Clinical guidelines are essentially recommendations for patient care based on the best available data. These guidelines are not absolute requirements, do not guarantee outcome or mortality benefits, and are certainly never a substitute for clinical judgment. In fact, at the bedside, clinical judgment always takes precedence over any societal guidelines. Nonetheless, clinical guidelines developed by medical specialty and subspecialty societies are some of the more rigorously supported documents in the literature. The current emphasis on evidence-based medicine mandates that guidelines be supported by current literature. Although the focus lies primarily on prospective randomized controlled trials (PRCTs), most guideline committees review other national and international societal guidelines and at times, include expert opinion or consensus recommendations. It is important that guidelines should have clinical practicality and should promote knowledge translation where the evidence in the literature ultimately relegates directly to patient care.

However, the explosion of guidelines in the literature can be frustrating for the clinician. Guidelines between societies often contradict each other, and certain guidelines often contradict practice at individual institutions. However, controversy offers an
opportunity for growth. The most important aspect of a good clinical guideline is transparency, that is, there should be a direct connection between the clinical recommendation and the underlying studies from which it gets its support. Identifying areas of controversy, seeking out the underlying studies, and determining individual interpretation of the studies should lead to the decision of whether or not to change clinical practice.

DERIVATION OF THE SOCIETY OF CRITICAL CARE MEDICINE/AMERICAN SOCIETY FOR PARENTERAL AND ENTERAL NUTRITION 2009 GUIDELINES

The predecessor for the Society of Critical Care Medicine (SCCM)/American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) guidelines was the 2002 A.S.P.E.N. Critical Care Guidelines. The development of these guidelines was a huge project for A.S.P.E.N., which included guidelines for nutrition therapy across a wide variety of patient populations and clinical scenarios. These guidelines were published in an older format, in which there were 3 or 4 pages of text followed by only 4 generalized recommendations. In July 2004, a guideline committee was requested to revise the critical care guidelines published in 2002. The original manuscript was written in the old style and submitted for review in July 2005.

However, as this committee was developing these revised guidelines, the overall landscape for clinical guidelines was already changing. In 2003, the Canadian Critical Care Group under the direction of Daren Hyland published the “Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients.” This publication was followed a year later by a multisociety task force publication entitled “Surviving sepsis campaign guidelines for management of severe sepsis and septic shock.” Both of these publications altered the format for societal guidelines. In contrast to the old style with long text and minimally brief generalized recommendations, the new style of these 2 publications was topic driven, brief, clear, and very specific. A particular clinical recommendation was followed by a brief discussion, which promoted transparency between the clinical guideline statement and the underlying supportive evidence. In addition, the guidelines were renewable and were freely accessible to the public (not simply reserved for societal members).

As a result of the changes in the overall landscape of guidelines, a voluntary revision of the A.S.P.E.N. Critical Care Guidelines was made and resubmitted a year later in 2006. At some point in the process, a decision was made that the guidelines should be a joint project between SCCM and A.S.P.E.N. The 2 guideline committees were merged, and all subsequent revisions of the manuscript were a joint effort by these 2 societies and this single combined committee. The committee was composed of critical care surgeons, gastroenterologists, nurses, and dietitians. Although 2 pharmacists were named to the original committee, they had little input into the final recommendations that were ultimately published.

Overall, the publication of guidelines involved a 5-year process from July 2004 to the final approval in January 2009. There were 5 full rounds of review, with more than 50 reviewers interpreting the manuscript, and the final approval was required from 3 separate boards (the A.S.P.E.N. Board of Directors, the SCCM Council, and the American College of Critical Care Medicine Board of Regents). The final guidelines were published in full text in the *Journal of Parenteral and Enteral Nutrition (JPEN)* in the May 2009 issue, with an executive summary being published in the same month in the journal *Critical Care Medicine*.

The process of development of guidelines began with the committee compiling a list of recommendations or action statements. The committee then referred to
the literature focusing on PRCTs as the primary source for support. The overall strength for a particular recommendation was based on 2 things: the level of the investigative studies and the number of studies that supported that particular recommendation. Controversy in interpreting the literature was resolved by consensus opinion of the committee members. However, for certain issues, the committee members actually downgraded the final recommendation out of respect for an opposing opinion. The philosophy of this particular committee was that they decided to include patient care recommendations even when the sole basis of support was expert opinion. It was clear on review of the literature that many aspects of clinical practice in nutrition therapy were not supported by PRCTs. In a lengthy process, such as the derivation of guidelines, in which so many expert reviewers would be involved, the committee saw a unique opportunity to derive guidelines even though support from the literature was solely based on expert opinion. The committee was also acutely aware of the polarity in the critical care community with regard to use of parenteral nutrition (PN) in the intensive care unit (ICU). Therefore, the committee decided that it was most important to provide specific recommendations for the use of PN, identifying those conditions in particular patients in whom outcome benefit could be assured with the use of PN.

