Journal of Parenteral and Enteral Nutrition

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JPEN J Parenter Enteral Nutr 2010 34: 21
DOI: 10.1177/0148607109354900

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Journal of Parenteral and Enteral Nutrition
Volume 34 Number 1
January 2010 21-31
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10.1177/0148607109354900
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Nutrition in the Intensive Care Unit: Year in Review 2008–2009

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Financial disclosure: none declared.

The Year in Review is a new feature of *JPEN* that highlights some of the more notable clinical research articles published in the last year and the potential effect this new research may have on present practice. This narrative review focuses on the evolving role of nutrition in the intensive care unit (ICU). Literature reviewed was selected based on search engine results, conference presentations, and *JPEN* readership. Although our goal was to review a majority of research from the past year, some significant research may have been overlooked. Regardless, this review will provide another valuable resource of new and exciting research in the area of critical care nutrition therapy and the prospective impact of this research on current bedside practice.

Estimating Energy Requirements

Accurate determination of energy requirements in the hospitalized patient remains a challenge. Many predictive equations have been developed; however, their accuracy in malnourished, elderly, critically ill, and obese patients has been questioned. The most accurate method for determining energy needs in the critically ill patient population (both obese and nonobese) remains indirect calorimetry (IC). However, given the costs associated with IC, the majority of impatient settings continue to rely on predictive equations.

The increasing obesity epidemic is evident in the ICU patient population as well as the general population. The recently released joint A.S.P.E.N./Society of Critical Care Medicine (SCCM) guidelines recommend permissive underfeeding or hypocaloric feeding in the critically ill obese patient, with a protein provision in the range of ≥2.0–2.5 g/kg ideal body weight depending on the degree of obesity.[1] However, techniques to determine accurate baseline needs in the obese population on which to base an underfeeding regimen remain elusive.

Energy Expenditure

Anderegg et al[2] reported the accuracy of several prediction equations with various stress factors and variations (13 different methods) compared with measured energy expenditure in 36 obese adult inpatients. The researchers reported that the Harris-Benedict equation using adjusted body weight and a stress factor of 1.5 in critically ill patients or 1.2 for floor patients achieved the greatest percentage of predictions within 10% of measured energy expenditure. However, this prediction strategy was accurate (within 10% of measured expenditure) only 50% of the time, leading the researchers to conclude that none of the calorie prediction equations tested had consistent acceptable accuracy.[2]

In a study with similar methodology, Frankenfield et al[3] reported on a much larger population (202 patients) of critically ill adults. The investigators compared the results of a single IC study with 17 different methods of predicting energy expenditure. They reported that a modification of the Penn State equation was the most consistent accurate formula, with 67% of the predictions falling within 10% of measured energy expenditure.

Another group compared the ability of their own developed equation (the Faisy equation[4]) with one IC measurement to determine resting energy expenditure (REE) in 2 separate groups of mechanically ventilated ICU patients.[4,5] The Faisy equation is based on height, weight, minute ventilation, and body temperature. The authors compared their equation to the Harris-Benedict with stress factors, Swinamer, Fusco, and Ireton-Jones equations for critically ill patients. The Faisy equation had the highest correlation with IC with limits of agreement of –735 to 351 kcal/d. The authors caution the use of their equation in postoperative, trauma, or burn patients as it has not been validated in the subset populations.[5]

The clinical significance of these trials is unclear because of the limitations of the study designs. All of these studies used only one IC measurement per patient for

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Received for publication September 17, 2009; accepted for publication October 21, 2009.

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comparison to the predictive equations. Yet it is known the metabolic rate can have significant day-to-day and week-to-week variability in critically ill patients.[6,7] Reid[7] measured daily IC in 27 critically ill patients and revealed that mean day-to-day variability in energy expenditure was 31.7% (range, 7%-22%) in the first week of critical illness.[7] None of the predictive equations used in the study by Reid were consistently accurate because of the daily variability of energy expenditure. When enteral feeding rates were adjusted each day based on the daily IC, the actual mean cumulative error in calorie provision was 883 calories (range, –6702 to 4791), whereas the cumulative error in energy provision with the predictive equations ranged from 604 to 1556 kcal (range, –6203 to 5951).

Considering that the daily variation of a patient's energy expenditure can be considerable and that the actual provision of nutrition can have even greater variability, the benefit of a formula's ability to predict within 10% of a single IC study is unclear in both obese and nonobese critically ill patients. However, what is perhaps most pertinent is that no randomized study has investigated what level of feeding affects the outcome of the critically ill patient. There is a need for randomized studies to determine what level of feeding will result in the best patient outcome before a strong recommendation can be made favoring a particular method to measure or calculate energy needs in the critically ill patient.

