

**PRACTICE MANAGEMENT GUIDELINES FOR
NUTRITIONAL SUPPORT OF THE TRAUMA PATIENT**

The EAST Practice Management Guidelines Workgroup

David G. Jacobs, MD, Danny O. Jacobs, MD,
Kenneth A. Kudsk, MD, Frederick A. Moore, MD,
Michael F. Oswanski, MD, Galen V. Poole, MD,
Gordon S. Sacks, PharmD, L.R. “Tres” Scherer, III, MD, and
Karlene E. Sinclair, MD

Introduction

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. While supportive data exist for many of our current nutritional practices, the trauma surgeon cannot assume that interventions which are successful in laboratory animals or even in the critically-ill *non*-trauma 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 versus Total Enteral Nutrition)
- B. Timing of Nutritional Support (Early versus Late)
- C. Site of Nutritional Support (Gastric versus 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 versus Enhanced)

Each sub-guideline 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 amongst the guidelines. Yet, due to 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 than they might have otherwise been. Recognizing the need to incorporate the major recommendations from the sub-guidelines into a logical overall approach to the nutritional support of the trauma patient, a summary algorithm is provided at the conclusion of the guideline. Due to the scope of this document, many of the recommendations from the sub-guidelines 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.

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 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 pair 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) trauma⁷⁻⁹ or burn patients¹⁰ given IV-TPN. In addition, burn patients have been studied after receiving a variety of enteral formulas (high versus standard protein,² enhanced versus standard diet¹¹), while patients sustaining severe head injury have been randomized to intravenous nutrition versus intragastric feeding^{12,13} or intragastric versus postpyloric feeding.^{14,15}

While 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 IgA 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” following 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 total body’s immunity and 70%-80% of immunoglobulin production by the body, primarily in the form of IgA.²⁹ Experimentally, dietary conditions which increase bacterial translocation (IV-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 immunity³¹ 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* increase 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.

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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 to deliver nutrition to the traumatized hypermetabolic patient with multisystem injuries including severe head injuries, burns, and blunt and penetrating mechanisms. 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 based on 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 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, non-comparative 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, since outcomes are similar compared with parenterally-fed patients. 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 post-injury day 7 should have TPN instituted but should be weaned when > 50% of enteral feedings are tolerated.

IV. SCIENTIFIC FOUNDATION

Moore and Jones¹ 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 TEN in patients suffering abdominal trauma with an ATI >15, <40. The TPN group reached a nadir in constitutive proteins at day 10, while the TEN group had a rise 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, ISS >20, transfusions >20 units, and re-operation) 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, interleukins 1, 2, 6, 11, and 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, due to frequent interruptions in feeding because of multiple operative procedures. Moncure and coworkers 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 peri-operative 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 colleagues⁹ 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 others¹⁰ 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 colleagues¹³ further defined nutritional support in the head-injured patient. In the laboratory, intravenous hyperosmolar solutions were found to potentiate cerebral edema following head injury. In 1987, Young et al.¹¹ reported no significant difference in peak ICP, failed therapy of ICP, 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 due 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 the post-injury week 1. This delayed and biphasic response persisted through the second week in $>50\%$ 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 colleagues¹⁴ confirmed the efficacy of enteral and parenteral support using early jejunal feedings in the enteral group and delayed gastric feeding (day 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 versus late) and site (gastric versus 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 about 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 post-injury 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.

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Route of Nutritional Support Evidentiary Table

First Author	Year	Class	Conclusions
Rapp (8)	1983	I	38 patients with blunt/penetrating head injury randomized within 48 hours to TPN (n=20, age 29.2 years, GCS score 7.7) or intragastric feeding (n=18, age 34.9 years, GCS score 7.2) with defined formula diet. Enteral caloric intake \leq 400 cal/day for first day, \leq 600 cal/day for first 10 days, and $<$ 900 cal/day for 14 days due to delayed gastric emptying. Eight of 18 patients fed enterally died within 18 days compared with 0 TPN patients. Prolonged gastroparesis occurred with intragastric feeding post severe head injury.
Hausmann (9)	1985	I	20 patients randomized to enteral-parenteral nutrition (n=10) and TPN (n=10) after suffering severe brain injury (GCS score 5-7). There were no differences in protein intake, nitrogen balance, or mortality between the groups. Both regimens were nutritionally effective, but impaired gastric emptying hampered enteral feedings.
Adams (22)	1986	I	46 multiple trauma patients post-laparotomy were randomized to receive enteral nutrition via needle catheter jejunostomy or TPN. There were no differences in nitrogen balance or postoperative complications. Early enteral nutrition is safe.
Hadley (10)	1986	I	45 head-injured patients with GCS score \leq 10 randomized to intragastric (n=21, GCS score 5.9) feeding with standard commercial diet or TPN (n=24, GCS score 5.8). Enteral patients achieved positive caloric balance (140% of BMR) in 5% on day 2, 45% on day 3, 70% on day 4, and between 70% and 85% on day 11. TPN achieved $>$ 80% by day 5 and 100% by day 9. Complication rate and infectious rate similar. Use TPN only when gastrointestinal tract fails to work. Editorial: gastroparesis begins to resolve on day 3 to 4. Do not wait for nasogastric drainage to drop or bowel sounds to return.
Young (11)	1987	I	96 severely brain-injured patients were randomized to receive early TPN or enteral feedings when tolerated. There were no differences in the groups including: admitting GCS score, number of craniotomies, MOI, ICP $>$ 20, failure of conventional therapy, barbiturate failure, or serum osmolality. TPN can be used safely, but there is no outcome advantage to enteral feeding.
Young (12)	1987	I	51 evaluable of 58 consented patients with GCS score 4-10 after blunt or penetrating head

First Author	Year	Class	Conclusions
			wounds randomized to TPN (n=23, age 30.3 years, GCS score 7.0) or intragastric feedings (n=38, age=34.0 years, GCS score 6.5) after bowel sounds return and nasogastric drainage dropped below 100 mL. Enteral patients received <500 cal/day for first 2 days (versus 1221 kcal TPN group), <1500 cal/day for days 6-8 (versus 2350 kcal in TPN group) due to gastroparesis. Infectious complications were the same and neurologic outcome similar at 1 year. Prolonged gastroparesis occurs after severe head injury.
Graham (28)	1989	I	32 patients with blunt/penetrating wounds and GCS score =10 randomized (by admission day) to nasojejunal feeding via fluoroscopy by 36 hours (age 25.5 years, GCS score 5.1) and started at goal rate or intragastric feedings after day 3 if gastrointestinal function returned (age 27.8 years, GCS score 7.1). Caloric intake matched measured need by day 3 with jejunal tube and approached 75% of need on day 5-7. With intragastric feedings, there were significantly fewer bacterial infections (bronchitis: 3-4 plus WBC in sputum with positive cultures) than with jejunal feedings. Goal rates achieved faster with small bowel access. Gastric residuals limit intra-gastric feeding rate. No change in metabolic rate by indirect calorimetry.
Jones (26)	1989	I	123 patients requiring emergent laparotomy (ATI ≥15) were prospectively randomized to non-enteral feeding (n=52) or enteral feeding (n=71) by means of a needle jejunostomy catheter. 50% of control group had gastrointestinal symptoms (12% moderate discomfort). 83% of enteral-fed group had symptoms; 16% moderate symptoms, 13% required TPN. 87% tolerated enteral feedings, 35 cal/kg/day and 14.5 g nitrogen/day by post-operative day 5.
Moore FA (3)	1989	I	59 patients with major abdominal trauma were randomized to receive TEN or TPN after laparotomy. Patients who received enteral nutrition had fewer septic complications. In addition, nutritional protein markers were restored faster in the TEN group.
Kudsk (5)	1992	I	98 trauma patients were randomized to receive TPN or enteral nutrition within 24 hours of penetrating or blunt abdominal trauma. There was a lower incidence of septic complications in the patients who received enteral nutrition.
Eyer (25)	1993	I	38 evaluable patients randomized to early (starting 31 hours after ICU admission) compared with late (82 hours) feeding via nasoduodenal tubes. ISS was similar; however, 58% of

First Author	Year	Class	Conclusions
			early group had severe acute lung injury versus only 21% in late group. Target rates in most patients were reached within 12 hours of start, with advancement to 25 mL every 4 hours. Excellent small bowel tolerance with no intra-abdominal injury within 1.5 days of injury but no differences in ICU or ventilator days, organ system failure, or infections (question of higher infection rate with early group but included eye, sinus, and urinary infections probably unrelated to enteral feeding).
Kudsk (6)	1994	I	68 patients randomized to enteral (n=34, ATI 28.0, ISS 27.0) or parenteral (n=34, ATI 27.8, ISS 26.8) nutrition. Significantly higher levels of constitutive proteins and lower levels of acute-phase protein were noted in the enteral group. An important factor related to route of nutrition was the significant reduction in septic morbidity (any infection, pneumonia, line sepsis) associated with enteral nutrition.
Borzotta (14)	1994	I	48 evaluable head-injured patients (GCS score <8) randomized to TPN (n=21, age 28.9 years, ISS 33.4, GCS score 5.4) or enteral feeding via surgically placed jejunostomies (n=27, age 26.2 years, ISS 32.5, GCS score 5.2) and started within 72 hours of injury. All TPN patients had initial attempts with intragastric feeding (and presumably failed). TPN transition to intragastric feedings started on day 5. Diarrhea was more common in TPN patients, and they had a high rate of nasogastric tube dislodgment. Enterally delivered calories equaled 90.5% of measured resting energy expenditure by indirect calorimetry by day 3. With direct small bowel access, nearly achieved calculated goal by day 3 (and subsequently over) with little intolerance.
Spapen (20)	1995	I	21 mechanically ventilated patients were randomized to receive cisapride 10 mg four times daily or no cisapride with tube feedings. Gastric residue was measured using bedside scintigraphy. Patients in the cisapride group had accelerated gastric emptying. This was statistically significant.
Page (24)	1979	II	199 patients post-elective major abdominal and post-emergent abdominal surgery were fed by needle-catheter jejunostomy and monitored for complications. Patients' nutritional status was adequately maintained. The complication rate was 2.5%. Jejunostomy feeding is safe in the postoperative period.