One of the early areas of controversy was in the definition of a large clinical trial. Any study that performed a formal power analysis, identified endpoint criteria, and then continued to enroll enough patients to meet those criteria was considered a large trial (in which the chances for alpha and beta errors were minimized). But most studies in the literature that dated more than 5 years from their date of publication did not have a power analysis. It was decided that an arbitrary number of more than 100 subjects would define a large study in the absence of a power analysis.

Another controversy that existed for the guideline committee was the use of meta-analysis. Some societal guidelines have used meta-analysis as the highest grade of literature. The SCCM/A.S.P.E.N. Guidelines Committee, however, thought that meta-analysis should be used to help organize information and derive a treatment effect from multiple trials but should not be used to grade the overall strength of the recommendation. The ultimate grade for the recommendation had to be based on the level of evidence of the individual studies. Review articles or consensus statements from expert panels were considered as expert opinion and given the lowest level of grading strength.

Despite the structured format followed by the Guidelines Committee and the extensive review by more than 50 experts and 3 societal boards of directors, there were still areas of intense controversy that made derivation of the final recommendations extremely difficult. The following are several examples of controversy, based on the literature itself, the perspective taken by the SCCM/A.S.P.E.N. Guidelines Committee, or the clinical implications of the recommendations that immediately followed publication.

**Permissive Underfeeding in the Morbidly Obese Critically Ill Patient**

In the section on dosing of enteral feeding, the SCCM/A.S.P.E.N. guidelines recommended that in the critically ill obese patient, permissive underfeeding with enteral nutrition (EN) should be considered. For all classes of obesity (in which the body mass index [BMI] calculated as the weight in kilograms divided by height in meters squared is >30), the goal of the enteral feeding regimen should be to provide 60% to 70% of target caloric requirements. These caloric requirements could be identified by simple weight-based equations such as 11 to 14 kcal/kg actual body weight...
(ABW)/d, or 22 to 25 kcal/kg ideal body weight (IBW)/d. Certainly, the use of indirect calorimetry provides a more accurate measure of caloric requirements, and setting the goal of feeding at 60% to 70% of the measured resting energy expenditure would be appropriate for permissive underfeeding. Protein requirements were slightly more complicated, such that for patients with class I and class II obesity with a BMI of 30 to 40, 2.0 g protein/kg IBW/d should be provided, whereas for patients with class III obesity and a BMI greater than 40, more than 2.6 g protein/kg IBW/d should be provided. The strength of these recommendations was grade D, based on retrospective data with historical controls. A report by Choban and Dickerson\(^6\) showed that 2.0 g/kg IBW/d of protein is required for patients with class I and II obesity to reach nitrogen balance, whereas more than 2.6 g/kg IBW/d of protein is required for an obese patient with a BMI greater than 40. However, there are virtually no data to define how much of protein is required for the superobese patients with BMI greater than 50.

Controversial reports from the literature provide information that obesity may be a benefit in the ICU setting, contradicting the rationale for permissive underfeeding. When critically ill obese patients in a surgical or medical ICU are compared with lean controls, obesity is associated with increased infection, ICU and hospital length of stay, multiple organ failure, and duration on mechanical ventilation.\(^7,8\) For reasons that are not entirely clear, mortality is increased in trauma patients in a surgical ICU, whereas mortality is decreased in obese patients in a medical ICU compared with lean controls.\(^7,8\) This observation has led pulmonary critical care clinicians managing patients in a medical ICU to see obesity as a benefit in critical illness, that is, excess fuel stores protect the patient and improve survival. A report by Alberda and colleagues,\(^9\) involving an international survey of ICUs around the world, showed that patients with a BMI greater than 30 showed a reduced mortality when an extra 1000 cal was provided in their nutrition regimen. The concepts presented by these articles would suggest that in the critical care setting permissive underfeeding might have deleterious effects, even in obesity.

