, controlled trials reviewed here, only 6 involved comparisons of isocaloric, isonitrogenous formulations.[23–26,29,30] Two trials compare isocaloric but nonisonitrogenous diets,[22,27] and the remaining two studies compare diets that are neither isocaloric nor isonitrogenous.[21,28] Given the well-documented association between increased protein feeding and improved outcomes,[31] conclusions drawn from studies comparing nonisonitrogenous formulas must be viewed with considerable suspicion.

Inadequately Powered Studies

Six of the 10 studies reviewed contained 50 or fewer patients.[21,23,24,26,27,30] Only two studies randomized more than 100 patients, and both are really ICU studies containing vastly dif-

ferent percentages (13% and 84%) of vaguely defined trauma patients.[28,29] Looking more closely at the eight remaining smaller studies, two demonstrated significant reductions in ventilator days, overall length of stay, and various measures of septic morbidity;[22,23] one study identified statistically insignificant trends toward poorer outcomes;[24] one noted no impact;[27] and four studies reported mixed results.[21,25,26,30] Furthermore, no study, including both ICU studies, demonstrated a reduction in mortality with enhanced formulas. Although larger studies are not likely to demonstrate an impact of enhanced feedings on mortality, they may yield more consistent results with regard to other clinical endpoints.

In light of the shortcomings identified in the currently existing literature, several studies, although they are prospective, randomized Class I trials, cannot be used to formulate recommendations in this guideline. Simply limiting our analysis to trials comparing isocaloric, isonitrogenous formulations without the supplemental use of TPN excludes 6 of the 10 studies discussed in the evidentiary table.[21,22,26–28,30] Of the four remaining studies,[23–25,29] none focuses on patients with burns, and thus no recommendations can be made in this guideline with regard to the use of enhanced formulas in burn patients. One of the four studies is ICU-focused, with only 13% of the study participants being trauma patients, thus greatly limiting its applicability to this guideline.[29] Another study focuses specifically on the impact of supplemental glutamine and therefore can only generate recommendations about this specific additive.[25]

The remaining two studies reach conflicting conclusions, one citing improved outcomes[23] and the other reporting statistically insignificant trends toward poorer outcomes.[24] Both studies enrolled patients of similar injury severity, initiated enteral feedings within 3 days of hospital admission, and continued the enhanced diets for 9 to 10 days. There were, however, some significant differences among the four formulas in these two studies, which could explain some of the conflicting results.

First, the nonprotein-to-calorie ratios of the formulas in the Mendez study were much greater[86,89] than the formulas compared in the study by Kudsk.[52,55] Thus, although the amounts of protein provided in the two studies were comparable, patients in the Mendez study received much greater caloric loads (26–27 kcal/kg/d by day 6 of feeding) than the patients in the study by Kudsk (~18 kcal/kg/d). Micronutrient composition of the formulas also varied. Although the two formulas compared in the Kudsk study differed primarily in their glutamine, arginine, nucleotide, and ω-3 fatty acid contents, there was no difference in the glutamine content of the two formulas compared in the Mendez study, and in fact, both formulas contained more glutamine than Kudsk's enhanced formula. Furthermore, although Mendez's enhanced formula contained almost twice the amount of arginine found in her control formula, there was a fivefold difference in arginine content between the two formulas in Kudsk's study. Given these observations, one plausible explanation for the failure of Mendez to demonstrate an advantage with her enhanced formula is that the control formula contained too much glutamine relative to the enhanced formula, whereas the enhanced formula lacked sufficient arginine compared with the enhanced formula used by Kudsk. Our explanation for the divergent conclusions reached by these two authors is supported by Houdijk's work, which showed improved outcomes when a standard enteral formula was supplemented only with glutamine.[25]

Beyond arginine and glutamine, there are also differences in omega-3 fatty acid content in these two studies (Mendez, 0 g/L vs. ~1.4 g/L; Kudsk, 0.65 g/L vs. 1.1 g/L), and only Kudsk's enhanced formula contained a nucleotide supplementation at all (1.0 g/L). Whether an additional nutritional impact can be ascribed to these two additives at these dosages is unclear, especially considering the five- to ninefold differences in glutamine and arginine concentrations in the two studies. Recognizing, therefore, the statistically significant improvement in outcomes reported by Kudsk, the statistically insignificant poorer outcomes noted by Mendez, and the differences in design and implementation between the two studies, we believe there is sufficient scientific support for a Level III recommendation for the use of enteral formulations enhanced with "adequate" doses of arginine and glutamine in severely injured trauma patients.

IV. Summary

The currently existing medical literature regarding enhanced enteral formulations in severely injured patients is characterized by small numbers of inconsistently defined patients who receive various noncomparable nutritional formulas for variable periods of time. Clinical outcome parameters are similarly poorly defined and/or agreed on. Until larger studies with improved methodology are completed, only a relatively weak recommendation can be made in severely injured patients (ISS $>$ 20, ATI $>$ 25) for the use of enteral formulations enhanced by the addition of arginine and/or glutamine. The specific impact of further supplementation with omega-3 fatty acids, nucleotides, and trace elements cannot be determined at this time. Similarly, the current literature gives no support to recommendations regarding the use of enhanced enteral formulas in patients with severe burns.

VI. Future Investigation

There is a dire need for additional studies that examine the role of enhanced enteral formulas in critically ill and injured patients. These studies must use large numbers of well-defined subsets of trauma patients (ISS, ATI, GCS score, penetrating/blunt, burn), with well-designed feeding strategies (time of initiation of feedings, duration of enhanced feeding, use of supplemental TPN) that are consistent from study to study. Most importantly, the composition of both the control and the enhanced formulas must be isonitrogenous and isocaloric and must also be standardized with regard to arginine, glutamine, omega-3 fatty acid, nucleotide, and trace element content. Finally, investigators should design studies limited to mutually agreed on clinically relevant outcome parameters.

EDITORIAL COMMENT

These "Practice Management Guidelines for Nutritional Support of the Trauma Patient" are the culmination of a long and dedicated effort by Dr. David Jacobs and his associates in the Eastern Association for the Surgery of Trauma Practice Management Guidelines Workgroup to document the evidence that defines best nutritional support practices for the injured patient. The authors' review of the literature is extensive, thorough, and honest. Their article consists of several chapters, each of which addresses a very basic issue in nutritional support: route, timing, site, composition, monitoring, and type of feeding. Each chapter stands on its own and includes the pertinent references.

The article clearly documents that the scientific basis for a best nutritional support practice for sick trauma patients is not strong. The authors found a substantial amount of incomplete, fragmentary, or contradictory evidence and a much smaller amount of definitive, class I data. Thus, they were unable to make many strong Level I or Level II recommendations. Clinicians must still rely to a large degree on their own clinical experience and best judgment when providing nutritional support to injured patients. For such a fundamental practice as nutritional support, that is a disappointing outcome. However, it does present an opportunity and a challenge for future surgical investigators. If some who read these guidelines are moved to define the issues better, the authors' efforts will have been richly rewarded and we will all be well served.

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