Intensive Insulin Infusion in the ICU

Following publication of the landmark article by Van den Berghe in 2001[8] demonstrating a 3.4% absolute mortality reduction in a surgical ICU population with a target blood glucose (BG) range of 80–110 mg/dL, ICUs around the globe scrambled to institute intensive insulin therapy (IIT). A follow-up study by the same group did not demonstrate a mortality reduction in the intent-to-treat medical ICU population, although a reduction in morbidity was realized.[9] Of concern was the significant increase in hypoglycemia observed in the follow-up study.[9]

Since the completion of these landmark trials, several recent large randomized trials have been completed in attempt to answer unanswered questions surrounding glycemic control in differing ICU patient populations. Two large randomized, controlled multicenter trials, the GLUCONTROL and VISEP, in mixed ICUs comparing target ranges of 80–110 mg/dL vs 120–150 mg/dL were terminated prematurely because of the incidence of severe hypoglycemia in the study group with no concurrent improvement in survival.[10-12]

The NICE Sugar trial was completed in >6000 patients admitted to a mixed ICU setting.[13] Hypoglycemia was reported in 6.8% of the patients in the intensive control group (BG target 81–108 mg/dL) and 0.5% in the conventional group (BG target <180 mg/dL, $P < .001$). There was no significant difference between the 2 groups in regards to length of stay in the ICU or hospital, days on mechanical ventilation, or renal replacement therapy. The mortality rate in the intensive-control group (27.5%) was higher than the conventional group (24.9%) (95% CI, 1.02–1.28, $P = .02$).[13]

Data from the Australia New Zealand Intensive Care Society (ANZICS) patient database obtained from a cohort of 66,184 adult patients from 24 ICUs were analyzed to determine the relationship between early glycemic control and hospital mortality. A total of 132,368 BG values were evaluated. Hyperglycemia and early hypoglycemia were both independently associated with hospital mortality.[14]

A meta-analysis reviewing 26 randomized controlled trials compared IIT with conventional glucose management involving >13,500 ICU patients.[15] The NICE-Sugar data were included; however, the analysis reached publication prior to the availability of the final Glucontrol data. The authors found that surgical ICU patients appeared to benefit from intensive therapy, whereas patients in other ICU settings did not. Overall, IIT significantly increased the risk of hypoglycemia and presented no overall mortality benefit among critically ill patients. In agreement with this meta-analysis are the recently published Surviving Sepsis Guidelines and A.S.P.E.N./SCCM Nutrition Guidelines, which suggest a target blood glucose of <150 mg/dL for all ICU patients.[1,16,17]

Numerous protocols have been published to aid in safe implementation of insulin therapy with available ICU resources. One such protocol was trialed in patients receiving concurrent specialized nutrition support.[18] None of the 40 patients experienced extreme hypoglycemia (<40 mg/dL) while remaining in the target BG range of 70–149 mg/dL for an average of 20 hours per day. Protocols may be complex and labor intensive and not practical for all ICUs.[19] Successful implementation may depend on the acceptance and support of the nursing staff. Nurse-driven protocols with nursing input during implementation appear to be safe and effective with relatively low incidence of hypoglycemia.[20] Computerized protocols are also being tested. In a comparison of a paper protocol to a computerized protocol of >21,000 BG measurements; the computerized method was found to be superior with more time in BG range and less incidence of hypoglycemia.[21]

Another concept receiving attention is that of glucose variability. It has been hypothesized that glucose variability may have a stronger association with in-hospital mortality in critically ill patients than glucose level. As part of the review of the ANZICS data, early glucose variability was found to be associated with greater odds of adjusted ICU (1.5; 95% confidence interval [CI], 1.4–1.6) and hospital (1.4; 95% CI, 1.3–1.5) mortality when compared with hypoglycemia.[22]

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Enteral Feeding

Enteral nutrition (EN), unlike glycemic control, is not often considered a patient safety issue in the ICU. However, the newly published A.S.P.E.N. comprehensive EN practice recommendations illustrate that both water and enteral formula safety should be considered when administering EN to immunocompromised ICU patients.[23] In addition, the guidelines review ordering and labeling of EN, enteral formula regulation, enteral access, EN administration, medication administration and monitoring of EN administration.[23] These guidelines should drive policy and procedures surrounding EN in the hospital setting.

Nasoenteric Tube Placement

Given the increasing popularity of blind bedside or assisted nasoenteric tube placement, recent studies have focused on the risks and benefits of placement and feeding tube tip position. Inadvertent intrabronchial placement is perhaps the most common, and at times lethal, risk-associated with nasoenteric tube placement. In a study by Gatt and MacFie[24] in which a "semi-blind" placement technique was used in 43 patients, a laryngoscopy was used to confirm esophageal placement of tubes in the ventilated patients. Once this technique was adopted into practice, no inadvertent intrabronchial intubations occurred. If trained personnel and equipment are available to perform laryngoscopy in those patients at increased risk of intrabronchial intubation, this technique should be considered. Historical studies by de Aguilar-Nascimento and Kudsk[25] and Sorokin and Gottlieb[26] both reported inadvertent intrabronchial intubations (3.2% and 2.4%, respectively). The authors of the combined studies reported adverse outcomes of pneumothorax and 6 deaths related to these misplacements. Methods to guide feeding tube insertion and reduce the incidence of intrabronchial intubation deserve further study, but for patient safety, the continued gold standard requires radiographic confirmation of tube position prior to initiation of feeds. A CO_2 detector attached to the feeding tube has been used to guide enteral tube placement. Munera-Seeley et al[27] reported that 3.5% of all nasoenteric feeding tubes placed by an experienced tube placement team inadvertently entered the airway.[27] The investigators reported that the use of a colorimetric CO_2 detector significantly decreased airway placement of nasoenteric feeding tubes compared with blind placement.