Resolving this controversy can be very difficult for the individual practitioner. At the authors’ institution, they reviewed the effect of morbid obesity and its interference with virtually every aspect of patient care. Special equipment is required with big boy beds, wheelchairs, and toilet seats. It is difficult to turn the patients adequately, which increases the chances for pressure sores, atelectasis, and pneumonia. The morbidly obese patient presents a risk to health care providers. Obese patients are difficult to ventilate and are prone to sleep apnea and restrictive lung disease. Development of complications is difficult to evaluate because of difficulties in transporting and performing diagnostic tests in morbidly obese patients. The failure to ambulate these patients adequately increases the risk for deep venous thrombosis. Underlying hepatobiliary diseases, such as nonalcoholic steatohepatitis and cirrhosis, and the respiratory abnormalities from obstructive sleep apnea and restrictive lung disease promote multiple organ failure.

Older physiologic studies from the past would suggest that as long as adequate protein is provided, calories can be restricted, the fat mass can be reduced, and the lean body mass can be maintained. In a study by Elwyn,\(^10\) reducing the energy intake as a percentage of energy expenditure to less than 60% still resulted in neutral or even positive nitrogen balance as long as the protein intake was increased to 2.2 g/kg/d. In a subsequent study by Hill and Church,\(^11\) total caloric energy intake could be reduced to as low as 20 kcal/kg/d and the body fat mass could be reduced successfully. By increasing the nitrogen uptake from 0.9 to as high as 2.2 g/kg/d of protein, erosion of the lean body mass could be prevented.\(^11\)
From these physiologic studies and the adverse effect of morbid obesity on every aspect of patient care, the authors’ institution interpreted the guideline recommendation for permissive underfeeding of the morbidly obese critically ill patient to be appropriate as long as adequate protein delivery is provided.

The Effect of Protocols for Gastric Residual Volumes on Tolerance of EN

In the section on tolerance of EN, the SCCM/A.S.P.E.N. guidelines recommended that evidence for bowel motility and resolution of ileus was not required before initiation of enteral feeding. But as enteral feeding is started, the patient should be monitored for tolerance. The guidelines recommend avoiding inappropriate cessation of enteral feeding, minimizing periods during which patients were kept nil per os for tests or procedures (to avoid prolonged ileus), and avoiding holding EN for gastric residual volumes less than 500 mL in the absence of other signs of intolerance.

Recommending that the cutoff value for gastric residual volume be raised to 500 mL was incredibly controversial. This recommendation, however, was based on 3 level 2 (small randomized) trials and 1 level 1 (large randomized) trial. In each study, patients were randomized to 2 different cutoff values for the gastric residual volume and adverse patient outcome, such as regurgitation, vomiting, aspiration, or overall complications, was less in the group randomized to the higher cutoff value for residual volume (reaching significance in 2 of the studies). By raising the cutoff value for the gastric residual volume, 2 of the studies demonstrated that patients received a significantly higher volume of EN. Two more prospective trials compared routine checking of residual volumes with no checking of gastric residual volumes. In the study by Powell and colleagues, incidence of aspiration pneumonia was not significantly different between the 2 groups but tube clogging was reduced 10-fold in the group for which no residual volumes were monitored. In the study by Reignier and colleagues, which was performed prospectively before and after the implementation of a protocol, the group for which no residual volumes were measured had less frequent evidence of intolerance, received a greater volume of enteral feeding that was infused, and had no difference in the incidence of vomiting or ventilator-associated pneumonia when compared with the group for which residual volumes were measured routinely. To better interpret the SCCM/A.S.P.E.N. guidelines, it is important to note that increasing the volume of EN delivered often decreases the incidence of pneumonia. Thus, lowering the gastric residual volume to protect the patient may impede EN delivery and the risk of pneumonia may actually increase. In a study by Meissner and colleagues, the narcotic antagonist, naloxone, was infused through the tube by enteral feeding in study patients, whereas controls received enteral feeding alone. This strategy, which reversed the effects of systemic analgesia at the level of the gut, succeeded in significantly increasing the amount of EN infused. As a result, the incidence of pneumonia was decreased significantly from 55% in study patients to 36% in controls (P < .05). In a study by Kudsk and colleagues on trauma patients, those who received enteral feeding had a 3-fold reduction in pneumonia compared with those randomized to PN. Again, in the study by Taylor and colleagues, use of an aggressive protocol with high gastric residual volumes in study patients succeeded in nearly doubling the percentage of goal calories infused compared with a more conservative protocol with lower gastric residual volumes in controls, and as a result the incidence of pneumonia was reduced from 63% to 44%, respectively (P = not significant [NS]).