First Author	Year	Class	Conclusions
Moore EE (1)	1986	II	75 patients post-celeiotomy for abdominal trauma were randomized to receive enteral nutrition via needle jejunostomy or intravenous fluids. Enteral nutrition was started within the first 24 postoperative hours. Nitrogen balance was improved in the patients receiving enteral nutrition, and there were fewer septic complications.
Norton (27)	1988	II	23 patients with blunt/penetrating head injury and GCS score 4-10 (average 6.6) were followed for enteral tolerance. Feedings were started when drainage was <200 mL/day, and bowel sounds were present. Seven patients tolerated feedings within 7 days, four between 7-10 days, and 12 never tolerated feedings with a trend toward greater intolerance with lower GSC. Tolerance did not correlate with bowel sounds. Gastroparesis occurs in most patients with severe head injury.
Peterson (2)	1988	II	Hepatic synthesis of acute phase reactant proteins was evaluated in 59 patients with an ATI between 15 and 40. 36 patients completed the trial, of which 18 patients received TPN and 18 received enteral nutrition. The group receiving enteral nutrition had earlier attenuation of the acute-phase reactant protein production.
Ott (13)	1991	II	12 head-injured patients (GCS score 4-10) were evaluated during their hospital stay for liquid gastric emptying. 50% had delayed gastric emptying for up to 7 days, 40% normal within 14 days, and 80% had normal or biphasic emptying by 16 days. Patients with normal or rapid emptying (30%) tolerated full feedings in 8.5 days, which was significantly earlier than the patients with delayed gastric emptying (50%, 13.7 days).
Moore FA (4)	1992	II	A meta-analysis of eight prospective randomized trials to compare the efficacy of early enteral nutrition with TPN in high-risk surgical patients. Patients who received enteral nutrition had fewer septic complications.
Hadfield (21)	1995	II	24 patients were randomly allocated to receive TPN or enteral nutrition. Gastrointestinal absorption was evaluated by measuring D-xylose and 3-O methyl glucose, and gastrointestinal tract permeability was determined by measuring lactulose and L-rhamnose. All critically ill patients had gastrointestinal tract dysfunction; however, mucosal integrity was restored by giving enteral nutrition.
Heyland (18)	1995	II	A prospective cohort study that evaluated the factors associated with initiation and tolerance of enteral nutrition in 99 critically ill patients. The authors reported that enteral nutrition

First Author	Year	Class	Conclusions
			was not initiated in all eligible patients, and 50% of the patients receiving enteral nutrition tolerated the regimen
Kalfarentzos (17)	1997	II	A prospective randomized trial of 38 patients with acute severe pancreatitis; 20 received TPN and 18 received elemental enteral nutrition. Enteral feedings were tolerated well, and patients had fewer complications.
Moncure (7)	1999	II	Prospective, non-randomized study of 82 trauma patients with jejunostomy tubes who required non-abdominal surgery. 46 patients had tube feedings continued up until the time of transport to the operating room (fed group), and 36 patients had feedings stopped at midnight before the operation. Aspiration of tube feedings did not occur in either group, and the fed group received more protein and calories on the operative day and on post-operative day 1.
Bethel (23)	1979	III	Enteral nutrition was given to 12 patients referred for TPN. Patients showed weight gain and improvement in serum albumin levels. Nasogastric feedings are a safe alternative to TPN.
ASPEN Board of Directors (16)	1993	III	Many trauma patients are hypermetabolic. The functional consequences of total or partial starvation evolve more rapidly in the stressed and catabolic patient than in healthy individuals. For injured patients, severely limited nutrient intake should not exceed 7 days.
Raff (19)	1997	III	A retrospective review of 55 burn patients receiving early intragastric feeding. Patients who tolerated the early feeding had significantly lower mortality rates.
Yanagawa (15)	2000	III	Review of 12 randomized, controlled trials, focusing specifically on the timing and route of nutritional support following acute traumatic brain injury. 257 patients of all ages with traumatic brain injury of any severity either isolated or part of multisystem injury were included. Authors conclude that early feeding may be associated with fewer infections and a trend toward improved survival and long-term disability. There was a trend toward better outcomes with parenteral nutrition (compared with enteral), but this observation may be related, in part, to the delay in starting enteral feedings due to associated gastric ileus. Overall, the quality of the trials was poor, and the authors recommended larger trials with more relevant clinical endpoints.

First Author	Year	Class	Conclusions
TPN, total parenteral nutrition; GCS, Glasgow Coma Scale; BMR, basal metabolic rate; MOI, Mechanism of Injury; ICP, intracranial pressure; ATI, abdominal trauma index; TEN, total enteral nutrition, ICU, intensive care unit			

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 post-injury) compared with feedings initiated at 72 hours post-injury. 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 following 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, non-comparative 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 to 72 hours after admission.

B. Level II

1. In burn patients, intragastric feedings should be started as soon after admission as possible, since 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 due to the risk of gastrointestinal intolerance and possible intestinal necrosis.
2. In 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 following 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 *post-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 post-injury was not early enough to demonstrate this advantage, or perhaps the metabolic advantages are not demonstrable until after the 10-day study period employed 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 post-injury achieved by these authors, given their very aggressive approach to post-pyloric 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 study³ randomized multisystem trauma patients (ISS >25, GCS score =12) to early (< 6 hours after resuscitation from shock) or late (=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 ICU length of stay, and duration of mechanical ventilation was 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 taken together would seem to raise serious questions regarding the significance of *early* enteral feeding, even if feedings are initiated as early as 6 hours following resuscitation.

The remainder of the prospective, randomized trials of blunt and penetrating trauma has 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 18-24 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} which 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 TPN⁷ 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 18-40 or ISS 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 following surgery due to 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 slower rate of progression necessary to improve tolerance.

Intragastric feedings have been studied most closely in burn patients. In a population of pediatric patients with > 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 following burn was well tolerated. In a population of patients with burns of 40% to 70% TBSA¹⁴, 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% or greater,¹⁷ tolerance of intragastric feedings was >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 <500-600 kcal/day over the first 2 days, < 800 cal/day on days 3-5, and <1,500 cal/day on days 6-8 due to gastroparesis. However, no attempts were made to feed patients until nasogastric drainage had dropped below 100 cc. 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 <200 cc per day 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 since gastric emptying may occur despite higher nasogastric drainage and prior to 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 due to 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. Intra-gastric-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.²⁵

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. Intra-gastric feeding becomes successful in the majority of head-injured patients at approximately day 3 or 4, at the earliest, due to 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. Intra-gastric 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 intra-gastrically, 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 which promote successful, safe advancement of feeding rate are needed, especially markers which identify patients who will be intolerant of enteral feeding due to 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, employing a precise definition of early feeding, together with clinically relevant outcome parameters (morbidity, infectious morbidity, neurologic outcome,

etc.) in a well-defined patient population (burns, head injury, or torso trauma) are needed to adequately resolve this important issue.

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Early versus Delayed Enteral Feedings Evidentiary Tables

Table 1. Blunt/Penetrating Trauma

First Author (Ref)	Year	Data Class	Conclusions
Moore EE (4)	1986	I	63 patients with ATI >15 prospectively randomized to IV fluids (TPN added at day 5 if still NPO) or enteral feedings started at 12 to 18 hours postoperatively and advanced to goal by 72 hours. 12% of enteral patients switched to TPN versus 29% of controls. Postoperative infections: control 29% versus enteral 9%, p<0.05. Enteral failures: ATI >40. Conclusions: Enteral feeding feasible, reduces septic complications and costs, less well tolerated with ATI >40 if feeding rate advanced aggressively.
Moore FA (7)	1989	I	59 evaluable patients with ATI >15 and <40 prospectively randomized to TPN or jejunal feedings starting 12 hours postoperatively and advanced to goal rate by 72 hours. Major infectious complications 3% with enteral versus 20% with TPN, p<0.03. Conclusions: Enteral feedings are well tolerated and reduce serious infectious complications.
Kudsk (9)	1992	I	96 evaluable patients with ATI ≥15 prospectively randomized to enteral feeding started 24 hours postoperatively or TPN started 22.9 hours postoperatively and advanced as tolerated. Two patients failed enteral feeding; TPN patients received more nutrition over the hospital course. Significantly lower pneumonia and abscess rates with enteral feeding; most benefit in patients with more severe injuries (ATI ≥25, ISS ≥20). More diarrhea with enteral feeding. Conclusion: Nearly all patients received successful enteral feeding when advanced at slower rate <u>as tolerated</u> , even with high ATI, high ISS, and gut injury.
Eyer (2)	1993	I	38 blunt trauma victims randomized to early (target < 24 hours) or late (target > 72 hours) enteral feeding. No differences were noted between the groups at days 5 and 10 with regard to urinary nitrogen levels or serum levels of epinephrine, nor-epinephrine, dopamine, or cortisol. Furthermore, no outcome differences were noted with respect to ICU length of stay, ventilator days, organ system failure, specific infections or mortality. Despite attempt to initiate feedings within 24 hours of injury, mean time from injury to feeding (early group) was 39 hours, perhaps not early enough to demonstrate a beneficial effect. Overall infectious morbidity was

First Author (Ref)	Year	Data Class	Conclusions
Moore FA (8)	1994	I	higher in the early group 96 evaluable patients with ATI 18-40 or ISS 16-45 randomized to supplemented diet or standard diet started within 24 hours and advanced to goal by 72 hours. Gastrointestinal intolerance of 22% in supplemented diets versus 30% in standard (overall 26%) requiring interruption or discontinuation in 13.5%. Fewer intra-abdominal abscesses and less organ failure with supplemented diet. One bowel necrosis possibly related. Conclusion: Patients with moderate degree of injury tolerated gastrointestinal feedings started within 24 hours of injury with rapid advancement.
Kudsk (10)	1996	I	35 high-risk patients with ATI >25 or ISS >20 included. If enteral access obtained at laparotomy, patients randomized to supplemented diet or isonitrogenous diet starting 1.63 and 1.97 days after operation, respectively, and advanced as tolerated. Third group without enteral access followed prospectively. Gastrointestinal symptoms (distension, diarrhea, or cramps) in 88% of enterally fed patients, requiring slowing of feedings in 45% of patients. Major infection rate highest in unfed group and lowest with supplemented diet. Conclusions: Increased intolerance in most severely injured patients; however, septic morbidity reduced compared with unfed group. "Early" is later as severity of injury increases.
Kompan (3)	1999	I	28 patients were randomized to early (<6 hours after shock resuscitation) or late (≥24 hours following resuscitation) gastric feeding, and parenteral nutrition was used to supplement nutrient needs. The early-fed group tolerated significantly greater volumes of enteral feeding by day 4 and reached 80% of their calculated nutrient goals by the end of the first week. The late-fed group only achieved 61% of their enteral goal by 1 week. Early patients had lower late (days 4-14) MOF scores compared with late patients. Intestinal permeability measured by the lactulose/mannitol ratio was greater in the late group compared with the normal controls. On day 2, lactulose/mannitol ratios correlated with late MOF scores and with liver failure. Day 4 lactulose/mannitol ratios correlated with ISS from time of injury to initiation of enteral feeding. Conclusion: Multiply-injured patients started on early intragastric feeding following resuscitation from shock are more rapidly advanced to nutrient goals than patients whose feedings are delayed for more than 24 hours. The early enteral feeding patients sustained much less late MOF and

First Author (Ref)	Year	Data Class	Conclusions
Moore EE (5)	1981	II	maintained normal gut integrity. 30 patients with two or more organs injured received jejunostomy feedings started 18 hours postoperatively. All patients advanced to 2.4 L/day at full strength within 72 hours but slowed in three patients. Conclusion: No evidence of pancreatic stimulation with pancreatic injuries.
Jones (6)	1989	II	123 patients (71 enterally fed with jejunostomy, 52 controls given TPN or IV fluids) followed for gastrointestinal symptoms. Feeding started 12 hours postoperatively. Gastrointestinal complaints in 50% of control patients and 83% of enterally-fed patients. Moderate to severe complaints in 12% of control versus 51% of enterally-fed. Risk factors for intolerance of enteral feedings: 1) ATTI >40 (45% symptomatic), 2) gunshot wounds (73% symptomatic), 3) gut injury (82% symptomatic). Nine patients converted to TPN. Conclusion: Advance enteral feedings slower in high-risk patients.
<p>ATTI, abdominal trauma index; IV, intravenous; TPN, total parenteral nutrition, NPO, nothing by mouth; ISS, injury severity score, ICU, intensive care unit; MOF, multiple organ failure</p>			

Early versus Delayed Enteral Feedings Evidentiary Tables

Table 2. Burns

First Author	Year	Data Class	Subject Type	Conclusions
Alexander (11)	1980	I	Children	22 children with burns >40% (with four early deaths) randomized to an enteral high-protein or standard-protein diet with IV-TPN supplementation and diet. 60% to 70% of intake successful via the gastrointestinal tract. Standard-protein diet group received 14% of caloric intake as IV-TPN versus 6% in high-protein group. Conclusions: Fewer bacteremic days, better immunologic and serum protein values, and better survival in high-protein group. The gastrointestinal tract usable in severely burned patients.
Gottschlich (12)	1990	I	Human	50 patients with burns >10% randomized to intragastric feeding via tube with standard diet (n=14, 38.3% TBSA burn, age 15.1 years), supplemented diet (n=17, 45.0% TBSA burn, age 21.3 years), or stress diet (n=19, 38.6% TBSA burn, age 21.3 years). Feedings started soon after burn (Group 1: 2.3 days; Group 2: 1.1 days; Group 3: 1.9 days post-admission). 3, 5 and 2 patients needed TPN supplementation in Group 1, Group 2, and Group 3, respectively. Diarrhea occurred in 40% of patients overall. Significant reduction in LOS/percent body burn and wound infections in Group 2 with trend toward higher mortality in Group 3. Conclusion: Burned patients tolerated early intragastric feeding.
Saffle J(16)	1997	I	Human	50 patients (49 completed the study) randomized to enteral supplemented diet (n=25, age 35.0 years, TBSA burn 35.4%) or standard high protein diet (n=24, age 38 years, TBSA burn 34.7%) fed intraduodenally within 48 hours of burn and advanced by 25 mL every 4 hours to goal. Discontinuation or reduced rate rare due to distension, reflux, diarrhea. Conclusion: No differences in outcome but successful feeding rates high. Discussion – Majority of patients had feedings initiated within 12 hours of burn.
McArdle (14)	1984	II	Human	12 patients with TBSA burns of 40% to 70% (second and third degree) fed via intraduodenal tube with semi-elemental diet. 6/12 fed within 48

