

THE IMPACT OF ENTERAL NUTRITION ON OUTCOMES IN CRITICAL CARE

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According to growing evidence, the likelihood of improving patient outcomes in the intensive care unit (ICU) can be increased by adopting a new view of the role of nutrition. With today's advances in pharmaconutrients and the availability of clinical guidelines that set forth best practices in nutrition, intensivists are urged to change their thinking and embrace therapeutic nutrition as an essential part of care. Implementing evidence-based nutrition guidelines, such as the Canadian Clinical Practice Guidelines for Nutrition Support for the Mechanically Ventilated, Critically Ill Adult Patient and those developed by the Society of Critical Care Medicine (SCCM) and the American College of Critical Care Medicine (ACCM), is an important step toward achieving better outcomes for critically ill patients.

A Look at SCCM's New Enteral Guidelines

Prior to discussing SCCM's new enteral feeding guidelines, Robert G. Martindale, MD, PhD, from Oregon Health and Science University in Portland, spoke generally about clinical guidelines. "Guidelines are not absolute requirements, and they do not guarantee a specific benefit in outcome or survival," he said. "Rather, they are basic guidelines supported by a review and analysis of all the pertinent data in the literature, other national and international guidelines, and expert opinions."

To be effective, guidelines must be clinically practical. However, because ICU patients are a heterogeneous group, every guideline cannot be applied to every patient. This is important to emphasize when introducing new guidelines to clinicians.

Beneficial outcomes have been reported with the use of nutrition guidelines for critically ill patients. For example, results from a multicenter trial demonstrated that improved delivery of nutrients, shorter ICU length of stay, and a trend toward lower mortality were achieved when algorithms for enteral and parenteral therapy were implemented (Martin et al. *Can Med Assoc J.* 2004;170:197). In another prospective evaluation of outcomes, the use of an evidence-based feeding protocol resulted in a significant decrease in mortality, along with increased delivery of nutrients and shortened duration on mechanical ventilation (Barr. *Chest.* 2004;125:1446).

Several organizations have developed nutrition guidelines for ICU patients. In addition to SCCM, these organizations include: Critical Care Nutrition (which comprises several Canadian medical societies), the European Society for Clinical Nutrition and Metabolism (ESPEN), the American Society for Parenteral and Enteral Nutrition (ASPEN), the Australian and New Zealand Intensive Care Society, the Eastern Association for the Surgery of Trauma, and the American College of Chest Physicians. "With all these guidelines available or soon to be released, deciding which set of guidelines to follow can be problematic," said Martindale.

Several similarities exist among these various sets of guidelines. For example, all of them favor enteral over total parenteral nutrition (TPN), and all consider early enteral feeding (initiated within 24 to 48 hours of arrival to the ICU) to be superior to TPN. "If the patient has been in the ICU for a day or two and was nourished when he or she arrived, there's no need to immediately begin TPN," said Martindale. "However, enteral nutrition is not feasible for malnourished patients undergoing major gastrointestinal (GI) surgery, so we should start TPN relatively early, rather than waiting." All the guidelines oppose starting TPN and enteral feeding simultaneously, as it may be harmful.

There also is general agreement favoring the use of glutamine, antioxidants, fish oils (in acute respiratory distress syndrome [ARDS] and acute lung injury), and promotility agents. "Soluble fiber is beneficial," Martindale explained, "but we need to be very cautious with the use of insoluble fiber in patients who have severe GI- or ICU-related dysmotility."

The Role of Specialized Enteral Nutrients in Critical Care

"Enteral nutrition therapy has every bit as much therapeutic value as other agents used in critically ill patients," stated Paul Wischmeyer, MD, from University of Colorado Health Sciences Center in Denver.

Wischmeyer began his discussion by noting the characteristics of the ideal therapeutic agent. In addition to being clinically effective, widely applicable, associated with minimal adverse effects, and inexpensive, the ideal agent would be physiologically justifiable and supported by strong evidence. Other attributes of the ideal agent

None of the guidelines recommend routinely using an immune modulating formula in patients with severe sepsis, as more data are needed. However, SCCM and most of the other organizations support the use of these formulas in other ICU patients.

"In terms of target goals, we believe we need to achieve about 50% to 65% nutrient delivery, and we'd like to see the benefit within the first week of feeding initiation," Martindale reported. "With therapeutic nutrition, at least 50% delivery of therapeutic compounds, such as protein, glutamine, arginine, or fish oils, is needed so that the feeding is therapeutic rather than supportive."