The use of an electromagnetic (EM)-guided device has been reported to overcome bedside placement difficulties. Much of the adult data have been presented only in abstract form. A recent prospective cohort study in pediatric patients evaluated tube placement success in 107 patients (57 in the standard "blind" placement group and 50 in the EM-guided group).[28] Successful placement occurred 82% of the time in the EM-guided group and 38% in the standard group ($P < .0001$), combined with a decrease in average time to placement from 21 hours (standard) to 1.7 hours (EM-guided) ($P < .0001$).[28] In addition, given less use of personnel resources and repeat radiographs, a cost savings of $55.46 per EM-guided tube placement was realized. However, both techniques proved equally safe with no episodes of pneumothorax reported in either group.[28]

Another risk associated with a nasally placed feeding tube is the potential injury associated with unsupervised tube dislodgement. A prospective quality improvement study by Gunn et al[29] examined the impact of a nasal bridle in reducing accidental tube removal. The authors prospectively followed 90 tubes (50 taped and 40 bridled into position) until accidental removal, planned removal, or patient discharge. Significantly fewer tubes were accidently removed in the bridle group (10%) vs the taped group (36%; $P < .05$). These results are similar to a study completed by Seder and Janczyk[30] determining whether routine bridling of nasoenteric feeding tubes in ICU patients would yield a low-morbidity, cost-effective method to reduce tube dislodgments and need for frequent tube replacements. Data collected from 62 bridled patients were compared with data from 172 unbridled patients with a nasally placed tube to determine differences in tube dislodgement, nasal ulceration, and estimated cost. Tube dislodgments were significantly decreased (6.5% vs 32.6%, $P < .0001$) in the bridled patients. More nasal necrosis was noted with the use of a red rubber bridle technique; however, this difference was negated when the authors changed to the use of umbilical tape bridles. An estimated cost savings of $4038 over 3 months was reported.[30]

One benefit often associated with postpyloric feeding as opposed to prepyloric feeding in ICU patients is optimization of enteral feeding. Hsu et al[31] compared the benefits of nasoduodenal (ND) feedings vs nasogastric (NG) feedings in 121 medical ICU patients in a prospective randomized clinical study. The ND group received significantly more calories (1658 ± 118 vs 1426 ± 110 kcal/d, $P = .02$) and protein (67.9 ± 4.9 vs 58.8 ± 4.9 g/d, $P = .03$) than the NG group. In addition, the NG group had a significantly higher rate of vomiting (12.9% vs 1.7%, $P = .01$). Other clinical outcomes including length of stay, ventilatory days, and mortality were not significantly different between the groups.[31]

No medical procedure is without risk, and bedside placement of a nasoenteric feeding tube is no exception. At a time when the evidence regarding the risks vs benefits of enteral feeding is still evolving, it is a forgone conclusion that we should do everything we can to minimize the risks associated with enteral feeding tube placement. We should expect to see more research directed to this topic in the future.

Enteral Feeding Tolerance

One of the ongoing considerations of providing EN in the critically ill population is that feeding goals are frequently

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not achieved. Gastrointestinal (GI) intolerance and perception of GI intolerance are among the primary contributors to inadequate provision of EN.[32] Although there is little debate that critically ill patients frequently have delayed gastric emptying, the relevance of gastric residuals and the potential threshold at which they may become significant for complications continue to be investigated. A recent observational study by Metheny et al[33] in 206 critically ill patients confirmed previous work[34] that demonstrates no consistent relationship between gastric residual volumes and aspiration. In a study of 100 mixed medical-surgical ICU patients, Desachy et al[35] evaluated the safety and effectiveness of starting enteral feedings at goal flow rate to improve the adequacy of enteral feeding. EN was started within 24 hours after intubation, and patients were randomized to begin feedings with either full goal rate (25 kcal/kg with 1 kcal per milliliter of formula) or 25 mL/h with feeding rate progressed incrementally by 25mL/h each day. Starting NG EN at goal flow rate resulted in significantly improved nutrition delivery, significantly less cumulative calorie deficit, and no increase in adverse effects compared with starting EN at reduced rates and then advancing feeding rate incrementally. Although starting feedings at goal flow rate resulted in increased incidence of gastric residuals >300 mL, there was no significant difference in aspiration, regurgitation, or emesis between the groups.[35]

Chang et al[36] used refractometry to estimate gastric residual contents and volumes. This study and previous work with refractometry by these investigators demonstrate that endogenous secretions can be a significant contributor to gastric residual volumes and that a significant volume of gastric residuals can remain even when there is adequate gastric emptying of feeding formula.[36-38]