Thus, although the recommendation of SCCM/A.S.P.E.N. to raise the cutoff value for gastric residual volume to 500 mL was highly controversial, the recommendation is very well supported in the literature.
Use of Pharmaconutrition Formulas

Out of 76 total recommendations, only 2 guideline statements in the SCCM/A.S.P.E.N. guidelines were given a grade A recommendation. For surgical ICUs, the recommendation that immune-modulating enteral formulations supplemented with agents such as arginine, glutamine, ω-3 fatty acids, and antioxidants should be used for major elective surgery was given a grade A. However, the use of arginine-containing pharmaconutrient formulas in the general ICU population was much more controversial. A meta-analysis by Heyland and Novak in 2001, a report by Bower and colleagues, and a study by Dent published only in abstract form showed a higher mortality in patients receiving an arginine-containing immune formula compared with controls receiving a standard formula. Patients who received the arginine-containing formula had a mortality of 15.7%, which was significantly greater than controls with a mortality of 8.4% (P = .055). The difference in mortality rate was even greater in those patients who died as a direct result of sepsis. This study was criticized for having a possible error of randomization, because the Acute Physiology and Chronic Health Evaluation (APACHE) II score in patients who died in the immune group was 19.2 ± 5.6, which was significantly greater than the mean APACHE II score of 12.7 ± 2.1 in patients who died in the control group (P < .05). However, this criticism is an error because the APACHE II scores on admission were not significantly different between study patients and controls (15.9 ± 5.4 vs 15.6 ± 4.8, respectively, P = NS).

In the Ross unpublished study, patients who received an arginine-containing formula had a mortality rate of 23.0%, which was significantly greater than that seen in controls at 9.6% (P = .03). However, this study was thought to have an error in randomization. Out of 35 elderly patients with pneumonia, 26 were included in the study group receiving the arginine formula. Half of the deaths in the immune group were attributed to this elderly population with preexisting pneumonia. The study was also criticized because the formula used for this study, Optimental (Abbott Nutrition Inc, Columbus, OH, USA), had only one-third the content of arginine in another formula, Impact (Nestlé Healthcare Nutrition Inc, Gland, Switzerland), that was used in previous studies. A third study by Bertolini and colleagues had an odd design in which an immune-modulating arginine-containing enteral formula was compared with PN. Although ICU mortality was significantly greater in the group that received the arginine-containing enteral formula when compared with controls receiving PN (44.4% vs 14.3%, respectively, P = .039), the 28-day mortality and overall hospital mortality were not significantly different between groups.

A study by Galban and colleagues was performed in a critically ill population in which 100% of patients had sepsis and the opposite results were found. Study patients receiving an arginine-containing formula had a significantly lower mortality than controls receiving a standard enteral formula (19.1% vs 32.2%, respectively, P < .05). Mortality directly related to infection was also significantly less in the group receiving the arginine formula compared with controls (14.6% vs 26.4%, respectively, P = .05). Heyland and Novak criticized this study because the mortality effect was seen only in those patients with an APACHE II score of 10 to 15. With higher APACHE II scores, the benefit effect lost significance. This criticism of the study by Galban and colleagues may not be fair, in that the study was powered to show a difference in overall mortality between the study group and controls and not powered to look at a subset of mortality between groups for different ranges of the APACHE II score.

This controversy made it difficult for the SCCM/A.S.P.E.N. Guidelines Committee to make their recommendations regarding the use of arginine formulas in the ICU population. When the guidelines were being developed, a large study by Kieft and
colleagues showed absolutely no difference in patient outcome between the study group that received an arginine-containing formula and controls that received a standard enteral formula with regard to mortality, infection, hospital length of stay, and duration of mechanical ventilation. When the committee analyzed the revised updated Canadian clinical practice guidelines’ meta-analysis on use of arginine-containing formulas, it was found that the ICU length of stay was still significantly reduced by 0.36 days (P = .50), hospital length of stay was reduced by 0.33 days (an effect which just missed significance, P = .06), and duration of mechanical ventilation was reduced by 0.30 days (P = .09) compared with use of standard enteral formulations. The Canadian Clinical Practice Guideline Committee interpreted this literature in such a way as to recommend that arginine-containing formulas not be used in the patient in medical ICU. The Evidence Analysis Library created by the American Dietetic Association made no recommendation on the use of arginine-containing formulas because of the controversy. However, the SCCM/A.S.P.E.N. Guidelines Committee interpreted this literature in such a way that the use of an arginine-containing formula in a surgical ICU was given a grade A recommendation, whereas the use of an arginine-containing formula in a medical ICU was given a grade B recommendation.