One area of controversy among the different guidelines involves the use of probiotic supplementation, which is supported by SCCM. "In developing the SCCM guidelines, we saw there was an abundance of data demonstrating the beneficial effects of probiotics," stated Martindale. However, he also pointed out a recent study that showed a slightly higher rate of mortality among patients with pancreatitis who received probiotics compared with those who did not.

Other comparative differences relate to the use of hypocaloric feeding in the obese and non-obese ICU patient populations. The guidelines from SCCM, the Canadian societies, and ASPEN all support relatively temporary hypocaloric nutrition in patients who are morbidly obese, but not in those of normal weight. Guidelines from other organizations do not address this issue.

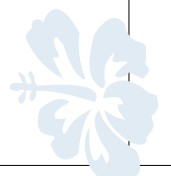
In trying to determine which set of nutrition guidelines to follow, a few potential problems should be considered. First, inconsistencies exist regarding terms and definitions. Authors of the SCCM guideline addressed this issue by adopting the same terminology used by ASPEN. Variable acceptance of guidelines by practitioners is another problem. In addition, some clinicians do not understand that these guidelines are not absolute rules or laws. "Rather, because patients are a heterogeneous group, we need to 'massage' the guidelines occasionally," remarked Martindale.

"What is the best way to get physicians to change their practice and implement new guidelines?" asked Martindale. He cited findings reported by Watkins that underscored the importance of linking the published evidence guidelines to everyday practice (Watkins. *Fam Pract.* 2004;21:661). "The study also revealed that stressing cost-effectiveness was counterproductive," he said. "Furthermore, it became apparent that clinical autonomy must be protected. Clinicians need to be able to make their own decisions. Therefore, the guidelines should be presented in a nonthreatening and non-confrontational manner."

Education and a sense of partnership are essential to the successful implementation of clinical guidelines, emphasized Martindale. "It takes strong leadership and team acceptance." Martindale also reiterated the need to make it clear that the guidelines are flexible and should be used based on the patient's condition.

include ease in administration and the ability to be used as pretreatment to prevent disease and complications.

Therapy involving three types of pharmaconutrients—specialized fat formulas, arginine, and glutamine—illustrate how far enteral nutrition has progressed over the years. In reviewing each of these, Wischmeyer showed how they all had therapeutic effects that made mechanistic sense and that were supported by the majority of studies on clinically relevant endpoint as well as by a meta-analysis. Just as important, they all showed no evidence of producing harm.



Specialized fat formulas. “Patients in the ICU are theoretically in the pro-inflammatory state,” said Wischmeyer. Two essential fatty acids (EFAs)—omega-3 and omega-6 fatty acids—possess anti-inflammatory properties, and both have been shown to have beneficial effects in patients with ARDS.

Gadek et al reported a significant decrease in organ failure among patients with ARDS who were treated with an omega-3 fatty acid (eicosapentaenoic acid [EPA]), an omega-6 fatty acid (gamma-linolenic acid [GLA]), and antioxidants (Gadek et al. *Crit Care Med.* 1999;27:1409). Other investigators have reported significant decreases in mortality when EPA + GLA + antioxidant therapy was given to ventilated patients who had acute lung injury or severe sepsis and sepsis shock (Singer et al. *Crit Care Med.* 2006;34:1033; Pontes-Arruda et al. *Crit Care Med.* 2006;34:2325).

A meta-analysis evaluation of outcome data also provides convincing support for the use of EFAs in ARDS (Pontes-Arruda et al. *Crit Care Med.* 2006;34:A95). “In looking at data from three trials in three countries, each evaluating the use of EPA + GLA + antioxidant therapy in more than 100 ICU patients, dramatic benefits with these EPAs are seen in several outcomes: ICU-free days, ventilator-free days, fewer organ failures, and reduction in mortality,” stated Wischmeyer.

Adding to this favorable clinical data is the economic reality of EPA therapy. The cost of fish oil supplementation, at \$25 per day, makes this therapy extremely cost-effective.

Arginine. “The use of arginine is very controversial,” said Wischmeyer. “In patients with sepsis, arginine has been associated with increased mortality. However, in perioperative patients and trauma patients, arginine appears to be very beneficial.” The reason for this difference may lie in the decrease in T-cells that occurs after trauma and surgery but does not occur in sepsis. Arginine is required for T-cell division.

Clinical data from 19 controlled trials have been analyzed to evaluate the impact of arginine immunomodulatory formulas on clinical outcomes for more than 2,000 perioperative patients. In 17 of these trials, arginine was associated with a 50% reduction in infection complications among 1,000 patients. “This supports the science that arginine has a role in preventing or modulating infection.” In 18 trials, arginine was linked to decreased length of stay. No difference in mortality rate was noted with arginine versus the control therapy.