The use of prokinetic medications has been associated with improved delivery of enteral feedings, and several recent studies have evaluated the efficacy of prokinetic regimens. McLaren et al[39] reported that both intravenous metoclopramide (10 mg) and erythromycin (250 mg) given every 6 hours decreased gastric residual and allowed increased feeding rate but that erythromycin may be more effective at improving gastric emptying. Nguyen et al[40] reported that intravenous erythromycin (200 mg twice daily) was superior to intravenous metoclopramide (10 mg 4 times per day) as a prokinetic in the ICU but that the effectiveness of erythromycin was short-lived. A follow-up study by the same group demonstrated that a combination of intravenous erythromycin and metoclopramide was superior to erythromycin alone, with significantly greater successful feeding and more daily calories provided compared with the group receiving erythromycin alone.[41]

However, long-term efficacy of erythromycin is limited by tachyphylaxis because of downregulation of the motilin receptors, an effect that may develop within 3–7 days.[42] Similar to erythromycin, rapid tachyphylaxis occurs with studies reporting that after 7 days of use, only 25% of patients given metoclopramide were able to continue EN successfully.[40,43] Metoclopramide has been shown to be ineffective in head-injured patients and potentially harmful in patients at risk of raised intracranial pressure.[44] This risk combined with the potential neurologic side effects of acute dystonia, Parkinsonian symptoms, and tardive dyskinesia suggests this drug should not be given to any patient with head trauma or history of neurological deficits.[42] Future studies should investigate the potential risks and benefits of these agents in specific subsets of critically ill patients (ie, septic patients) and the optimal length of therapy.

Lipid Emulsions

The fat source for parenteral lipid emulsions used in the United States is soybean oil, which contains predominantly ω-6 polyunsaturated fatty acids (PUFA). Evidence that ω-6 PUFA–rich parenteral lipid emulsions alter the composition of cell-membranes[45] and influence the generation of prostaglandins, leukotrienes, and thromboxanes,[46] which may have unfavorable effects, has generated an interest in alternative lipid sources for parenteral lipid emulsions. Fish oils containing ω-3 PUFA have the potential to modulate some of the detrimental effects of ω-6 fatty acids through direct and competitive inhibition of prostaglandins generated via linoleic and thus arachidonic acid.[47]

Parenteral nutrition (PN)–dependent infants who started a lipid emulsion based on fish oil (Omegaven, Fresenius Kabi, Bad Homburg, Germany) appeared to have faster resolution of cholestasis compared with historic controls who received conventional lipid emulsions.[48] However, a double-blind randomized study of fish oil–containing lipids in critically ill adult medical patients produced equivocal results. Friesecke et al[49] randomized 166 medical ICU patients who required PN to receive their calculated lipid calories as either a medium-chain triglyceride/long-chain triglyceride (MCT/LCT) 1:1 mix (Lipofundin MCT, B. Braun Medical, Melsungen, Germany) or 83% of the lipid dose as MCT/LCT +17% of the lipid dose as a fish-oil emulsion. There was no significant difference between the groups in terms of serum markers of inflammation and immunosuppression and no difference in clinical outcomes such as infectious complications, ICU length of stay, or mortality.[49]

In contrast, a fish oil–containing lipid emulsion appeared to alter leukotriene production and decrease length of stay after elective abdominal surgery, compared with patients receiving a soy oil–based lipid emulsion.[50] Wichmann et al[50] randomized 256 patients to receive either a 100% LCT emulsion (Intralipid) or a lipid emulsion providing 50% MCT, 40% LCT, 10% fish oil, and 200 mg of α-tocopherol per liter. Leukotriene B-5 was significantly increased and length of

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hospital stay was significantly decreased in the group receiving the fish oil and vitamin E–supplemented lipid emulsion compared with the group receiving the LCT emulsion.[50] The difference between the Friesecke and Wichmann studies may relate to the use of an MCT/LCT lipid emulsion as the control formula in the former study vs the use of a 100% LCT control in the latter. This benefit of a fish oil–containing lipid emulsion compared with an all-LCT emulsion is further supported by a study of 40 patients with severe acute pancreatitis. Patients were randomized in a double-blind study to 5 days of identical PN except for the lipid composition. The control group received 100% LCT (Lipovenoes 20%; Fresenius Kabi) vs a lipid emulsion with 10% fish oil (Omegaven 10%, Fresenius Kabi).[51] Patients treated with the fish oil had higher eicosapentaenoic acid (EPA) concentrations ($P < .01$), lower C-reactive protein (CRP)levels ($P < .05$), and better oxygenation ($P < .05$) with significantly less need for continuous renal replacement therapy ($P < .05$).[51]

These studies suggest that the addition of fish oil may reduce the augmented inflammatory response by 100% LCT lipid emulsions, thereby preserving the inflammatory capacity and avoiding further decrease in organ function. Additional prospective randomized trials of fish oil emulsions are warranted to investigate the optimal dose of fish oils, study effects in different populations, and verify the potential benefit or requirement for increased antioxidant supplementation in patients receiving fish oils. For now the wide use of fish oil lipid emulsions in the United States is prohibited by the Food and Drug Administration except for experimental or compassionate use.

Pharmaconutrients

Our understanding of the impact of specific nutrients in the treatment of hospitalized patients has advanced significantly over the past decade. The focus has changed from one of supporting patients as they recover from their underlying disease to one of therapeutic intervention to modulate the underlying disease process. This has led to the concept of "pharmaconutrition," in which specific nutrients or combination of nutrients have been shown to have profound effects on underlying inflammatory, immunological, and metabolic processes of hospitalized patients, especially the critically ill population. In the following paragraphs, advancements in pharmaconutrition therapy over the past year are discussed.