To further complicate an already strong controversy, Luiking and colleagues performed studies in which arginine was infused directly into the systemic circulation of septic medical and surgical patients. Results showed no evidence of hemodynamic compromise with the administration of arginine comparable to the doses seen with the provision of enteral pharmaconutrition formulas. Another issue complicating this controversy involves asymmetric dimethylarginine (ADMA), an agent that competes with L-arginine for production of inducible nitric oxide synthetase (iNOS). L-Arginine stimulates iNOS production and results in a clinical effect of vasodilation, stimulation of host defense, and perfusion of tissue. ADMA has the opposite effect, inhibiting iNOS production, causing vasoconstriction, and reducing tissue perfusion. In a large study of patients with critical illness, ADMA levels were shown to be elevated, correlating with increased ICU length of stay, multiple organ failure, and mortality. Response to infusion of L-arginine was predicated by the levels of ADMA and the balance between these 2 agents. In a normal setting, the volume of L-arginine is greater than ADMA in the systemic circulation and as a result, nitric oxide synthetase is induced and vasodilation occurs. However, when an excess of ADMA accumulates, iNOS production is inhibited, less nitric oxide is produced, and vasoconstriction occurs. Providing L-arginine reverses the effects of ADMA, restores balance between the 2 agents, and promotes vasodilation, tissue perfusion, and protection of endothelial function.

With a controversy of this degree, there may be no correct answer. The SCCM/A.S.P.E.N. Guidelines Committee was careful to base their recommendations on the strength of the literature, acknowledge the controversy, and downgrade the recommendation for use of arginine-containing pharmaconutrient formulas in the patient in medical ICU (adding a provision that use in severely septic patients should be done with caution). Individual practitioners are encouraged to review the literature themselves to determine institutional policy.

Safety of Fish Oil

The only other grade A recommendation out of the 76 guideline statements published in the SCCM/A.S.P.E.N. guidelines involved the use of fish oil in patients with respiratory failure. The recommendation specifically stated that patients with acute
respiratory distress syndrome (ARDS) and severe acute lung injury should be placed on an enteral formula characterized by an antiinflammatory lipid profile (eg, ω-3 fish oils, borage oil) and antioxidants. Within months of the publication of this recommendation, the safety of fish oil was called into question because of the cessation of a grant through the National Heart, Lung, and Blood Institute (NHLBI) involving the ARDS clinical network (ARDSNet) group. The ARDSNet group is a pulmonary critical care NHLBI-sponsored study group that has performed excellent studies in critical care for the past 10 to 15 years. In the summer of 2009, a portion of the EDEN-Omega study by this group was terminated for reasons of futility. The study was originally of a 2×2 design, involving a bronchodilator versus placebo, trophic feeds (ramp-up slowly over several days) versus full feeds (reach the goal within 24 hours), and a fish oil/borage oil supplement versus placebo. The fish oil/borage oil supplement was designed by Abbott Nutrition Inc to replicate the ingredients in the commercial product Oxepa. However, instead of being infused continuously as part of the enteral formula, the supplement was given as a bolus twice a day separated from the enteral formula. Controls received a placebo that was composed of a formula with none of the active ingredients of the antiinflammatory lipids or antioxidants. Halfway through the study, at the interim analysis, the study was stopped for reasons of futility and not for ethical reasons. Although nothing has been formally published so far, communication with the primary investigators indicated that the control group had a very low mortality rate, which was far less than that seen in the controls from any of the other studies involving the ARDSNet group (Todd Rice, MD, Personal communication, 2009). The study group receiving the fish oil/borage oil supplement had a higher mortality. Halfway through the study, it seemed that there was no chance, regardless of the value of the supplement, for the study patients to catch up with the controls in regard to mortality. Had there been a clear signal of danger, it would have mandated that the study be stopped for ethical reasons. Another interpretation expressed by the investigators was that the supplement seemed to have no effect, raising concern that the bolus infusion resulted in simple catabolism and breakdown of the supplement without use (Todd Rice, MD, Personal communication, 2009). It is also possible that bolus dosing of a large dose of fish oil to the gut of a critically ill patient leads to malabsorption of the fat and this contributes to lack of efficacy. The controversy surrounding this issue is related to whether the difference in mortality rates raised a danger signal that would contradict the original recommendation in the SCCM/A.S.P.E.N. guidelines. Little data exist elsewhere in the literature to suggest an adverse effect from fish oil, and communication expressed by the investigators of the Omega arm of the EDEN-Omega study up to this point indicates that they do not think there is any signal of harm involved with fish oil use in ARDS.