First Author	Year	Data Class	Subject Type	Conclusions
Chiarelli (13)	1990	II	Human adult	hours of burn. No distension or diarrhea and positive nitrogen balance at 9.8 days. Conclusion: Early enteral feeding well tolerated when started within 48 hours of burn. 20 patients with 25% to 60% TBSA burn started on intragastric feeding of blenderized diet 4.4 hours after burn (n=10, average burn 38 %) or 57.7 hours postburn (n=10, average burn 38.5%). Probability of survival 0.71 versus 0.74, respectively). Urinary catecholamine and glucagon levels lower in first 2 weeks in early fed group. Conclusion: Early intragastric feedings well tolerated after severe burn.
McDonald (17)	1991	III	Human	Retrospective study of 106 patients with $\geq 20\%$ TBSA burn started on intragastric bolus feedings within 6 hours of burn. Tolerance of feeding by day: day 1: 82%; day 2: 90%, day 3: 92%, day 4: 95%. Vomiting occurred in 15 % of patients. Patients age ≤ 12 years exceeded goal by day 3 and patients >12 years by day 4. Conclusion: Immediate intragastric enteral feeding safe and effective after major burns.
Raff (15)	1997	III	Human	Retrospective review of 55 intubated, ventilated patients (≥ 5 days) with TBSA burn of 44.2% (35.0 % third degree) and ABSI ≥ 7 (average 9.1) intragastrically fed with commercial, supplemented diet. Cisapride given via nasogastric tube TID and metoclopramide given IV TID. Diet started 15.3 hours post burn. 45 patients (81.8%) reached nutritional goal within 72 hours. Five (9.1%) tolerated but missed their goal, and five failed entirely. Only 4/48 patients who started feedings within 18 hours failed, while 6/7 who started after 18 hours failed with no significant difference in percent burn, ABSI, or age between success and failure groups. There was increased mortality with feeding failure. Conclusion: Early feeding is successful and should be started within 18 hours of burn.

IV, intravenous; TPN, total parenteral nutrition; TBSA, total body surface area; LOS, length of stay; ABSI, abbreviated burn severity index; TID, three times a day

Early versus Delayed Enteral Feedings Evidentiary Tables

Table 3. Head Injury

First Author	Year	Data Class	Conclusions
Rapp (18)	1983	I	38 patients with blunt/penetrating head injury randomized within 48 hours to TPN (n=20, age 29.2 years, GCS score 7.7) or intragastric feeding (n=18, age 34.9 years, GCS 7.2) with defined formula diet. Enteral caloric intake \leq 400 cal/day for first day, \leq 600 cal/day for first 10 days, and $<$ 900 cal/day for 14 days due to delayed gastric emptying. Eight of 18 gastrically fed patients died within 18 days compared with 0 TPN patients. Conclusion: Prolonged gastroparesis occurs with intragastric feeding post severe head injury.
Hadley (21)	1986	I	45 head-injured patients with GCS score \leq 10 randomized to intragastric (n=21, GCS score 5.9) feeding with standard commercial diet or TPN (n=24, GCS score 5.8). Enteral patients achieved positive caloric balance (140% of BMR) in 5% on day 2, 45% on day 3, 70% on day 4, between 70% and 85% by day 11. TPN achieved $>$ 80% by day 5 and 100% by day 9. Complication and infectious rates were similar. Conclusion: Use TPN only when gastrointestinal tract fails to work. Editorial: Gastroparesis begins to resolve on day 3 to 4. Don't wait for nasogastric drainage to drop or bowel sounds to occur.
Young (19)	1987	I	51 evaluable of 58 consented patients with GCS score 4-10 after blunt or penetrating head wounds randomized to TPN (n=23, age 30.3 years, GCS score 7.0) or intragastric feedings (n=38, age 34.0 years, GCS score 6.5) after bowel sounds return and nasogastric drainage dropped below 100 cc. Enteral patients received $<$ 500 cal/day for days 1-2 (versus 1221 kcal in TPN group), $<$ 800 cal/day for days 3-5 (versus 2367 kcal TPN group), $<$ 1500 cal/day for days 6-8 (versus 2350 kcal in TPN group) due to gastroparesis. Infectious complications were the same, and neurologic outcomes were similar at 1 year. Conclusion: Prolonged gastroparesis occurs after severe head injury.
Graham (22)	1989	I	22 patients with blunt/penetrating wounds and GCS score $<$ 10 randomized (by admission day) to nasojejunal feeding started at goal rate by 36 hours (age 25.5 years, GCS score 5.1) or intragastric feedings after day 3 if gastrointestinal function returned (age 27.8 years, GCS score 7.1). Caloric intake matched measured needs by day 3 with jejunal tube and approached 75% of needs on day 5-7. With intragastric

First Author	Year	Data Class	Conclusions
			feedings, significantly fewer bacterial infections (bronchitis: 3-4 plus WBC in sputum with positive cultures) than with jejunal feedings. Conclusions: Goal rates achieved faster with small bowel access. Gastric residuals limit intragastric feeding rate. No change in metabolic rate by indirect calorimetry.
Borzotta (23)	1994	I	48 evaluable, head-injured patients (GCS score \leq 8) randomized to TPN (n=21, age 28.9 years, ISS 33.4, GCS score 5.4) or enteral feeding via surgically placed jejunostomies (n=27, age 26.2 years, ISS 32.5, GCS score 5.2) and started within 72 hours of injury. All TPN patients had initial attempts with intragastric feeding (and presumably failed). TPN transition to intragastric feedings started on day 5. Diarrhea was more common in TPN patients. High rate of nasogastric tube dislodgement. Enteral delivered calories equaled 90.5% of measured resting expenditure by indirect calorimetry by day 3. Conclusion: With direct small bowel access, nearly achieved calculated goal by day 3 (and subsequently over) with little intolerance.
Norton (20)	1988	II	23 patients with blunt/penetrating head injury and GCS score 4-10 (average 6.6) followed for enteral tolerance. Feedings started when drainage $<$ 200 cc/day and bowel sounds present. Seven patients tolerated feedings within 7 days, 4 between 7 and 10 days, and 12 never tolerated feeds with trend toward greater intolerance with lower GCS. Tolerance did not correlate with bowel sounds. Conclusion: Gastroparesis occurs in most patients with severe head injury.
Taylor (24)	1999	II	82 patients receiving the same tube feeding were randomized to either intestinal feeding using a pH-directed tube and started at goal rate or to intragastric feeding at 15 cc/hour with gradual advancement as tolerated. Patients receiving the intestinal feeding advanced to their goal rate significantly faster than patients fed intragastrically. By the fourth post-injury day, these patients received $>$ 70% of their nutrient requirements (compared with 40% in the intragastrically-fed group) and by day 6 received $>$ 90% of their calculated requirements (compared with 55% in the intragastrically-fed group). Patients were similar with respect to GCS score, APACHE II score, CT scan results, and age. Their neurologic outcomes at 6 months were similar with a trend toward better 3-month outcomes in the group fed into the intestine. Infectious morbidity was significantly less in the intestinal-fed group.
Yanagawa (25)	2000	III	Review of 12 randomized, controlled trials with regard to timing or route of nutritional support following acute traumatic brain injury. Authors conclude that

First Author	Year	Data Class	Conclusions
			<p>early feeding may be associated with fewer infections with a trend toward improved survival and long-term disability. There was a trend toward better outcomes with parenteral nutrition (compared with enteral), but this observation may be related, in part, to the delay in starting enteral feedings due to associated gastric ileus. Overall the quality of the trials was poor, and the authors recommend larger trials with more relevant clinical endpoints.</p>
<p>TPN, total parenteral nutrition; GCS, Glasgow Coma Scale; BMR, basal metabolic rate; WBC, white blood cell;</p>			

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, non-comparative 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, early gastric feeding, is feasible, and clinical outcome is equivalent to patients fed into the duodenum. For this reason 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 due to gastric retention or gastroesophageal reflux should receive enteral feedings into the jejunum.

IV. SCIENTIFIC FOUNDATION

Since Moore and Jones¹ and Adams and colleagues² 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 following 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 which 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) following 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 non-trauma 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 (PEG) has recently been compared with percutaneous endoscopic gastrojejunostomy (PEGJ) in a consecutive group of severely injured patients, finding more rapid attainment of feeding goals in the PEGJ 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 following severe injury is intuitively apparent, especially in patients who cannot resume oral intake within a few days following 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 following 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.

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Table 1. Site of Enteral Support: Gastric versus Jejunal: The Brain-Injured Patient

First Author	Year	Data Class	Injury Type	Conclusions
Rapp (3)	1983	II	CNS injury	20 brain-injured patients randomized to early TPN, 18 randomized to delayed gastric feedings. GCS scores were similar in the two groups, but eight enterally-fed patients died within 18 days of injury, while none of the TPN patients died in the same time span. TPN patients had more positive nitrogen balance, higher serum albumin levels, and higher total lymphocyte counts than enterally-fed patients.
Young (4)	1987	II	CNS injury	51 brain-injured patients with GCS score 4-10 were randomized to TPN or enteral nutrition. TPN patients had higher mean intake of nitrogen and calories, but there were no differences in rates of pneumonia, urinary infections, septic shock, or all infections. Anergy screens, lymphocyte counts, and serum albumin levels were not different between the two groups. TPN patients had greater initial improvement in GCS scores and more favorable outcomes at 3 months, but outcome differences at 6 months and 1 year were not significant.
Borzotta (10)	1994	II	CNS injury	48 patients with severe brain injury were randomized to early TPN (n=21) or jejunal feeding (n=27). Measured energy expenditure and nitrogen excretion were similar in the two groups. Both routes of nutrition were equally effective in meeting nutritional goals, and infections were equal in frequency in the two groups.
Clifton (9)	1985	III	CNS injury	20 brain-injured patients were randomized to enteral feeding with either 14% or 22% of calories as protein. Those fed with higher protein formula had improved nitrogen retention, but nitrogen equilibrium was rarely achieved in either group.
Hadley (21)	1986	III	CNS injury	45 brain-injured patients randomized to TPN or gastric feedings. TPN patients had greater daily nitrogen intake and greater daily nitrogen losses than gastric-fed patients. There were no differences in maintenance of serum albumin levels, weight loss, infection rates, nitrogen balance, or mortality.
Norton (5)	1988	III	CNS injury	23 patients with acute brain injury and GCS scores 4-10 were fed enterally.