Combination Therapy

An enteral pharmaconutrient supplement containing glutamine (Gln) dipeptides, antioxidative vitamins and trace elements, and butyrate was studied in a prospective, randomized controlled, double-blind clinical trial in 55 critically ill, septic patients starting EN.[52] The patients were randomized to receive the pharmaconutrient supplement vs a control supplement within 24 hours of enrollment for a total of 10 days. Additionally, on day 2, patients in the study group started on an immunonutrition formula and the control group started on a standard formula. Organ dysfunction was assessed by daily total Sequential Organ Failure Assessment (SOFA) score. After the interim analysis of data from 50 patients, the study was suspended secondary to the significant difference in the decline of the SOFA score in the treatment group ($P < .0001$). Vitamin C was used as a marker of supplement absorption and was noted to increase in the study group but remain below normal in the control group. Despite the different rate of decline in SOFA scores, there were no significant differences in length of stay or infectious complications. Given the early stop of enrollment, the strength of the analysis is limited by the sample size. In addition, the authors decided to combine the pharmaconutrient supplement with an immunonutrition product as opposed to a standard formula. This makes it more difficult to ascertain the effect of the supplement vs the immunonutrition product vs the combination of the two. Regardless, this study provides encouraging data regarding the potential effectiveness and safety of an enteral pharmaconutrition supplement.[52]

A prospective study of a historical control group of critically ill trauma and burn patients (40 patients with burns, 46 trauma patients) was undertaken to determine the effect of an enteral solution containing 30 g of Gln plus antioxidants (selenium, zinc, and vitamin E) provided for 10 days on clinical outcomes. The study group and historical controls received EN and trace elements as outlined by the ICU feeding protocol. The daily SOFA score and other outcome variables did not differ significantly between the 2 groups.[53]

A prospective, randomized, double-blind, placebo-controlled trial in patients admitted to an ICU with clinical evidence of organ failure post cardiac surgery, major trauma, or subarachnoid hemorrhage received intravenous supplements for 5 days (selenium 270 µg, zinc 30 mg, vitamin C 1.1 g, and thiamine 100 mg) with a double-loading dose on days 1 and 2 or placebo. Of the 200 patients enrolled, 102 received treatment and 98 placebo. Organ function end points, infectious complications, and length of hospital stay did not differ significantly between the groups.[54]

Combination therapy with antioxidants and amino acids has demonstrated promise, but results have been equivocal. Further study is required before the ideal combination of nutrients, dose and route for various populations can be established.

Nutrition Therapy for ARDS

Acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) are severe illnesses that may lead to death in ICU patients. Although advances have been

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made in understanding the pathophysiology of these conditions, a safe and effective intervention remains elusive. Fish oil–based EN rich in ω-3 PUFAs, borage oil, and antioxidants was shown to improve clinical outcomes in 3 previous prospective, randomized trials in ARDS patients.[55-57] The results of these trials have led to recommendations from scientific societies to provide these specialized formulas to patients meeting the criteria for ARDS or ALI (level A for the Canadian Society, A.S.P.E.N., and SCCM).[1,17] A meta-analysis of the 3 trials mentioned above was recently completed demonstrating a significant reduction in the risk of mortality, rate of new organ failure, length of ICU stay, and time on mechanical ventilation in patients who received ω-3 PUFAs, specifically EPA + γ-linolenic acid (GLA) and antioxidants.[58] A different meta-analysis focusing on the use of immune-modulating enteral formula in the general ICU population again pooled the data from the 3 afore-mentioned studies and described robust efficacy for ω-3 PUFA and antioxidants in patients with ARDS/ALI.[59] The authors posited that the failure of previous studies of ω-3 PUFA–containing formulas to demonstrate a benefit may have been attributable to excessive arginine supplementation.[59]

These finding are encouraging; however, the inherent limitations in the 3 studies and meta-analysis should be mentioned: lack of blinding in 1 trial,[57] the differing fatty acid content in the later 2 trials, and heterogeneity of pooled data of ICU length of stay and time on ventilation. A phase 3, multicenter study on 1000 patients with ALI/ARDS (The EDEN-Omega Study, ClinicalTrials.gov identifier NCT00609180) was recently stopped due to futility and thus failed to confirm the previous findings. It will be difficult to resolve the differences between the various ARDS studies and reach any conclusions until the full results of the EDEN-Omega Study are published.

Glutamine

Gln is a central amino acid in major metabolic processes and has numerous potentially beneficial actions, including acting as a metabolic fuel for gut epithelial and immune system cells, attenuating cytokine release, acting as an antioxidant by enhancing glutathione levels, and delaying the induction of nitric oxide synthase.[60] A possible mechanism behind these actions is the ability of Gln to upregulate heat shock protein 70 and peroxisome proliferator-activated receptor-γ and downregulate activator protein 1.[61-64] During times of critical illness, skeletal muscle exports large amounts of Gln and there is a marked increase of Gln uptake into Gln using tissues.[65] Several studies have shown that provision of Gln-enriched PN or EN may benefit septic or surgical patients by decreasing the acute inflammatory response. The more stable concentrated alanyl-Gln dipeptide is only available for research purposes in the United States.