Use of Supplemental PN

One of the most controversial areas of the SCCM/A.S.P.E.N. guidelines was the recommendations for the use of supplemental PN in a patient already receiving EN. In the section regarding dosing of EN, recommendations were made to provide more than 50% to 65% of goal calories during the first week to achieve the clinical benefits of EN (grade C recommendation). Further recommendations were to add supplemental PN only if provision of EN alone was unable to meet goal calorie requirements after 7 to 10 days (grade E recommendation). Adding PN before 7 to 10 days did not seem to improve outcome and might increase risk to the patient (grade C recommendation). This recommendation was one of many by the Guidelines Committee to minimize the polarity involved with the use of PN in the ICU. The recommendation for use of supplemental PN was based on 5 PRCTs of EN alone versus EN supplemented
with PN\textsuperscript{32–36} and a meta-analysis by Heyland and colleagues\textsuperscript{3} published in 2003. The meta-analysis showed significantly greater cost and a trend toward greater mortality when EN was supplemented with PN and no difference in infection, hospital length of stay, or duration of mechanical ventilation in patients in whom EN was supplemented with PN when compared with patients receiving EN alone.\textsuperscript{3} In a study in burn patients, there was evidence of immune suppression when PN was added to EN, and the mortality increased from 26% in patients receiving EN alone to 63% in patients receiving EN supplemented with PN ($P<.05$).\textsuperscript{32}

These recommendations for use of PN were highly controversial in that they contradicted practice and recommendation of the European nutrition community and the European Society for Parenteral and Enteral Nutrition (ESPEN) guidelines. A very important study by Villet and colleagues\textsuperscript{37} evaluated the concept of cumulative caloric deficit, showing that patients in ICU accrue an energy deficit because ongoing energy expenditure is not met by caloric provision due to delays in delivery of nutrition therapy. The cumulative energy deficit in this study was shown to correlate with the increased hospital length of stay, infections, overall complications, and duration of mechanical ventilation (all endpoints $P<.04$).\textsuperscript{37} As a result of this study and others, the ESPEN recommended supplementing EN with PN if, by 24 hours, more than 80% of energy requirements are not met by EN alone.\textsuperscript{38}

Again, in a controversy of this nature, there seems to be no correct answer based on the available literature. Studies support and refute the recommendation provided by the SCCM/A.S.P.E.N. Guidelines Committee. The Glue Grant study was a large multicenter trial, which evaluated severely injured trauma patients and use of PN.\textsuperscript{39} Data were gathered prospectively and then reviewed retrospectively in 567 trauma patients, of whom 17% received PN only, 87% received EN only, and 13% received a combination of both. Results showed that any use of PN was associated with an increased risk of infection ($P<.01$). Mortality was higher in patients who received EN supplemented with PN when compared with those receiving EN alone ($P<.06$).\textsuperscript{39} A second national prospective observational study of similar design from Germany studied the same issues in 415 patients with severe sepsis or septic shock.\textsuperscript{40} Again, 20.1% received EN alone, 35.1% received PN alone, and the remaining 34.6% received a combination of both. Exclusive use of PN was associated with the highest mortality at 62.3%, whereas the mortality with the use of EN only was lowest at 38.9% (the difference being statistically significant, $P<.005$).\textsuperscript{40} Even when adjusted for comorbidities, use of PN was still predictive of increased mortality. In a study similar to that of Villet and colleagues,\textsuperscript{37} Dvir and colleagues\textsuperscript{41} also looked at cumulative energy deficit. The investigators showed that a negative cumulative caloric deficit correlated significantly with ARDS, sepsis, renal failure, pressure sores, need for surgery, and total complications ($P<.02$ for all outcome effects), whereas there was no correlation to ICU or hospital length of stay, duration of mechanical ventilation, or mortality.\textsuperscript{41}

The criticism of these studies relates to the fact that because they were nonrandomized, patients receiving EN alone may not have been as sick as those who were underfed by the enteral route and thus had to be supplemented by PN. Therefore, it is difficult to resolve this particular controversy based on the literature that is available at present. Four large international research groups have designed and initiated similar studies evaluating hospitalized patients randomized to EN alone versus EN supplemented with PN soon after their admission. The primary investigators for these research groups include Greet Van den Berghe, Daren Heyland, Claude Pichard, and Gordon Doig. Hopefully, any one of these large, well-designed studies should provide valuable data to help resolve the seemingly contradictory recommendations.
from the ESPEN and SCCM/A.S.P.E.N. guidelines regarding use of supplemental PN in the ICU.1,38