First Author	Year	Data Class	Injury Type	Conclusions
				Tolerance of feeding was inversely related to increased intracranial pressure and to severity of brain injury (low GCS scores).
Ott (6)	1991	III	CNS injury	12 patients with brain injury and GCS scores 4-10 were evaluated with liquid gastric-emptying scans. These showed delayed gastric emptying in the first week after injury and rapid emptying by the third week. All patients tolerated full-rate feedings by post-injury day 16 except two patients with persistent delayed gastric emptying.
Saxe (8)	1994	III	CNS injury	16 patients with acute brain injury and GCS score <12 underwent esophageal manometry within 72 hours of admission, and five patients had repeat studies 1 week after injury. All had minimal or no gastric-to-esophageal pressure differential initially, and 4/5 had normal differential at 1 week. Aspiration rate was not studied.
Spain (18)	1995	III	CNS trauma	Retrospective review of 74 patients with brain injury who received nasogastric tubes. They remained intragastric in 42 and were transpyloric in 32 patients. There were no differences in days to full feeding, ventilator days, ICU-LOS, incidence of pneumonia, or incidence of aspiration.
Kao (7)	1998	III	CNS injury	Gastric emptying of liquids was prolonged in 35 patients with moderate-to-severe brain injury, especially in females, older patients, and patients with lower GCS scores.
Klodell (11)	2000	III	CNS injury	118 head-injured patients were started on gastric feedings at an average of 3.6 days post-injury. 80% were fed via a PEG tube, while 20% via small-bore nasogastric tube. All patients received prokinetic agents initially. Overall, 97% of patients tolerated gastric feedings, and only two of 118 patients required conversion to jejunostomy feedings. The incidence of aspiration was 4%.
TPN, total parenteral nutrition; GCS, Glasgow Coma Scale; PEG, percutaneous endoscopic gastrostomy				

Table 2. Site of Enteral Support: Gastric versus Jejunal Evidentiary Tables: Non-CNS Injury

First Author	Year	Data Class	Injury Type	Conclusions
Korbeek (15)	1999	I	ISS >16	Prospective, randomized (not blinded) study of 80 patients. Forty-three received gastric feedings, and 37 received duodenal feedings via a fluoroscopically-placed nasoduodenal tube. Patient groups were similar with respect to injury severity, age, gender. APACHE II scores, narcotic/paralytic use, and energy requirements. There was no difference in ICU or hospital LOS, ventilator days, overall morbidity, or mortality. The incidence of pneumonia was 42% in the gastric group and 27% in the duodenal group, not statistically significant; however, this may represent a type II statistical error. Patients in the duodenal group tolerated full-strength feedings an average 10 hours earlier than the gastric group.
Montecalvo (20)	1992	II	Non-trauma	38 selected medical and surgical ICU patients randomized to gastric (n=19) or jejunal (n=19) feeding. Patients fed in the jejunum received a higher proportion of their daily goal caloric intake and had a greater increase in serum prealbumin. Although the pneumonia incidence was lower in the jejunal (n=0) than in gastric-fed patients (n=2), this difference was not significant.
Strong (19)	1992	II	Non-trauma	33 patients randomized to gastric (n=17) or postpyloric (n=16) feedings. Pulmonary aspiration occurred in 31% of the gastric-fed patients compared with 40% of the postpyloric-fed patients.
Burtch (12)	1987	III	Non-trauma	Retrospective comparison of complications in 56 patients with surgical gastrostomy and surgical jejunostomy. Nine of 26 (35%) patients with gastrostomy had pulmonary aspiration, which was fatal in two patients. Only 2/30 (7%) patients with jejunostomy had aspiration (both nonfatal). Overall survival at 1 year was 4% and 10%, respectively.
Ho (13)	1988	III	Non-trauma	Retrospective review of 133 patients who underwent radiologically-placed percutaneous gastrojejunal catheters, compared with 100 patients who underwent surgical gastrostomy. Complication rate

First Author	Year	Data Class	Injury Type	Conclusions
				was 5.2% in the gastrojejunal catheter group, with no pulmonary aspiration, and a 7.5% 30-day mortality. Complications occurred in 33% of the gastrostomy patients, including eight episodes of postoperative aspiration. Mortality in the gastrostomy group was 12%.
Kadakia (17)	1992	III	Non-trauma	Retrospective review of 79 patients who underwent PEG or PEGJ (the latter procedure was chosen in six patients because of prior aspiration). Aspiration occurred in nine patients, including six of seven patients treated with jejunostomy.
Mullan (16)	1992	III	Medical-surgical (10% trauma)	Retrospective review of 276 patients receiving enteral nutrition. Only 12 (4.3%) episodes of aspiration occurred, and there was no difference in the risk of aspiration between nasogastric, gastrostomy, or jejunostomy tubes.
Fox (22)	1995	III	Non-trauma	Retrospective study of 155 medical/surgical patients. Four of 69 (5.8%) gastrostomy patients had aspiration pneumonia (respiratory symptoms, leukocytosis, and an infiltrate on chest radiograph), compared with two of 86 (2.3%; not significant) jejunostomy patients.
Adams (14)	2000	III	Trauma	Prospective, non-randomized study of 89 trauma patients fed by either PEG or PEGJ. Although the latter group reached feeding goals earlier (80% at goal rate by day 3 versus 65% of PEG patients; 93% versus 79% by day 15, respectively), there were no differences in complications between the groups. The only complications tracked were pneumonia, ileus, and sepsis. There were no differences in ventilator days or hospital LOS.
ICU, intensive care unit; LOS, length of stay; PEG, percutaneous endoscopic gastrostomy; PEGJ, percutaneous endoscopic gastro-jejunostomy.				

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, non-comparative 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 1

There appears to be no advantage to the routine use of calorimetry to determine the caloric requirements of burn patients.

B. Level II

1. For moderately to severely injured patients (ISS 25-30), energy requirements are estimated to be 25-30 total kcal/kg/day or 120% to 140% of predicted BEE (per Harris-Benedict equation).
2. There appears to be no consistent relationship between ISS and measured resting energy expenditure (MREE) in trauma patients.
3. For patients with severe head injury (GCS score <8), energy requirements may be met by replacing 140% of MREE (~30 total kcal/kg/day) in non-pharmacologically paralyzed patients and 100% of MREE (~25 kcal/kg/day) in paralyzed patients.

4. Within the first 2 weeks after spinal cord injury, nutritional support should be delivered at 20-22 total kcal/kg/day (55% to 90% of predicted BEE by Harris-Benedict equation) for quadriplegics and 22-24 total kcal/kg/day (80% to 90% of predicted BEE by Harris-Benedict equation) for paraplegics.
5. For patients with burns exceeding 20% to 30% TBSA, initial caloric requirements may be estimated by several available formulas.
6. The Curreri formula (25 kcal/kg + 40kcal/TBSA burn) overestimates caloric needs of the burn patient (as estimated by calorimetry) by 25% to 50%.
7. The Harris-Benedict formula underestimates the caloric needs of the burn patient (as estimated by calorimetry) by 25% to 50%.
8. In patients with burns exceeding 50% TBSA, TPN supplementation of enteral feedings to achieve Curreri-predicted caloric requirements is associated with higher mortality and aberrations in T-cell function.
9. Caloric requirements for major burns fluctuate during the hospital course but appear to follow a biphasic course with energy expenditure declining as the burn wound closes. Therefore, direct measurement of energy expenditure via calorimetry once or twice weekly may be of benefit in adjusting caloric support throughout the hospital course.
10. Intraoperative enteral feeding of the burn patient is safe and efficacious, leads to fewer interruptions in the enteral feeding regimen, and, therefore, more successful attainment of calorie and protein goals.
11. Approximately 1.25 grams of protein per kg body weight per day is appropriate for most injured patients.
12. Up to 2 grams of protein per kg body weight per day is appropriate for severely burned patients.
13. In the burn patient, energy as carbohydrate may be provided at a rate of up to 5 mg/kg/min (~25 kcal/kg/day); exceeding this limit may predispose patients to the metabolic complications associated with overfeeding. In the non-burn trauma patient, even this rate of carbohydrate delivery may be excessive.
14. Intravenous lipid or fat intake should be carefully monitored and maintained at <30 percent 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.
15. Proteins, fat, and carbohydrate requirements do not appear to vary significantly according to the route of administration, either enterally or parenterally.
16. Fat or carbohydrate requirements do not appear to vary significantly according to the type of injury, i.e., burned versus traumatically injured.

C. Level III

1. Provision of excess calories to trauma patients may induce hyperglycemia, excess CO₂ production, fluid/electrolyte abnormalities, lipogenesis, and hepatic steatosis.
2. Energy requirements for patients with less than 20% to 30% TBSA burns are similar to those of patients without cutaneous burns.
3. Protein requirements in burn patients and in those with severe CNS injuries may be significantly greater than anticipated, up to 2.2 grams/kg body weight per day. However, the ability to achieve positive nitrogen balance in a given patient varies according to the phase of injury. Provision of large protein loads to elderly patients or

to those with compromised hepatic, renal, or pulmonary function may lead to deleterious outcomes.

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 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, hypocaloric) on protein catabolism and nitrogen loss when protein administration was fixed at 1.7 g/kg/day.¹ Caloric needs were provided at 125% of measured resting energy expenditure (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/day for all patients on day 4 of the study. However, 80% (24/30) of the patients were sedated with fentanyl, and 7% (2/30) 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/day 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/day. 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/day (range, 21-32 kcal/kg/day), 33 kcal/kg/day (postabsorptive state [range, 25-41 kcal/kg/day]), 37 kcal/kg/day (while receiving parenteral nutrition [range, 29-46 kcal/kg/day]), 38-48 kcal/kg/day (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 post-injury week at 59 kcal/kg/day, compared with only 31 kcal/kg/day during the first post-injury 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 injury severity score (ISS), others⁴ have reported a relatively high correlation between ISS and MREE/kg ($r=0.84$).

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 HBEE.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 following spinal cord injury, metabolic rates 94% (range, 55% to 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/day) 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: (1) impaired glucose control, (2) suppression of chemotactic/phagocytic actions of monocytes due to hyperglycemia, (3) respiratory dysfunction from excessive CO₂ production, (4) lipogenesis, and (5) 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. Wilmore¹⁴ 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 9 patients, derived a formula, now bearing his name, relating energy expenditure to preburn weight and the percent 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 which include a factor for TBSA burned and those which do not. The majority of formulas in this latter category are based on calculations of basal energy expenditure (BEE) 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 colleagues¹⁷ 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%, while the

Curreri formula overestimated energy expenditure by 58%. Long and coworkers¹⁸ 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 employed 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%, while 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 1.5²⁰ 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 Xie²² and Allard²³ 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 which 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, Williamson¹⁶ 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 were 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 patients, recognizing that formulas may over-estimate 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 survey¹⁶ documents that most patients in North American burn centers are kept NPO 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 due to closure of the burn wound and other undetermined factors. Saffle and colleagues²⁷ 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 post-burn day and then decline thereafter but remain elevated at the time of discharge. This observation was confirmed by Cunningham²¹ 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 percent of burn wound remaining open and the measured energy expenditure. Even in the absence of a demonstrated relationship between the percent 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 and on protein, fat, and carbohydrate requirements in traumatically injured or burned patients to provide any Level One recommendations. One major problem is the difficulty 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 physiological and biochemical environment to his or her advantage through the administration of specific nutrients, growth factors, or other agents, often in pharmacological 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 based on 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 intakes that appear 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 CO₂ 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 administered⁵⁵⁻⁵⁷ 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. While 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 over-feeding.

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-blinded 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

macronutrients 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?