In a double-blind, randomized, controlled study, alanyl-Gln dipeptide–supplemented PN vs control PN was provided to a selected subgroups of surgical ICU patients.[60] Fifty-nine patients who underwent surgery for pancreatic necrosis or cardiac, vascular, or colonic injuries were randomized. Initial plasma Gln concentrations were low in both groups and were found to increase in the Gln-supplemented PN group ($P < .07$). Although no difference was noted in infection rates in patients diagnosed with pancreatic necrosis, in the other surgical subgroups there was a significant decrease in the incidence of pneumonia ($P < .05$) and bacteremia/fungemia ($P < .01$). Although patients post vascular, cardiac, or colonic surgery supplemented with Gln had significantly less time on ventilation ($P < .025$), there was not a difference in length of stay or glycemic control.[60] Another group specifically studied the effects of Gln-supplemented PN in a randomized fashion in 44 patients with severe acute pancreatitis.[67] Although infectious morbidity was more frequent in the control group, there was no significant difference between the groups in length of stay or mortality.[66]

Although PN-supplemented Gln trials have demonstrated significant positive benefits, the results for EN supplementation of Gln have been equivocal, and a systematic review of Gln studies did not report a mortality benefit for enteral Gln supplemtation.[67,68] This remained the case in a double-blind trial of 44 surgical/medical ICU patients.[65] Further research demonstrating the benefits of enteral Gln in specific patient subsets will need to be completed before any recommendations regarding its use can be made. Although there is proven benefit of parenteral Gln, it is not readily available in a usable form in the United States.

β-*Hydroxy*-β-*Methylbutyrate*

Catabolism of some lean muscle mass is unavoidable during the early stages of critical illness regardless of the adequacy of nutrition support. Persistent negative nitrogen balance can have significant consequences for patients with existing malnutrition, extended hospitalizations, or recurrent illness. In an increasingly elderly population that may be more "anabolically challenged" because age-related decreases in growth hormone or gonadal steroids, a delay or failure to reverse negative nitrogen balance may have particular consequences in terms of negative outcome and increased use of healthcare resources.

A nutrition approach to reduce catabolism, increase anabolism, or both has obvious appeal. Although the branched chain amino acids, especially leucine, have been investigated as potential anticatabolic agents, the results have been equivocal.[69] β-Hydroxy-β-methylbutyrate (HMB) is a metabolite of leucine that may decrease proteolysis and has been investigated alone and with other amino acids with the aim of improving nitrogen balance and lean muscle mass.

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In 2007, Kuhls et al[70] reported the effects of 14 days of HMB in 100 trauma patients. Patients were randomized to receive either 3 g of HMB; isonitrogenous gelatin with alanine, glycine, serine, and glutamic acid (control); or 3 g of HMB with 14 g of arginine and 14 g of Gln. In the 72 patients who completed the full protocol, those receiving the HMB had a significantly less negative average nitrogen balance (–6.5 ± 1.2 g) compared with patients receiving the isonitrogenous control (–9 ± 1.3 g, $P < .05$) or patients receiving HMB + arginine/Gln plus Gln (–10.9 ± 1.3 g, $P < .02$). When nitrogen balance was viewed as the change in values from day 7 to day 14, the value was –4.3 g for HMB, –5.6 g for HMB + arginine/Gln, and –8.9 g for the control ($P < .05$ HMB compared with control).[70]

Baier et al[71] reported on the effects of 1 year of supplementation of HMB, arginine, and lysine compared with a control mix of nonessential amino acids (alanine, glutamic acid, glycine, and serine) in a population of elderly nonhospitalized patients. Subjects were recruited from senior centers or adult assisted-living facilities, with 104 subjects randomized and 77 subjects ultimately completing the protocol. The HMB-arginine-lysine dosing was based on weight, with patients ≤68 kg receiving 2 g of HMB, 5 g of L-arginine, and 1.5 g of L-lysine per day and those weighing >68 kg receiving 3 g of HMB, 7.5 g of L-arginine, and 2.25 g of L-lysine per day. The elderly subjects receiving the HMB-arginine-lysine supplementation for 1 year had a significant linear increase ($P = .002$) in fat-free mass compared with the subjects receiving the control supplement. However, both groups of subjects had a similar gradual loss of handgrip and leg strength, and there was no significant difference between the 2 groups in functionality tests at any time point.[71] Overall, HMB appears to have potential as an agent to improve nitrogen balance, but additional studies are need to collect adequate data for conclusions regarding potential outcome benefits of its use in specific patient populations.