None of the data showed any significant evidence of harm in perioperative patients. The cost savings of using arginine in surgical and trauma patients is very promising, according to Wischmeyer.

Glutamine. Glutamine is a non-essential amino acid that is vital to the gut, kidneys and immune cells. It serves as metabolic fuel and is the precursor to purine and pyrimidine synthesis. Glutamine concentrations fall precipitously after injury, illness and stress (including exercise). “We know there’s a dramatic deficiency of glutamine in critically ill patients,” stated Wischmeyer. “We also know that the body runs out of glutamine in 48 hours, and that patients who arrive in the ICU with a low glutamine level are more likely to die.”

Because critical illness leads to a massive decrease in the glutamine pool, replacement of glutamine is a rationale therapy. Glutamine is postulated to provide benefits through one or more of four proposed mechanisms: tissue protection, anti-inflammatory or immunologic activity, metabolic activity, and antioxidant activity or attenuation of nitric oxide formation.

A meta-analysis of all the reported glutamine trials revealed an approximate 25% percent risk reduction in mortality rates among ICU patients who received glutamine. Glutamine also was associated with significant reductions in ICU length of stay (approximately 4.5 days). In addition, infectious complications were reduced with glutamine, although not as dramatically as they were in terms of length of stay. Parenteral administration of glutamine appears to produce better outcomes than enteral feeding.

“Given the mechanisms and effects of glutamine and the other two nutrients discussed, I propose a new paradigm for glutamine, EFAs and arginine,” said Wischmeyer. “We need to begin seeing them as more than nutrients. They actually serve as vital drugs that signal molecules within the body and, as such, these pharmacognitrials have an important role in critical care medicine.”

Wischmeyer closed by urging clinicians to create change in the ICU by placing more emphasis on therapeutic nutrition. “I want you to challenge the old thinking that nutrition therapy is just a supportive therapy that doesn’t need much of our attention,” he said. “Demand data on nutrition therapy, and then demand change. If we could start treating diabetic patients worldwide with insulin only a year after its benefits were published, we can certainly do this with nutritional intervention.”

Implementing Nutrition Guidelines: The Canadian Experience

“Information overload is a real factor that we face in medicine in general, and in critical care medicine specifically,” said Daren K. Heyland, MD, from Kingston General Hospital Ontario. “There are scores of data related to nutrition in critical care medicine, but it’s no easy task to stay on top of it all.”

Mixed results from a variety of randomized controlled trials (RCTs) make it difficult for the individual clinician to make sense of the data. “That’s why rigorous, evidence-based guidelines are so valuable,” he continued. “They provide best practice statements that can help guide the clinician.”

Of the various levels of evidence available in the literature, systematic reviews rank at the top, providing the most unbiased data and offering the strongest inferences. The next highest level comprises RCTs. Following such trials are cohort studies, case control studies and case series. Clinical practice guidelines, which are based on the best evidence available, ideally lead to improved patient outcomes when they are adopted.

Heyland shared his experiences with the development and implementation of the Canadian Clinical Practice Guidelines for Nutrition Support for the Mechanically Ventilated, Critically Ill Adult Patient. In developing the guidelines, a multiprofessional committee was formed which included physicians, registered nurses, registered dietitians, and pharmacists. The team appraised and prepared systematic reviews of the best available evidence on 34 different topics. “Since then, we’ve been validating our guidelines, and more importantly,

taking steps to get these to the bedside,” said Heyland.

As a first step in validating the guidelines, a prospective observation study was conducted involving the practice patterns at 60 ICUs across Canada. “We noted that among the ICUs whose patterns were more consistent with our guidelines, better adequacy of enteral nutrition was achieved compared with ICUs that did not follow the guidelines,” said Heyland.

Bringing evidence-based knowledge to the bedside for improved outcomes is now a major focus for the Canadian guidelines. “Realizing that we needed to find ways to move practitioners from where they currently were to where they need to be, we developed a multifaceted guideline implementation strategy,” he said.

A study was conducted to evaluate different approaches to disseminating and implementing the guidelines. In a randomized cluster trial, ICUs throughout Canada were randomized to one of two methods of dissemination of the Canadian guidelines (Jain et al. *Crit Care Med.* 2006;34:2362). The passive method consisted of receiving a copy of the guidelines and attending a presentation at a national meeting. The active method consisted of several additional strategies, including attending interactive workshops and using various Web-based tools, such as benchmark site reports showing performances at all sites. See www.criticalcarenutrition.com for examples of tools and site reports. Dietitians positioned as local opinion leaders were also part of the active method. “With our Web-based tools, the idea was to make everything as automated, systemized and easy as possible,”

Heyland said.