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Assessment of Energy and Substrate Requirements for the Trauma Patient

Table 1: Energy Requirements in Trauma Patients

First Author	Year	Data Class	Patient Type and Number (n)	Conclusion
Frankenfield (1)	1997	I	Blunt and penetrating trauma n = 30	Prospective, randomized study evaluating the effect of energy balance on nitrogen balance in multiple trauma patients (ISS>25). Achievement of energy balance (NPC or total) failed to decrease catabolic rate or nitrogen loss at a fixed protein intake of 1.7 g/kg/day.
Schneeweiss (2)	1992	I	Polytrauma n = 12	Prospective, randomized, cross-over study comparing fat-based versus CHO-based enteral nutrition in 12 critically-ill patients. Only 2/12 patients were trauma patients. Approximately 35% of enteral CHO was stored as glycogen, and 50% to 60% of energy needs were met by fat oxidation. MREE ~ 26 kcal/kg/day.
Lapichino (5)	1982	II	Trauma n = 19	Maximum protein sparing effect reached when caloric intake was equal to 130% MEE (~38-48 kcal/kg/day). Increased doses of insulin were used with TPN.
Paauw (6)	1984	II	Blunt trauma (n=8) Total patients n=119	Caloric intake of 25 kcal/kg/day(~ MREE) ~ 7% of patients were trauma
Dempsey (12)	1985	II	Head injury n = 10	Patients with severe head trauma without barbiturate therapy exhibit an average REE 26% above predicted by HBEE.
Kosanovich (62)	1985	II	Trauma (n=8) Surgery (n=11)	Prospective, nonrandomized observational study. Increased caloric intake from 27.8 to 34.2 kcal/kg/day on fixed protein of 1.27

First Author	Year	Data Class	Patient Type and Number (n)	Conclusion
				g/kg/day decreased the protein catabolic rate. Only 42% of patients were trauma patients.
Mollinger (63)	1985	II	Spinal cord injury n = 48	20% to 30% below REE for quadriplegics and 12% to 15% below REE for paraplegics; however, patients were 3.8 to 8.6 years from injury.
Clifton (11)	1986	II	Head injury n = 57	The authors recommend use of a nomogram to estimate REE at the bedside of comatose patients.
Swinamer (64)	1987	II	Critically Ill Patients n = 112 (52 trauma patients)	Mean MREE was 47% above predicted energy expenditure based on HBEE.
Kolpek (65)	1989	II	Spinal cord injury and head trauma n = 14	44% below BEE (22 kcal/kg/day) for spinal cord injury patients during the first week after injury versus 144% x BEE (35 kcal/kg/day) for head trauma patients during first week. Protein losses for both groups were between 1.3 and 1.4 g/kg/day
Shaw (9)	1989	II	Blunt trauma n = 43	The use of TPN in trauma patients results in an increase in glucose oxidation and decreased fat oxidation and attenuation of protein synthesis. Recommend regimen of 2000-2500 kcal/day and 1.7 g protein/kg/day.
Dickerson (66)	1990	II	Head trauma n = 6	Protein requirements are accentuated in excess of kcal needs in head-injured patients. UUN excretion of 16.5 g/day.
Jeevanandam (4)	1990	II	Blunt trauma n = 9	Prospective, nonrandomized observational study REE = 33.4 to 37.7 kcal/kg/day for trauma patients with mean ISS = 34. Daily protein losses ~ 1.34 g/kg/day. Also found traumatic injury increased rate of fat mobilization.
Sedlock (67)	1990	II	Paraplegics	~21kcal/kg/day for MREE of four paraplegics with a mean of 7.4

First Author	Year	Data Class	Patient Type and Number (n)	Conclusion
			n = 4	years post injury
Rodriguez (68)	1991	II	Spinal cord injury n = 30	Nonrandomized, prospective comparative trial. Nitrogen losses are obligatory in spinal cord injury patients. Recommend protein at 2 g/kg IBW/day due to losses.
Rodriguez (3)	1995	II	Multisystem trauma (no description of blunt vs penetrating) n = 35	Prospective, observational study. Demonstrated no correlation between ISS and MREE. Suggested correlation between predicted and MREE.
Klein (69)	1997	II	Trauma (no description of blunt vs penetrating) n = 8	Study which evaluated the quality of nutrition provided to trauma patients at risk for MODS. Endpoints included dietitian documentation, percent kcal/protein goals met based on HBEE.
Uehara (7)	1999	II	Trauma patients with ISS > 16 (median ISS=33.5) n = 24	Derived TEE in 12 trauma patients by measuring energy intake and changes in total body fat, protein, and glycogen. Authors noted a significant rise in TEE, which averaged 31 kcal/kg/day during the first week but peaked at 59 kcal/kg/day during the second week. Based on this, authors recommend multiplying the HBEE by factors of 1.4 and 2.5, respectively for the first two post-injury weeks.
Brain Trauma Foundation (10)	2000	III	Head injury (REVIEW)	Replace 140% of REE in non-paralyzed patients and 100% of REE in paralyzed patients receiving enteral or parenteral nutrition containing at least 15% of kcal as protein by the day 7 post-injury.

ISS, Injury Severity Score; NPC, non-protein calories; CHO, carbohydrate; MREE, measured resting energy expenditure; REE, resting energy expenditure; TPN, total parenteral nutrition; HBEE, Harris-Benedict energy equation; BEE, basal energy expenditure; UUN, urinary urea nitrogen; MODS, multiple organ dysfunction syndrome; TEE, total energy expenditure; IBW, ideal body weight

Assessment of Energy and Substrate Requirements for the Trauma Patient

Table 2. Energy Requirements in Burn Patients

First Author	Year	Data Class	Conclusions
Ruten (28)	1986	I	Prospective, randomized study of 13 patients with burns >45% TBSA. One group had burn excised within 72 hours and covered with autograft or allograft. Second group treated with hydrotherapy and dressings. No significant difference in REE at any time up to 30 days post-burn but trend toward decreased REE with excision. Small number of patients, and groups were not comparable.
Herndon (25)	1989	I	Prospective, randomized study of 39 patients with >50% TBSA burns. Sixteen patients received intravenous supplementation of enteral nutrition to achieve Currier formula-predicted requirements. Supplemented group had significantly higher mortality and greater depressions in T-helper/suppressor ratios. Patient groups questionably comparable.
Saffle (24)	1990	I	Prospective, randomized study of 49 patients with 25% to 79% TBSA burns. Patients received feedings based on Currier formula or on indirect calorimetry. Currier-based caloric goals exceeded MEE by 43%. Caloric goals for calorimetry patients were MEE X 1.2 (activity factor). Caloric intakes were the same for both groups. No differences in outcomes or complications.
Jenkins (26)	1994	I	Prospective, randomized study of 80 patients with >10% TBSA burns. 40 patients fed peri-operatively; remainder had feedings held pre-, intra- and immediately postoperatively. No aspiration occurred in either group. Same LOS, mortality, and percent pneumonia. Unfed group had significant caloric deficit, increased incidence of wound infection, and required more albumin supplementation.
Currier (15)	1974	II	Prospective study of nine patients with TBSA burn between 40% and 73%. Used regression analysis to determine equation for caloric requirements using pre-burn weight, weight at 20 days post-burn, and actual caloric intake over the 20-day period. Formula derived: Caloric

First Author	Year	Data Class	Conclusions
			intake = 25 kcal/kg + 40 kcal/percent burn (Curreiri formula).
Wilmore (14)	1974	II	Classic paper relating increased burn wound size to increased energy expenditure. Prospective study of 20 patients with 7% to 84% TBSA burns and four unburned control patients. Noted hypermetabolism to be modified by ambient temperature and infection and to be mediated by catecholamines. Increase in energy expenditure is maximal with ~60% TBSA burn.
Bartlett (70)	1977	II	Prospective study of indirect calorimetry in 15 patients with 20% to 70% TBSA burns. Indirect calorimetry performed once or twice daily until burn wound coverage. Oxygen consumption and caloric expenditure was 1.5 to 2 times normal and was consistent hour-to-hour and day-to-day. MEE correlated best with the extent of full thickness burn.
Long (18)	1979	II	Measured energy expenditure in 39 sepsis/trauma/burn patients and 20 normal volunteers. Energy expenditure of burn patients exceeded that predicted by the HBEE equation by 132%. Developed equation: Caloric expenditure = HBEE X stress factor X activity factor. Values for stress and activity factors are given and are still in use today.
Saffle (27)	1985	II	Prospective study of indirect calorimetry in 29 patients with 3% to 80% TBSA burns. Actual MEE was only 76% of Curreiri-predicted requirements and was 1.47 times the Harris-Benedict-predicted requirement. Neither formula addresses biphasic character of actual MEE, which rises from admission through day 10-20, then declines but still remains elevated at discharge.
Turner (17)	1985	II	Prospective study of 35 patients with 10% to 75% second/third degree TBSA burns. Calculated energy expenditure predicted by the HBEE underestimated actual energy expenditure by 23%. Curreiri-derived energy requirements overestimated actual energy expenditure by 58%. In patients with TBSA >20%, HBEE was a more accurate predictor of actual energy expenditure.
Ireton (20)	1986	II	Prospective study of indirect calorimetry in 17 patients with 26% to 79% TBSA burns. Each patient had indirect calorimetry only once between post-burn day 2 and 26. Actual MEE best estimated by HBEE X 1.5. Curreiri formula overestimated MEE by a factor of 1.53, and HBEE underestimated MEE by 0.72. Mean caloric intake was only 81% of Curreiri formula,

First Author	Year	Data Class	Conclusions
			indicating difficulties attaining this goal.
Iretton-Jones (29)	1987	II	Prospective study of 20 patients with 31% to 74% second/third degree TBSA burns. Serial MEE and UUN excretion determined as wounds were reduced to <15% TBSA with healing and grafting. No correlation between percent open wound and MEE or UUN excretion. Also poor correlation between MEE and caloric requirement as predicted by Currier formula, even modified for reduced burn size.
Schane (19)	1987	II	Prospective study of 21 patients with 21% to 81% TBSA burns. Currier-formula-derived energy requirements overestimated actual MEE by 25% to 36%. Harris-Benedict predictions modified by stress and activity factors overestimated actual MEE by 32% to 39%. CEE and HBEE were good estimates of maximal MEE. Serial determinations of MEE are recommended.
Allard (71)	1988	II	Prospective study of indirect calorimetry in 23 patients with 7% to 90% TBSA burns. Currier formula overestimated MEE by 52%, and HBEE underestimated MEE by 29%. Energy expenditure increased from 6.5% to 34.1% above HBEE with feeding, suggesting that 25% of the caloric intake is used to increase MEE.
Cunningham (21)	1989	II	Prospective study of indirect calorimetry in 122 patients with 2% to 98% TBSA burns. Actual MEE best estimated by 2 X HBEE, not by Currier formula, BEE X activity factor X injury factor, or 2000 X TBSA. Confirms biphasic MEE noted by Saffle (27). TBSA burns <30% are associated with MEEs which are difficult to differentiate from normal variability in MEE.
Allard (23)	1990	II	Prospective study of 10 patients with 30% to 90% TBSA burns. Compares actual MEE with energy requirements predicted by the Currier and the Toronto formulas and twice the HBEE formula. Best approximation of actual MEE was Toronto formula, which uses TBSA burned, caloric intake of prior 24 hours, number of days post-burn, temperature, and HBEE.
Iretton-Jones (72)	1992	II	Developed equations predicting energy expenditures based on 200 patients with a variety of diagnoses including burns. Tested equation on 100 patients and observed a high correlation with MEE. Factors predictive of energy expenditure included age, sex, ventilator dependency, weight, presence of obesity, trauma, or burns. Burn size, however, was not a

First Author	Year	Data Class	Conclusions
			predictive factor.
Xie (22)	1993	II	Prospective study of 75 patients with 5% to 98% TBSA burns. Compares new formula [1000 X m ² (surface area) + 25 X %TBSA] to Curreri formula and to [2000 X m ²], [2 x BMR] and [20 X Kg + 70 X %TBSA]. Data suggest Chinese formula more closely approximates actual MEE.
Khorrarn-Sefat (31)	1999	II	Resting energy expenditure determined in 27 patients, daily for the first post-burn week and twice a week thereafter. Patients grouped according to predicted mortality (<20%, 20% to 80%, and >80%), and REE patterns in the three groups were compared. REE similar in all groups for first 20 days (~50% above HBEE). After this, REE declined in patients with predicted mortality <80%; however, it continued to be elevated up to the 45 th day in patients with predicted mortality >80%. Finding no clear relationship between REE and TBSA burn during the first 15 days post-burn, the authors conclude that the only reliable way to calculate the caloric needs of burn patients is to perform indirect calorimetry. If this is not feasible, a caloric load of no more than 50% to 60% above HBEE is recommended.
Schumer (73)	1979	III	Expert panel discussion of the metabolic effects of burn injury and some of the treatment strategies required to overcome them. Despite being written almost 20 years ago, this report is still quite applicable to current discussions of burn nutrition.
Williamson (16)	1989	III	Interesting study documenting actual burn nutrition practices at North American burn centers. Most centers use a Curreri-based formula to determine energy requirements. Centers that use metabolic carts do so only occasionally or for research purposes. Most centers keep patients NPO at least 6 to 8 hours before surgery.
Mancusi-Ungaro (74)	1992	III	Retrospective study of 12 patients with 7% to 82.5% TBSA burns. Measured caloric balance (calories consumed minus calories expended as determined by weekly calorimetry). Positive caloric balance correlated with good patient and nutritional outcomes and was easier to determine than nitrogen balance. Caloric expenditure did not correlate with burn size.
Waymack (30)	1992	III	Recommends weekly or preferentially twice-weekly measurement of resting metabolic