Zinc

Zinc is an important cofactor for most antioxidant cocktails due to its role in Cu-Zn superoxide dismutase and glutathione activity.[72] Zinc also plays a role in immune function, glucose homeostasis, and wound healing.[71] Two studies of gene-expression profiles have noted the zinc-related genes are downregulated in septic shock.[74,75] These studies lead to the question: could supplemental zinc play a key role in correcting pathophysiologic derangements of sepsis? In a meta-analysis of 4 randomized trials of zinc supplementation in critical illness, only a nonsignificant reduction in mortality and length of stay in the ICU was associated with supplementation. However, a wide range of supplemental zinc was provided, and in 3 of the studies zinc was part of an antioxidant cocktail.[73] Future large randomized trials are required to clarify the potential role for zinc in the treatment of critical illness.

Antioxidants/Selenium

Studies consistently demonstrate decreased plasma concentrations of various antioxidants in some critically ill patients, especially those with septic shock. There is increasing evidence that supplementing with antioxidants, specifically selenium, may improve clinical outcomes by reducing infectious complications and organ dysfunction in septic patients.

A retrospective cohort study in 2272 patients admitted to a trauma unit after the start of a 7-day antioxidant protocol (100 mg of intravenous vitamin C every 8 hours, 100 IU of vitamin E via NG or oralgastric (OG) every 8 hours, and 200 μg of intravenous selenium every day) were compared with 2022 patients who were admitted in the year prior to the antioxidant protocol.[76] Patients who received enteral feeds in both groups received an immunonutrition formula containing fish oil, Gln, and arginine.

Hospital mortality was significantly less in the patients receiving antioxidants compared with the patients admitted in the year prior to the start of the antioxidant protocol (139 of 2272 [6.1%] vs 171 of 2022 [8.5%], respectively, $P < .001$). Median ICU length of stay and hospital length of stay were significantly less in the group that received antioxidants ($P < .001$). The survival benefit of antioxidants appears to be primarily in those patients who are less likely to survive their acute injury.[76] The primary limitation of this study was the use of historic controls, but these results support the need for a large randomized study.

In patients suffering from severe sepsis or systemic inflammatory response syndrome, there is an early 40% decrease in plasma selenium concentrations that could be associated with a decrease of antioxidant defences.[77] A phase 3, multiple-center, double-blind, randomized placebo-controlled trial in 249 ICU patients with severe SIRS, sepsis, and septic shock was published in 2007.[78] The study group received a 1000-mcg bolus (within 30 minutes) of intravenous sodium-selenite, followed by a continuous drip of 1000 mcg of sodium-selenite per day for 14 days (total dose 15mg).[7] The control group received 0.9% NaCl in a similar pattern.

Although there was no significant difference in the primary outcome of 28-day mortality based on intention-to-treat analysis (n = 238), in the 189 patients who received the full dose of selenium there was a significant reduction in 28-day mortality. Thirty-nine of 92 (42%) patients in the selenium group compared with 55 of 97 (57%) in the control group died within 28 days ($P = .049$; relative risk of 0.56; 95% CI, 0.32–1.00). The absolute reduction in mortality was 14.3%.[78]

Also in 2007, a prospective, placebo-controlled, randomized, double blind, phase 2 study was conducted in 7 centers in France.[77] The primary end point was the time to vasopressor therapy withdrawal during the ICU stay. Secondary end points were the duration of mechanical

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ventilation, the ICU and hospital lengths of stay, and the mortality rates in the ICU, at hospital discharge, and at 7, 14, 28, and 180 days and 1 year after randomization. Sixty patients were randomized. Patients in the treatment group received sodium selenite for 10 days (4000 mcg on the first day, 1000 mcg/d on the 9 following days) or placebo. No significant differences were noted in the primary or secondary endpoints between the 2 groups.[77]

The REducing Deaths due to OXidative Stress study (The REDOXS Study), a large-scale multicenter randomized trial in >1200 mechanically-ventilated, critically ill patients, is currently underway to determine the effects of Gln and antioxidants on potential physiological derangements in this patient population.[79] Patients admitted to an ICU with severe organ dysfunction will be randomized to 1 of 4 treatments: Gln, antioxidant therapy, Gln and antioxidant therapy, or placebo. The primary outcome for the study is 28-day mortality. The secondary outcomes are ICU and hospital length of stay, duration of mechanical ventilation, and health-related quality of life. Initial results are expected in 2009–2010.[79]

Future studies are needed to confirm optimal antioxidant dosing regimens associated with improved outcomes and to identify in which critically ill patients this approach is likely to be most effective. Studies are also needed to determine the precise mechanism of action. Until then, doses below the tolerable upper intake levels may be considered for supplementation.

Probiotics

In this era of rising incidence of antimicrobial resistant infections in the ICU setting, nonantibiotic strategies for prevention of infections are gaining interest. One such strategy is the use of probiotics, although the mechanism of action remains theoretical. It is postulated that immunomodulation results from the interaction of GI probiotic elements, the gut mucosa, and underlying mucosal lymphoid elements.[80] A recent study by Forestier et al[81] demonstrated enteral administration of a probiotic *Lactobacillus* preparation delayed respiratory tract colonization with *Pseudomonas aeruginosa* resulting in a significantly reduced rate of ventilator-associated pneumonia.