The results of this trial showed that a 7% change from baseline in enteral nutrition adequacy (i.e., prescribed calories received) for all ICU patients (medical and surgical) was achieved by both the active and passive groups. However, among a subgroup consisting of medical ICU patients, the adequacy of enteral nutrition increased from baseline by 10% in the active group versus 1.9% in the passive group.

The groups did not obtain differences for clinical outcomes (e.g., ICU length of stay, mortality) or for nutrition support practices (e.g., type of nutrition support received, enteral feeding starting within 48 hours). “These disappointing results prompted us to try to identify the barriers and enablers to nutrition guideline adherence in the ICU,” remarked Heyland. “So we went back and did some research.”

Heyland described the results of a multiple-case study involving four ICU sites and 28 semi-structured key informant interviews with frontline clinicians and healthcare administrators (Jones et al. *Nutr Clin Pract.* 2007;22:44).

Identified barriers regarding the guidelines included information overload, weak evidence, and impracticality or complexity. Institutional barriers included the community hospital setting, an open ICU, slow administrative process, and resource constraints. Barriers among clinicians included lack of awareness, limited critical care experience, resistance to change and nursing workload. Patient barriers included poor clinical outcome and being a surgical patient (see Table 1).

The study also revealed the factors that enabled or encouraged

and protocols, which we placed on the Web site—is also a critical component to implementation.”

Another important key to implementation is having a dietician who is knowledgeable and available to the team as a resource. In addition, interviewees said it was important to have the guidelines easily accessible and visible. “That’s why we posted them on the Web site and provided the guidelines on posters, pocket cards, and so forth,” Heyland noted. Making the guidelines easy to follow and perform enables implementation, as does providing education and open discussion opportunities.

When interviewees were asked to identify the most valuable strategies, many said informal one-on-one discussions about the guidelines were helpful. They also appreciated bedside reminders, such as checklists and algorithms. In addition, feedback and audits, as reflected in the benchmark site reports, ranked among the successful implementation strategies.

“In summary, we need to make sure our staff is educated and motivated,” Heyland said. “In Canada, we rely principally on dietitians and other key opinion leaders to make that happen. We have constant reminders in our bathrooms, on our walls and in the lunchroom to reinforce key concepts related to nutrition. We make it easy by automating the system with preprinted orders and algorithms. We constantly audit our practice so that we can clearly identify our strengths and weaknesses.

“These are all system tools that need to be applied. But with an individual patient, there needs to be accountability and responsibility every day,” he continued. “We need to ask: Is the best nutrition being practiced here? If not, why not?” He urged that someone, probably the nurse, monitor the nutrition success daily. “That would help draw attention to what needs to happen to achieve the best outcome.”

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Table 1. Barriers and Enablers to Guideline Implementation

Barriers:	Enablers:
• Resistance to change	• Agreement of ICU team
• Lack of awareness	• Easy access to guidelines
• Lack of critical care experience	• Ease of application
• Clinical condition of patient	• Incorporation into daily routine
• Resource constraints	• Education and training
• Slow administrative process	• Dietician as opinion leader
• Workload	• Open discussion
• Numerous guidelines	
• Complex recommendations	
• Paucity of evidence	
• Outdated guidelines	

Jones et al. *Nutr Clin Pract.* 2007;22:44

implementation of the guidelines. “Interviewees said that when they functioned as a team and the attending physician was on board with our best practice statements, the guidelines were implemented. So, creating a sense of teamwork is intrinsic to making any type of clinical guidelines,” he reported. “Making the guidelines easy to become part of the routine practice—through preprinted orders, algorithms

Continuing Education Self-Assessment

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7. Among the various nutrition guidelines developed by organizations for the care of critically ill patients, which of the following is considered controversial?
 - a. Antioxidant supplementation in patients with acute lung injury
 - b. Initiation of enteral feeding within 24 to 48 hours of arrival to the ICU
 - c. The use of probiotic supplementation in critically ill patients

8. According to a meta-analysis, the use of omega-3 fatty acids with borage oils and antioxidants in patients with acute respiratory distress syndrome resulted in increased ICU-free days and ventilator-free days, but did not improve mortality outcomes.
 - a. True
 - b. False

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