First Author	Year	Data Class	Conclusions
			energy expenditures using indirect calorimetry for patients with severe burns. TBSA, total body surface area; REE, resting energy expenditure; MEE, measured energy expenditure; LOS, length of stay; HBEE, Harris-Benedict energy equation; UUN, urinary urea nitrogen; CEE, Currier formula derived energy requirements; BEE, basal energy expenditure, BMR, basal metabolic rate; NPO, nothing by mouth

Assessment of Energy and Substrate Requirements for the Trauma Patient

Table 3. Macronutrient Requirements in Trauma And Burn Patients

First Author	Year	Data Class	Patient Type and Number (n)	Conclusion
Moore (42)	1986	I	ATI >15 N = 75	Protein intake estimated from body weights was 1.5 - 2.0 g/kg body weight/day
Hausmann (59)	1990	I	Polytrauma N =20	Nandrolone decanoate improved nitrogen balance by reducing nitrogen excretion and 3-methylhistidine and renal amino acid losses.
Kuhl (75)	1990	I	Polytrauma N =20	Nitrogen balance, IGF-1, fibronectin, and prealbumin levels measured in patients randomized to receive standard (21% branched chain amino acids) or enriched formula (46% branched chain amino acids). No differences in these variables were detected.
Cerra (58)	1991	I	Critically ill N = 20	Enteral diets supplemented with arginine, fish oil, and RNA stimulated <i>in vitro</i> lymphocyte proliferative responses and reduced 3-methyl histidine excretion but had no observed beneficial effects at follow-up 6 and 12 months.
Brown (56)	1994	I	Trauma N = 41	An enteral formula enriched with arginine, linolenic acid, beta carotene, and hydrolyzed protein led to a decreased incidence of infection and better nitrogen balance.
Petersen (45)	1994	I	Trauma	Protein given as 1.6 g/kg body weight/day. Recombinant human growth hormone increased the efficiency of protein synthesis.
Garrel (57)	1995	I	Burns	Three groups: control (35% fat), low (15% fat), low fat (15%)

First Author	Year	Data Class	Patient Type and Number (n)	Conclusion
			N =43	plus fish oil. Low fat nutritional support decreases infectious morbidity and LOS. Fat composition did not matter.
Jeevanadann (60)	1995	I	Trauma, ISS = 31 N =20	Recombinant human growth hormone plus TPN in the period immediately after traumatic injury improves nitrogen retention (less negative) and normalizes plasma amino acid levels.
Jeevanadann (48)	1995	I	Polytrauma N =10	Amino acids as 20% of energy needs, CHO as 50%, and lipids as 30%. A medium-chain triglyceride/long-chain triglyceride mixture may be better for trauma patients because the formula allows more rapid and efficient fuel use.
Jeevanadann (61)	1996	I	Trauma, ISS = 31 N = 20	Less negative nitrogen balance, increased whole-body protein synthesis, increased efficiency of protein synthesis, increased plasma glucose levels, and enhanced lipolysis in patients treated with recombinant human growth hormone.
Battistella (54)	1997	I	Polytrauma N = 57	Patients receiving TPN, who received the same amino acid and CHO dose, randomized to receive standard fat emulsion or to have fat withheld for 10 days. IV fat increased the susceptibility to infection, prolonged pulmonary dysfunction, and delayed recovery (question if secondary to underfeeding or fat).
Frankenfield (1)	1997	I	Trauma, excluding burns, spinal cord injuries, and isolated brain injuries N =30	Randomized, prospective study of patients to three groups: 1) CHO + lipid = MEE; 2) CHO, lipid, + protein = MEE; and 3) CHO + lipid = 50% of MEE. Protein = 1.7 g/kg body weight/day. Achieving energy balance did not decrease the catabolic rate or nitrogen loss.
Bernier (53)	1998	I	Burns > 20% TBSA; n = 37	Low-fat feeding with or without fish oil did not change IL-6 production.

First Author	Year	Data Class	Patient Type and Number (n)	Conclusion
Lapichino (5)	1982	II	Trauma N =19	Caloric intake of 130% of energy needs provided maximal protein sparing effect. Amino acids should be provided as 20% of energy requirements.
Kagan (51)	1982	II	Burns: 1%-10%, 11%-30% and 31%-60% TBSA n = 18	Caloric:nitrogen ratios of 150:1 may not provide adequate nitrogen to achieve equilibrium.
Matsuda (52)	1983	II	Burns n = 52	Caloric:nitrogen ratios of 150:1 OK for patients with BSA less than 10%. Patients with > 10% wounds need ratios of approximately 100:1.
Nordenstrom (34)	1983	II	Mixture of trauma and septic patients n = 23	Nitrogen sparing effects of lipid-and glucose-based systems are similar. Factors other than nitrogen balance should be used to decide which system to use.
Wolfe (35)	1983	II	Burns (average 70% TBSA) n = 6	Protein intake was 1.4 to 2.2 g protein/kg body weight/day. With the higher dose, there was additional increase in protein synthesis, but nitrogen excretion was decreased.
Twyman (33)	1985	II	Head Injuries n = 21	Data indicate that protein requirements are higher in head-injured patients at approximately 2.2 g/kg body weight/day.
Cunningham (21)	1989	II	Burns n = 122	For burns exceeding 30% TBSA, 2 X the resting metabolic rate most closely approximated the measured energy expenditure. Cal:nitrogen ratio of 150:1 preferred.
Jeevanadam (39)	1990	II	Trauma n = 8	Prospective study suggesting that 0.35 g nitrogen or ~2.2 g protein/kg body weight/day required to minimize loss of lean body mass.
Larsson (46)	1990	II	Burns or fracture	Nitrogen requirements vary over time. 0.20 g nitrogen/kg body

First Author	Year	Data Class	Patient Type and Number (n)	Conclusion
			of >2 long bones n = 39	weight/day or 1.25 g protein/kg body weight/day is optimal.
Jeevanadam (47)	1992	II	Trauma, ISS 32±2 n = 18	Study suggests that intravenous glucose should be given at a rate that does not exceed the REE.
Eyer (43)	1993	II	Blunt trauma, ISS 10; n = 38	Purpose of this randomized controlled study was to evaluate metabolic responses to early enteral feeding (unaltered) but protein was set at 1.5 g/kg body weight/day.
Guenst (49)	1994	II	Mixed patient Population n = 140	Use indirect calorimetry to measure energy expenditure or give total calories up to 140% of the BEE with glucose infusions = 4 mg/kg body weight/minute. Fat can be given as 40% to 60% of calories.
Chuntrasakul (44)	1998	II	Trauma, burns and cancer (ISS 24, average % TBSA burned 48); n = 26	Goal of study was not to determine CHO, protein or fat requirements but energy provided as 35-50 kcal/kg body weight/day and protein at 1.5-2.5 g/kg body weight/day.
Homsy (32)	1983	III	Critically ill and marasmic patients (REVIEW)	30-40 kcal and 1.5 g protein/kg body weight/day recommended.
Alexander (55)	1990	III	Burns (REVIEW)	Authors suggest that optimal enteral diet provides 20% energy from whey, 2% from arginine, 0.5% from histidine and cysteine, with lipids as 15% of non-protein calories. Lipid should be 50% fish oil and 50% safflower oil. This diet is believed to improve outcome (decreased wound infections, hospital stays, and death).
Tredget (50)	1992	III	Burns (REVIEW)	CHOs are an important fuel source for burned patients. The theoretical maximum is 5-6 mg/kg body weight/minute.

First Author	Year	Data Class	Patient Type and Number (n)	Conclusion
Wolfe (37)	1997	III	Critically ill (REVIEW)	Review by leading researcher in the field suggests that carbohydrates should be the predominant source of non-protein calories.
Isibashi (38)	1998	III	Immediately post-trauma or severely septic patients (ISS 16); n = 23	Retrospective study that used very sophisticated techniques. 1.2 g protein/kg pre-illness weight is optimal amount.
DeBiasse (40)	1994	III	Critically ill including burns and trauma patients (REVIEW)	Authors suggest that 70% of energy should be provided as CHO, 30% or less as lipid, and 1.5 to 2 g protein/kg body weight/day (the latter for burn patients).
Wolfe (36)	1996	III	Critical ill including burns and trauma patients (REVIEW)	Non-protein energy should be provided largely as CHO. Protein should be set at 1.5 g/kg body weight/day.
Pomposelli (41)	1994	III	Critically III (REVIEW)	Protein should be provided between 1.5-2 g/kg body weight/day. Calories should be limited to the patient's energy expenditure.

ATI, abdominal trauma index; RNA, , ribonucleic acid; LOS, length of stay TPN, total parenteral nutrition, CHO, carbohydrate; ISS; Injury Severity Score; IV, intravenous; MEE, measured energy expenditure; IL-6, interleukin 6; TBSA, total body surface area; REE, resting energy expenditure; BEE, basal energy expenditure

E. Monitoring Nutritional Support in the Trauma Patient

I. STATEMENT OF THE PROBLEM

Previous sections of this guideline 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 under-feed 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 which occur in this patient population. Accordingly, nutritional monitoring tests which 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* guideline 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, non-comparative 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

1. No recommendations

B. Level II

1. In head-injured patients, serum pre-albumin levels appear to correlate well with nitrogen balance. Albumin and transferrin levels correlate poorly with nitrogen balance. Retinol binding protein also correlates well with nitrogen balance but lags behind pre-albumin.

2. In multi-trauma patients, serum pre-albumin levels appear to correlate well with nitrogen balance. Albumin levels correlate poorly with nitrogen balance.
3. In burn patients, there are insufficient data to make any recommendations regarding the correlation between serum levels of pre-albumin, retinol binding protein, or transferrin and nitrogen balance. However, serum levels of these proteins must be interpreted with caution as they are affected not only by nutritional state but also by other factors (age, burn wound size, post-burn day and nitrogen intake). Albumin levels correlate poorly with nitrogen balance.
4. Nitrogen balance calculation in burn patients may not be accurate due to inability to account for nitrogen losses via the burn wound.
5. When calculating nitrogen balance in burn patients, use of urinary urea nitrogen instead of total urinary nitrogen may result in overestimation of nitrogen balance.