**EFFECT OF GUIDELINES ON PATIENT OUTCOME**

The manner in which guidelines are derived at present implies that recommendations supported by evidence-based medicine should result in better patient care. Early data addressing this question have shown a lack of effect from use of such societal guidelines. A study by Jain and colleagues42 using cluster randomization assigned medical centers to active dissemination of the Canadian clinical practice guidelines (which involved education, training, and feedback on the guidelines) or passive dissemination (which involved only receipt of the guidelines). At the end of the study there were no significant differences in adequacy of EN delivery, mortality, hospital length of stay, or ICU length of stay between the 2 groups. The only benefit from active dissemination of the guidelines (compared with passive) was improved glycemic control.42 In a study of similar design, Doig and colleagues43 prospectively evaluated patients in medical centers who were randomized to aggressive use of the Australian/New Zealand guidelines versus controls who were delivered nutrition support without the benefit of the guidelines. A slight but significant improvement in the time to initiate EN was seen in the guideline study group compared with controls (0.75 days vs 1.37 days, respectively, \(P<.05\)). However, mortality, hospital length of stay, and ICU length of stay were not different between the 2 groups.43

The negative results from these 2 studies would suggest that guidelines have little effect on patient outcome. However, most studies were performed immediately after a period of intense study and development of guidelines for each of the national groups in those countries. In both the studies, the control group received early, effective, adequate nutritional therapy.42,43 It may have been nearly impossible for the study groups, regardless of the quality or efficacy of the guidelines, to improve on the excellent nutrition therapy delivered to controls. The lack of response, however, does raise questions about barriers to delivery of nutrition therapy, whether guidelines successfully equate to practical bedside action statements, or whether guidelines have to be translated into clinical pathways, nurse-driven protocols, or physician orders to be effective.

**DO GUIDELINES OVERLY RELY ON EVIDENCE-BASED MEDICINE AND PRCTS?**

After more than a decade of emphasis on evidence-based medicine and the mandate that clinical practice should be supported by the highest level of clinical research, a controversy has arisen over the reliance of guidelines solely on PRCTs. For the SCCM/A.S.P.E.N. guidelines, any A, B, or C grade recommendation had to be supported by PRCTs.1 Recommendations based on expert opinion or studies with historical or concurrent nonrandomized controls were relegated to grade D or E. More than 60% of the SCCM/A.S.P.E.N. recommendations were A, B, or C grade recommendations and were based on PRCTs.1 The Canadian practice guidelines use only PRCTs in the derivation of their guidelines.9 Several major societies such as the World Health Organization, SCCM, A.S.P.E.N., and The Endocrine Society have adapted the grading of recommendations, assessment, development, and evaluation (GRADE) system, formulated by the GRADE working group, for creating guidelines.44 This system is designed to add structured subjectivity to interpretation of the PRCTs from the literature. The GRADE system starts by evaluating and ranking individual studies from the highest grade at 4+ to the lowest at 1+ and then applies several subjective qualifiers.44 The qualifiers include methodological quality, magnitude of the treatment effect, precision estimate of the treatment effect, outcome importance,
risk of therapy, resource use, and varying other subjective values that may be deemed important by the Guidelines Committee. Based on the strength of the original study and the filter of the subjective qualifiers, the final guideline statement is then rated as either a strong recommendation (desirable effects outweigh the undesirable effects) or a weak recommendation (recommendation is suggested with the knowledge that desirable effects probably outweigh the undesirable effects).44

A recent letter to the JPEN editor in response to the SCCM/A.S.P.E.N. guidelines demonstrates some of the difficulties that could arise when a guideline committee interprets clinical studies through the filter of subjective qualifiers.45 In the letter to the editor, Bistrian45 refuted the SCCM/A.S.P.E.N. recommendation that EN should be used preferentially over PN in the critically ill patient. Bistrian argued that the opposite is true, that is, PN should be preferred over EN, based on the meta-analysis by Simpson and Doig46 showing that there was lower mortality with PN compared with EN. He thought that there was less bias in this meta-analysis because of the emphasis on intent-to-treat basis, despite the fact that the results of this meta-analysis were exactly opposite to that of 4 other meta-analyses by Gramlich and colleagues,47 Moore and colleagues,48 Peter and colleagues,49 and Heyland and colleagues.50 In the introduction of the meta-analysis by Simpson and Doig,46 the investigators discussed methodological quality and the importance of 3 key components: intent-to-treat analysis, concealed randomization, and appropriate use of blinding. Applying a subjective filter (based on these methodological components) to their selection of studies for the meta-analysis, the investigators ended up aggregating the data from 9 studies. Results showed a reduced mortality with use of PN compared with EN in critically ill patients. The meta-analysis also showed that infectious morbidity was worse with PN than with EN. Yet the investigators made no attempt to provide an explanation for the differential effect on mortality.46