However, although this and other studies with probiotics in the critically ill population have produced encouraging results, a recent study in patients with severe acute pancreatitis has raised concerns of potential negative consequences of probiotics in some populations. Besselink et al[82] reported the results of a multicenter, double-blind study of 298 adult patients with severe acute pancreatitis randomized to receive either a multispecies probiotic or placebo. Patients received either Ecologic 641 (Winclove Bio Industries, Amsterdam, Netherlands, containing *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus salivarius*, *Lactococcus lactis*, *Bifidobacterium bifidum*, and *Bifidobacterium lactis* in a total daily dose of 10^{10} bacteria, plus cornstarch and maltodextrins) or placebo twice per day no later than 72 hours after onset of symptoms of pancreatitis continuing for 28 days. All patients had a nasojejunal tube placed for feeding, study medication, or placebo and had a 1-kcal/mL polymeric, fiber-enriched formula advanced to goal feeding (~30 kcal/kg) over 4 days.[82] There were significantly more deaths in the probiotic group than in the placebo group (24 vs 9) ($P = .01$; relative risk 2.53, 95% CI 1.22–5.25). Most of the deaths were caused by multiorgan failure: 20 of 24 (83%) of deaths in the probiotics group and 7 of 9 (78%) in the placebo group. Bowel ischemia was detected during operation or autopsy in 9 patients in the probiotics group; 8 of these patients died as a result. No cases of bowel ischemia were seen in the placebo group ($P = .004$). The 9 cases of bowel ischemia were all diagnosed within the first 14 days of admission in 7 different hospitals: 4 university and 3 teaching hospitals. All of these patients had early onset of organ failure (median 2 days after admission; range, 1–6 days).[82]

Additional studies are needed to determine which probiotic species, doses, and formulations should be used in which ICU patient population. It may be that specific strains should be used to treat specific diagnoses. In addition, further understanding of the mechanism of action will help to address the controversies surrounding the use of probiotics. At present insufficient data exist to safely use these agents routinely in the ICU setting.

Global Guidelines for Nutrition Support

In response to the publication of different and sometimes contradictory guidelines for nutrition support from various international societies, there has been a call for global guidelines for nutrition support practice. In September 2007, at the 29th Congress of the European Society for Clinical Nutrition and Metabolism (ESPEN) in Prague, representatives from 8 different international nutrition societies met to plan a route toward universal guidelines. The following societies are contributing to the establishment of these guidelines: ESPEN, Federation of Latin American Societies for Parenteral and Enteral Nutrition (FELANPE), Parenteral and Enteral Nutrition Society of Asia (PENSA), Australasian Society for Parenteral and Enteral Nutrition (AuSPEN), Canadian Society for Clinical Nutrition (CSCN), A.S.P.E.N., South African Society for Parenteral and Enteral Nutrition (SA.S.P.E.N.) and Japanese Society for Parenteral and Enteral Nutrition (JSPEN). The 24 representatives of these societies reported their goals: to combine the good and generally accepted points of existing guidelines, to identify the weak points and areas of conflict, and to identify the path towards new research where needed.

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Guidelines/Protocols for Feeding

Practice guidelines are not absolutes and are intended to provide an overview of present recommendations based on pertinent literature and often, in the absence of data, expert opinion. Establishing guidelines for use in the ICU setting can be challenging based on the heterogeneity of this patient population and therefore should always be used in conjunction with clinical judgment. A time gap exists as clinical practice travels from bench to bedside, requiring that guidelines undergo periodic review and revisions to remain useful to the practitioner. The authors of the Canadian clinical practice guidelines for nutrition support published in 2003 have opted to make their periodic revisions readily available on their Web site: www.criticalcarenutrition.com.[83]

The Canadian guidelines served as a model and reference source for the recently released A.S.P.E.N./SCCM guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient.[1,17] This joint effort illustrates the transformation from nutrition as adjunctive care in the ICU setting to one of therapy actively focusing on attenuating the metabolic response to stress, preventing oxidative cellular injury, and positively modulating the immune response. Recommendations to achieve these goals are clearly presented, in addition to a thorough literature review in table format. Although differences in mortality have been demonstrated in individual studies regarding components of nutrition support, there continues to be controversy as to whether following evidenced-based guidelines will affect mortality in the ICU patient population. Doig et al[84] performed a cluster randomized trial in ICUs of 27 hospitals to determine whether implemented guidelines would improve feeding practices and reduce mortality. The study included a 5-week run period (to allow training and familiarity with the guidelines) and a 20-week guideline implementation and evaluation period. Although the ICUs following the guideline fed patients earlier and achieved caloric goal sooner, there was no significant difference in length of stay or mortality.[85] However, although time to enteral feeding was different (0.75 days in the guideline group and 1.37 days in the control group) compared with other published guidelines,[1] both groups received "early enteral" feeding and achieved a similar caloric intake level within 72 hours.

All study ICUs in the Doig trial successfully implemented the guidelines, which the authors attributed to the incorporation of the recommendations into a simplistic algorithm.[85] The key to successful protocol/algorithm execution is simplicity. Cumbersome protocols are more likely to be ignored completely or erroneously applied to patient care. Algorithms for nutrition support in the ICU setting have been published; however, prior to implementation they may need to be "personalized" based on staffing, patient population, and resources.

Regardless of whether a personalized or published version is used, protocols facilitate timely implementation of care in the ICU.

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