C. Level III

1. Nitrogen balance is the gold standard for monitoring the appropriateness of a trauma patient's nutritional prescription.
2. Serial determinations of serum levels of acute phase reactants (C-reactive protein, fibrinogen, alpha-1-glycoprotein, etc.), along with constituent proteins (pre-albumin, 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, non-existent. Although a recommendation can be made for the relative superiority of pre-albumin 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 pre-albumin 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 assuring complete collection of nitrogenous waste (urine, feces, wound exudate, etc.) 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 Total Urea Nitrogen (TUN), can possibly lead to a significant overestimation in nitrogen balance in burn patients.³ Iapichino, in a series of multiply injured patients 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 intake⁴. Thus, nitrogen output, if properly determined, might not need to be repeated frequently, at least early on following trauma. Given the theoretical, as well as 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 guideline, 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 employed 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 (weight change, anthropometric determinations, etc.), body composition studies (determinations of body fat, lean body mass, total body water, etc.), urine analyses for metabolic byproducts (urea, creatinine, etc.), immunological tests (antibody production, delayed hypersensitivity skin tests, etc.), functional tests (handgrip strength, etc.), and serum chemistry analyses (albumin, pre-albumin, etc.).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, while 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 biological 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, pre-albumin, 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 below.^{2, 7-9}

	Half-Life	Body Pool Size	Levels Increased by:	Levels Decreased by:
ALB	20 days	large	dehydration, insulin, infection, anabolic steroids	CHF, edema, cirrhosis, renal failure, burns, over-hydration
PA	2 days	small	renal failure (minor impact)	cirrhosis, hepatitis, inflammation,

				stress
TFN	8-10 days	medium	iron deficiency, chronic blood loss, pregnancy, estrogens, hepatitis	renal failure, cirrhosis, cancer, aminoglycosides, tetracycline
RBP	12-24 hours	very small	renal failure	cirrhosis, stress, Vitamin A & zinc deficiency, hyperthyroidism
SMC	2-4 hours	minute	growth hormone, re-feeding	protein deprivation
FN	15 hours	small	-	shock, burns, infection,
ALB, albumin; PA, pre-albumin ; TFN, transferrin; RBP, retinal binding protein; SMC, somatomedin C; FN, fibronectin; CHF, congestive heart failure				

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. Secondly, 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 pre-albumin. Thus, it has been suggested that the increase in serum levels of the short-lived constitutive proteins (pre-albumin, 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 due primarily to its long half-life and its high exchange rate between the intravascular and extravascular fluid compartments, which is ten 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, pre-albumin 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 pre-albumin appeared to be affected not only by nutritional status but also by the extent of the burn injury; albumin and pre-albumin 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 pre-albumin, transferrin, and retinol binding protein, though reflective of nutritional status, also appeared to be affected by the extent of the burn injury, patient age, post burn day, and nitrogen intake. Serum albumin levels correlated poorly with nitrogen balance.¹³ Finally, the improved performance of pre-albumin 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, taken together, reveal a pattern of improved performance of pre-albumin 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 pre-albumin determinations, with some authors making these determinations on a daily basis, while others only on a weekly basis.

In addition to serum pre-albumin, other serum markers have been investigated as nutritional monitoring tools. In a relatively large study of 45 head-injured patients, only pre-albumin and retinol binding protein were found to correlate with nitrogen balance, with pre-albumin 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 balance¹⁶.

Several authors have questioned the monitoring capabilities of these serum proteins. Lown was unable to document an increase in transferrin or pre-albumin 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 pre-albumin 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 pre-albumin, transferrin, or 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 post-burn 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 due to 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 post-burn 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 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 while 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 based on the available scientific literature. Similarly, the use of indirect calorimetry as a monitoring tool for patients with thermal injury cannot be recommended based on 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 overestimations in nitrogen balance, particularly in burn patients. Serial determination of serum pre-albumin 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, due to 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.

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MONITORING NUTRITIONAL SUPPORT in the TRAUMA PATIENT

First Author	Year	Data Class	Injury Type	Number of Subjects	Conclusion
Nataloni (15)	1999	II	Head injury	45	Compared serum levels of albumin (ALB), pre-albumin (PA), retinol binding protein (RBP) and transferrin (TFN) with nitrogen balance (NB) in patients fed enterally, parenterally, or both. PA was found to be the most sensitive marker, with significant changes in levels seen as early as 3 days after initiating nutritional support. RBP was also sensitive but did not reliably show changes in levels until 7 days following initiation of nutritional support. No recommendations were provided regarding frequency of monitoring of these serum proteins.
Mancusi-Ungaro (5)	1992	III	Thermal injury	12	Correlated caloric balance (measured by indirect calorimetry [IC]) and NB measurements with nutritional outcomes. Concluded that caloric balance was superior to NB in monitoring response to nutritional support in burn patients. Authors perform IC weekly. Criteria for “successful” nutritional outcome are vague and questionable.
Konstantinides (3)	1992	II	Thermal injury	27	Compared two methods of determining urinary nitrogen content: Total Urinary Nitrogen [TUN] (determined by Kjeldahl’s method) and Urinary Urea Nitrogen [UUN] (usually assumed to be ~ 80% of total urinary nitrogen). Study revealed that UUN was actually ~ 65% of TUN, thereby possibly over estimating NB. Authors recommend measurement of TUN to determine NB in burn patients.
Boosalis (10)	1989	II	Thermal injury	20	Attempt to correlate serial measurements of ALB and PA with NB. Authors concluded that visceral proteins reflect severity of injury and prognosis, but not nutritional status. However, actual NB data were not provided. PA levels appear to be increasing at the time that authors state that positive NB was achieved, with increases in PA seen within 7 days of thermal injury. Serum ALB levels lagged significantly behind NB.
Boosalis (10)	1989	II	Head injury	27	Attempt to correlate serial measurements of ALB and PA with IC. Authors concluded that visceral proteins reflect severity of injury and prognosis but

First Author	Year	Data Class	Injury Type	Number of Subjects	Conclusion
					not nutritional status. However, although PA levels lag behind protein and caloric intake, they do appear to correlate well with NB, with increases in PA seen within 7 days of injury. Serum ALB levels lagged significantly behind NB.
Carlson (13)	1991	II	Thermal injury	10	Attempt to correlate serial measurements of ALB, PA, TFN and RBP with NB. No correlation was evident with ALB. Correlation with PA, TFN, and RBP, although statistically significant, was poor overall. Furthermore, the ability of PA, TFN, and RBP to predict even the <i>direction</i> of change in NB (positive, negative or neutral) was poor, with efficiencies of < 50%. Authors advise against serial measurement of visceral proteins in burn patients and instead recommend use of a formula incorporating percent total body surface area (TBSA) burn, post-burn day, age, and nitrogen intake.
Vehe (12)	1991	II	Multiple trauma	15	Serial measurement of ALB, PA and NB in enterally-fed trauma patients. NB (measured at days 7, 14, 21, and 28) did not show statistical increases until day 14, while ALB (measured at days 4, 7, 10, 14, 21, and 28) did not increase significantly until day 28. PA (measured at days 4, 7, 10, 14, 21, and 28) increased significantly at day 10.
Erstad (11)	1994	II	Post-operative, including trauma	16	A comparison of changes in ALB (measured weekly) and PA (measured twice weekly) levels in patients receiving total parenteral nutrition (TPN) postoperatively. Only 6 of the 16 patients were trauma patients. Significant increases were noted in PA levels after approximately one week, whereas no such increases were noted in ALB levels.
Retzner (19)	1992	II	Thermal injury	15	A comparison of two types of blood tests (serum protein levels or functional tests) as measured against NB. Serum protein levels measured included ALB, TFN, and PA, as well as carotene, retinol, ascorbic acid, and iron. Functional tests included enzymatic activity assays for thiamin, riboflavin and pyridoxine, and the zinc protoporphyrin/heme ratio, as a functional measure of iron status. All blood tests were measured only once during the study, on post-burn day 15, at which time, despite a positive NB, each of the serum protein levels listed above were below normal, while each of the functional

First Author	Year	Data Class	Injury Type	Number of Subjects	Conclusion
					tests suggested a normal nutritional status. Authors acknowledge that NB determinations may not have been accurate due to inability to measure nitrogen losses via the burn wound.
					Attempt to correlate serial measurements of ALB, PA, TFN, RBP, Complement C3, C-reactive protein, ribonuclease, and creatinine with NB in two groups of patients fed for 7 days with parenteral diets that differed only in the amount of nitrogen provided. Although NB was better in the high nitrogen group, no difference was noted between the two groups in any of the above serum levels. However, the sum of plasma levels of branch-chain amino acids and the sum of the essential amino acids, as well as the glycine/valine ratio were significantly different between the two groups and correlated with NB. It is important to note, however, that positive nitrogen balance was not achieved in either of the two groups.
Shenkin (16)	1980	II	Trauma (includes burns, but not head injury)	14	Attempt to correlate serial measurements of fibronectin (Fn) and somatomedin-C (SMC), with NB in patients receiving at least 7 days of enteral feeds. Significant correlations were found between Fn and NB, Fn and cumulative caloric intake, and between Fn and cumulative nitrogen intake. No significant correlations were noted between SMC and either cumulative caloric intake, cumulative nitrogen intake, or NB.
Buonpane (21)	1989	II	Multi-trauma	12	Twice weekly determinations of laboratory parameters and measurements of resting energy expenditure (REE) and calculation of respiratory quotient (RQ) were carried out in 29 patients receiving enteral and oral nutrition. While positive NB was achieved in all patients by post-burn day 14, great variations in REE were observed over the course of burn wound closure, in the entire patient group and also in individual patients, with daily fluctuations as large as 100%. Adjustments in nutritional support were made on the basis of RQ values, leading to increases in support in 9.2% of determinations and decreases in support in 24%. No attempts were made to correlate NB directly with RQ values. Serum ALB levels were not useful as a monitoring tool.
Saffle (28)	1985	II	Thermal injury	29	Descriptive analysis of a nutrition protocol using TFN and PA measurements
Lown (17)	1991	III	Thermal	6	

First Author	Year	Data Class	Injury Type	Number of Subjects	Conclusion
			injury		(weekly) and REE measurements (3 times per week). NB studies were not performed. Despite an average caloric intake of 80% of predicted needs (REE x 1.2), TFN and PA levels increased minimally over the 3-week study and appeared to more closely reflect burn wound size than nutritional status. Overall very small number of patients studied, with no clear evidence that patients were in positive nitrogen balance at the time of serum protein determination.
Mattox (22)	1988	II	Multi-trauma	12	Attempt to correlate serial measurements of Fn and SMC, with NB in patients receiving at least 7 days of enteral feedings supplemented with branched-chain amino acids. NB increased significantly from baseline by the 4 th day of enteral feeding, while both FN and SMC demonstrated statistically significant increases by day 7. NB and SMC levels continued to demonstrate statistically significant increases on days # 14 and 21, while FN levels did not. Significant correlations were observed between SMC and NB.
Brose (9)	1990	III	Thermal injury	10	A comparison of ALB and PA as markers of nutritional status in burn patients. ALB and PA levels were measured weekly and correlated with “percent nutritional requirements met”, as determined by various nutritional formulas. Although no statistical analysis was provided, PA increased and normalized more quickly than did ALB. However, both serum protein levels were affected by the extent of burn injury and were lower in patients with > 40% TBSA burns.
Clark (18)	1996	II	Multi-trauma	10	A comparison of serial measurements of Insulin-Like Growth Factor I (IGF-1), PA, TFN, and various acute phase proteins, with measurements of total body protein (TBP). Despite provision of adequate nutritional support (80% and 91% of energy needs for the first and second 5-day periods of the study, respectively), TBP levels <i>fell</i> significantly through study day 15. At the same time however, IGF-1, PA, and TFN levels showed significant <i>increases</i> throughout the study period. Authors conclude that IGF-1, PA, and TFN levels may be more related to reprioritization of hepatic protein synthesis and are therefore not useful markers of nutritional progress in multiply injured

First Author	Year	Data Class	Injury Type	Number of Subjects	Conclusion
Waxman (20)	1987	II	Thermal injury	29	<p>patients. No NB studies were performed (TBP used as a surrogate for NB), and calculation of TBP required several estimations and assumptions.</p> <p>An attempt to quantitate protein loss via burn wounds. Burn wound exudate was captured via occlusive sponges, then eluted, and the effluent analyzed for total protein, albumin, and globulin content. Protein losses via the burn wound decreased after the 3rd post-burn day and averaged 1.2 x TBSA (m²) x percent burn mg/day during the first post-burn week. Other factors affecting protein loss included dressing type and the use of topical anti-microbials and hydrotherapy.</p>
Bastow (14)	1983	II	Hip fracture	122	<p>A prospective randomized study of the impact of providing supplemental nighttime nasogastric feedings to malnourished elderly women with hip fractures. Supplemented group received an average of 26 days of supplemental feedings and demonstrated significant increases in weight, triceps skinfold thickness, and mid-arm circumference. Changes in serum ALB levels were seen only in severely malnourished patients but were significantly delayed relative to changes in PA levels. Significant changes in PA levels were noted almost immediately on initiation of supplemental feeding, approximately 6-7 days following injury. No NB studies were performed, and therefore it is not possible to determine how the additional 28 gm of protein per day impacted overall NB.</p>
Lapichino (4)	1984	III	Multi-trauma	22	<p>Retrospective analysis of the relationship between NB and nitrogen and energy intake in trauma and critically ill surgical patients receiving TPN. Throughout the 5 days of TPN, nitrogen output remained constant, while both nitrogen intake and NB increased. Regression analysis showed nitrogen intake to be the major determinant of NB, followed by energy intake corrected to predicted basal energy expenditure.</p>

ALB, albumin; PA, pre-albumin; RBP, retinol binding protein; TFN, transferring; NB, nitrogen balance; IC, indirect calorimetry; TUN, total urinary nitrogen; UUN, urinary urea nitrogen; TBSA, total body surface area; TPN, total parenteral nutrition; Fn, fibronectin; SMC, somatomedin C; REE, resting energy expenditure; RQ, respiratory quotient; IGF-1, insulin like growth factor; TBP, total body protein

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, non-comparative 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

1. 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 arginine and glutamine required to obtain this effect have not yet been determined. Whether an additional benefit is gained from further supplementation with omega-3 fatty acids, nucleotides, and trace elements is unclear.
2. No recommendations can be made at this time regarding the role of enhanced enteral formulations in patients with severe burns.