The treatment effect of PN on mortality in this meta-analysis was driven specifically by 2 studies conducted by Rapp and colleagues51 and Woodcock and colleagues.52 Although the study by Woodcock and colleagues52 was large, including a total of 562 patients, only 11.4% were actually randomized to EN or PN. The mortality was lower in the PN group than in the EN group but the difference did not reach statistical significance. The report by Rapp and colleagues51 was the first of 3 studies performed by a neurosurgery group from the University of Kentucky evaluating EN versus PN in trauma patients with head injury. This initial study conducted in 1983 showed a significantly lower mortality in the PN group compared with the EN group (0% vs 44%, respectively, \( P < 0.05 \)).51 However, although the study design was described by Simpson and Doig46 as a comparison between early PN and early EN, controls really received standard therapy or no nutritional support (patients were on their own to advance to oral feeding).51 In subsequent publications, this research group from the University of Kentucky referred to the controls from this study as undergoing starvation.53 The second study published 4 years later, again in trauma patients with head injury, compared early PN with early EN (this time EN was delivered by infusion into the stomach via a nasogastric tube).53 The frequency of a favorable outcome based on recovery of neurologic injury was significantly higher at the 3-month mark in the PN group compared with controls receiving EN (43.5% vs 17.9%, respectively, \( P < 0.05 \)).53 Mortality was actually higher in the PN study group than in the controls (43.5% vs 35.7%, respectively, \( P = 0.95 \)).53 This same research group published a third study in 1994 (in abstract form only), in which trauma patients were randomized to 1 of 3 groups: early PN, standard therapy with no nutrition support, or early EN (this time delivered directly into the small bowel via a nasojejunal tube).54 In the second study the patients on early gastric feeding had problems with tolerance and received
significantly less calories and protein than patients on PN. In the third study, tolerance of early nasojejunal feeds was better, such that patients received several calories similar to that received in the PN group. Results were exactly opposite to those reported in the original study by Rapp and colleagues in 1983. In the third study by Charish and colleagues in 1994, pneumonia was significantly more frequent in the PN group (50% vs 18%, \(P<.05\)) and mortality was significantly higher (23% vs 0%, \(P<.05\)) when compared with controls receiving early EN. It is ironic that the study by Rapp and colleagues was used to support this meta-analysis by Simpson and Doig, deriving a treatment effect favoring PN that was directly opposite to that of the clinical experience of the original investigators at University of Kentucky.

There was another ironic aspect of the meta-analysis by Simpson and Doig and their subjective filter of the literature. Of the 9 studies included in their meta-analysis, none had concealed randomization and only 1 study was blinded. Had they emphasized all the 3 quality components (intent-to-treat analysis, concealed randomization, and appropriate blinding of patients and investigators), they would have been obligated to exclude virtually all of the studies. Instead, they focused only on 1 quality, intent to treat, and as a result, specifically excluded 5 important studies. As Koretz pointed out in an editorial, there is “no reason to single out one elemental quality as being more important than the others.” The 9 studies selected for the meta-analysis by Simpson and Doig still had high risk for bias based on failure to conceal randomization and to blind researchers and patients. Therefore, as Koretz commented, there is “no reason to consider the Simpson-Doig meta-analysis more reliable than any of the others.”

The controversy over the preferential use of PN versus EN and the contradictory results of the meta-analysis by Simpson and Doig highlight the difficulties that may arise when subjectivity of a scientific group (such as a guidelines committee) is applied to interpretation of the clinical studies from the literature. Whether the GRADE system succeeds in providing structure for the subjective analysis and whether it improves the transparency of the decisions made by the Guidelines Committee remain to be seen.

**SUMMARY**

The most important element in the integration of guidelines to clinical practice is transparency, that is, the reader is able to track the recommendation back to the supporting studies. As a large institution, a small group, or a specific individual, it is important to resolve one’s own interpretation of each of the controversial issues within a set of guidelines after reviewing the supporting literature. Controversy affords the opportunity for growth and understanding. And yet, the clinician providing nutrition support therapy should understand that with any controversy there may not be a correct answer. The most important step in the conclusion of this process is to determine whether the interpretation of the guidelines and the supportive evidence should alter clinical practice.

**REFERENCES**

2. ASPEN Board of Directors and the Clinical Guidelines Task Force. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. JPEN J Parenter Enteral Nutr 2002;26:1SA–138SA.