IV. SCIENTIFIC FOUNDATION

The concept of “immuno-nutrition”, 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 glutamine, arginine, nucleotides, and the omega-3 fatty acids.

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 non-essential 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), while 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 (ATP) and may also play a role as physiologic mediators (c-AMP). 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 reviews¹⁷⁻¹⁹ and the recently published consensus statement from the American Society for Parenteral and Enteral Nutrition²⁰ 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 if 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 immuno-nutrition 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 immuno-nutrition-in-trauma literature:

Lack of Uniformity in the Study Population: Of the 10 studies included in this review, only six focus specifically on trauma patients,^{11,21-25} while two 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 versus 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. On the

other hand, 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 comprising the enhanced diets. While most recent enhanced formulas contain arginine, glutamine, omega-3 fatty acids, and nucleotides, one study compares two formulas which 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. While 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 MSOF syndrome and ARDS 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 following admission to as late as 7 days, although 48 hours was the most frequently employed 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 > 2.5L 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. While most studies required a minimum of 5-7 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 time²¹ 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 days²² 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 ten 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. While patients received their enteral formulations for an average of about 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 ten prospective, randomized, controlled trials reviewed here, only six involved comparisons of isocaloric, isonitrogenous formulations.^{23-26,29-30} Two trials compare isocaloric but non-isonitrogenous diets,^{22,27} and the remaining two studies compare diets, which 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 non-isonitrogenous 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 different 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 LOS, 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. While 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 six of the ten 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 outcomes²³ 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 non-protein: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/day by day 6 of feeding) than the patients in the study by Kudsk (~18 kcal/kg/day). Micronutrient composition of the formulas also varied. While 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 *five-fold* 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 employed 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 gm/L versus ~ 1.4 gm/L; Kudsk: 0.65 gm/L versus 1.1 gm/L), and only Kudsk's enhanced formula contained a nucleotide supplementation at all (1.0 gm/L). Whether an additional nutritional impact can be ascribed to these two additives at these dosages is unclear, especially considering the 5- to 9-fold differences in glutamine and arginine concentrations in the two studies. Recognizing, therefore, the statistically significant improvement in outcomes reported by Kudsk, the statistically *in*significant 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.

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 non-comparable 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 employ 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.

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Standard Versus Enhanced Nutritional Support Evidentiary Table

First Author	Year	Data Class	Characteristics of Enhanced Formula	Conclusions
Gottschlich (26)	1990	I	ARG, ω-3 FAs, Zn, cysteine, histidine. Enhanced formula also contained less overall fat and more overall carbohydrate	Prospective, randomized, controlled trial of three isocaloric, isonitrogenous enteral diets in 50 burned patients (mean age 20 years; mean TBSA burn 41%). Diets were started early (not defined) and continued for an average of 27 days (range, 7-61 days). 20% of patients received TPN to supplement enteral diet. Enhanced group had fewer days on TPN, but this was statistically insignificant. Enhanced group experienced fewer burn wound infections, reduced hospital LOS, and a trend toward reduced pneumonia and overall infectious complications. Small numbers of patients (14, 17, 19) in the groups.
Brown (21)	1994	I	ARG, ω-3 FAs, beta-carotene, and hydrolyzed protein	Prospective, randomized, controlled trial of two <i>non-isocaloric, non-isonitrogenous</i> enteral diets in 37 trauma patients (mean ISS 31, mean APACHE II score 14). Numerous exclusion criteria for study participation. Diets were initiated within 7 days of injury, and continued for 5-10 days. Enhanced group experienced improved nitrogen balance and less pneumonia but no difference in LOS, ICU-LOS, or ventilator days. Patients receiving the enhanced diet were fed significantly earlier and received more calories but not protein, compared with the standard group. Small numbers of patients (18, 19) in the groups.
Moore (22)	1994	I	BCAAs, GLN, ARG, RNA, ω-3 FAs, Vitamin E, selenium and Zn. Enhanced formula contained > 7 times as much fat as the control diet.	Prospective, randomized, controlled trial (non-blinded) of two isocaloric, but <i>non-isonitrogenous</i> enteral diets in 98 trauma patients (mean ISS ~30; mean ATI ~20; mean GCS score 13.7). Many exclusion criteria for study participation. Diets were started within 24 hours of injury, and patients had to receive at least 72 hours of enteral feeding. Although the enhanced group received fewer days of enteral feeding (7.0 versus 8.2 days [p=0.007]), this group received much more protein compared with the standard group. After 7 days of feeding, enhanced group had fewer intra-abdominal abscesses, episodes of MOF, ventilator days, ICU days, and hospital days.
Bower (28)	1995	I	ARG, RNA, ω-3 FAs	A prospective, randomized, double-blind multicenter trial with 279 ICU patients (84% trauma patients). The two formulas were neither isocaloric nor isonitrogenous. Diets were started within 48 hours of injury, and patients had to receive at least 7 days of

First Author	Year	Data Class	Characteristics of Enhanced Formula	Conclusions
				<p>enteral feeding. Overall mortality in both groups was less than predicted but not significantly different between the two groups. Overall septic morbidity and LOS was also similar between the two groups. Significant differences were noted in LOS and in septic morbidity in three specific subpopulations; 1) 8 day shorter LOS in patients who received at least 5750 cc of enhanced formula over the first 7 days of feedings; 2) 10 day shorter LOS and significant reductions in overall septic morbidity and bacteremia in <i>septic</i> patients who received the enhanced formula compared with the standard formula; 3) 11.5 day reduction in LOS and significant reductions in overall septic morbidity in <i>septic</i> patients who received at least 5750 cc of enhanced formula over the first 7 days of feeding. Subgroup analysis is quite complicated and seems somewhat arbitrary.</p>
Kudsk (23)	1996	I	GLN, ARG, RNA, ω -3 FAs	<p>Prospective, randomized, blinded controlled trial of two isocaloric, isonitrogenous enteral diets in 33 trauma patients (mean ISS ~27, mean ATI ~34, mean GCS score ~14). Many exclusion criteria for study participation. All patients were started on their formulas within 48 hours of admission and received enteral feedings for an average of 9-10 days. Patients receiving enhanced feedings experienced fewer major infectious complications (including intra-abdominal abscess), reduced antibiotic use, and shorter hospital LOS. Small numbers of patients (16, 17) in the groups.</p>
Mendez (24)	1997	I	ARG, ω -3 FAs, selenium, chromium, molybdenum, taurine, carnitine	<p>Prospective, randomized, controlled trial of two isocaloric, isonitrogenous enteral diets in 43 trauma patients (mean ISS ~30; mean APACHE II ~15). Enteral formula was started within 3 days of hospital admission and was given for a minimum of 5 days. Overall mortality was similar between groups. The authors claim a trend toward <i>more</i> ARDS (increased incidence and severity), <i>higher</i> ventilator days, <i>longer</i> hospital LOS, and <i>greater</i> septic morbidity for the enhanced group, although no p-values are provided. Small numbers of patients (21, 22) in the groups.</p>
Saffe (27)	1997	I	Enhanced formula had much more ARG and RNA but less ω -3 FAs, compared with	<p>Prospective, randomized controlled trial of two isocaloric, but <i>not</i> isonitrogenous diets in 49 burn patients age 4 or older (mean TBSA burn 35%). Feedings were begun within 48 hours of injury, and continued until patients supported themselves with oral intake. No differences between groups with respect to morbidity, mortality, LOS, or ventilator days. However, the enhanced formulation contained no glutamine, and <i>less</i> total protein and</p>

First Author	Year	Data Class	Characteristics of Enhanced Formula	Conclusions
			control diet.	<i>less</i> ω-3 FAs compared with the standard formula.
Atkinson (29)	1998	I	ARG, RNA, ω-3 FAs	Prospective, randomized, controlled trial of two isocaloric, isonitrogenous enteral formulas in ICU patients (mean APACHE II ~19). Enteral support was started within 48 hours of ICU admission and continued throughout entire ICU stay. Of 390 patients randomized, 369 received some enteral feeding, but only 101 received >2.5L of enteral feeding within 72 hours of ICU admission (early enteral nutrition group). Of the 101 early enteral nutrition patients, those receiving the enhanced formula (50 patients) had fewer ventilator days, ICU LOS and hospital LOS, and SIRS days compared with those receiving the standard formula (52 patients). Only 13% of patients in this study were trauma patients (69% medical, 18% surgical).
Houdijk (25)	1998	I	GLN	Prospective, randomized, controlled trial of standard versus glutamine-supplemented enteral feedings in 72 trauma patients (mean ISS ~32; mean APACHE II~16; mean GCS score ~8.6). Feedings were isocaloric and isonitrogenous and were begun within 48 hours of injury. Only 60 patients received 5 or more days of feedings; the minimum duration believed necessary by the authors to realize a benefit from the glutamine supplementation. Within this 60 patient subset, the glutamine group had statistically fewer episodes of pneumonia, bacteremia, and overall sepsis, but no difference was reported with respect to ventilator days or overall LOS.
Weimann (30)	1998	I	ARG, RNA, ω-3 FAs	Prospective, randomized, double-blind controlled trial of two isocaloric and isonitrogenous enteral formulations in 29 trauma patients (mean ISS ~40). Feeding started within 2 days of injury and was continued until oral intake was adequate. TPN was provided as needed to achieve nutritional goals and accounted for the majority of caloric and protein intake for the first 5 days of nutritional support. Enhanced formula patients experienced fewer SIRS days and lower MSOF scores but no differences were noted in septic morbidity, mortality, hospital or ICU LOS, or ventilator days. Small numbers of patients (16, 13) in the groups.
ARG, arginine; ω-3 FAs, omega-3 fatty acids; Zn, zinc; TBSA, total body surface area; TPN, total parenteral nutrition; LOS, length of stay; ISS, Injury Severity Score; ICU, intensive care unit, BCAAs, branched chain amino acids; GLN, glutamine; RNA, ribonucleic acid; ATI, abdominal				

First Author	Year	Data Class	Characteristics of Enhanced Formula	Conclusions
trauma index; GCS, Glasgow Coma Scale; MOF, multiple organ failure; ARDS, acute respiratory distress syndrome; SIRS, systemic inflammatory response syndrome; MSOF, multi-system organ failure				

