42nd Critical Care Congress Review

Supported by education grants from Hospira, Inc. and Nestlé HealthCare Nutrition.

CE/CME Enduring Material
Release Date: June 2013
Expiration Date: June 2014

Learning Objectives

At the conclusion of this activity participants should be able to:

- Discuss approaches to screen for delirium and consider both pharmacologic and nonpharmacologic approaches to prevention and management
- Minimize the development of malnutrition through goal-directed therapy combining the use of enteral and parenteral nutrition
- Recognize new therapies for sepsis in the intensive care unit and the limitations of current research for better translation of evidence to the bedside

Type of Activity

This activity was designed as an evidenced based forum to review expert opinions of various topics in critical care. This activity will focus on increasing knowledge and its application to practice.

Competencies

SCCM supports recommendations that will promote lifelong learning through continuing education. SCCM promotes activities that encourage the highest quality in education that will enhance knowledge, competence or performance in critical care practice. This activity will meet the following:

- Patient- and Family-Centered Care
- Practice Applications
- Quality Improvement
- Multiprofessionalism

Target Audience

This continuing medical education offering is intended to meet the needs of all physicians, nurses, pharmacists, respiratory therapists and other providers who care for critically ill patients.

Physicians

Accreditation Statement

The Society of Critical Care Medicine (SCCM) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Designation Statement

SCCM designates this home study educational activity for a maximum of 1 AMA PRA Category 1 credits™. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

Nurses

SCCM is approved by the California Board of Registered Nursing, Provider No. 8181 and approves this panel for 1 contact hour.

Pharmacists

The Society is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmaceutical education. This monograph will provide 1 continuing education hour. (0236-0000-13-469-H01-P) SCCM reports to a continuing pharmacy education (CPE) tracking service, CPE Monitor that will authenticate and store data for completed CPE units received by pharmacists and pharmacy technicians. The tracking system will make CPE data for each participant available to the state boards of pharmacy where the participant is licensed or registered. After CPE units are processed by ACPE and NABP, pharmacists and pharmacy technicians will be able to login to a comprehensive electronic profile to access information about their completed CPE.

Obtaining Credit

To claim credit, a learner must purchase the free course via the SCCM store at www.sccm.org/CongressReview13. There is no cost for this transaction.

Upon completion of this free purchase and the complete review of the material, please login to www.mysccm.org with your SCCM Customer ID and password. In the My Learning section of MySCCM.org, links will appear for this activity's posttest and evaluation under Congress Review. After earning a passing score of 70% or higher on the posttest, you will be able to claim credit for this activity.

For more information on the Congress Review, please contact SCCM at **support@sccm.org** or call **+1 847 827-6888.**

For additional information on these topics and other areas, please visit **www.learnicu.org**

Disclosures

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Maximizing Clinical and Surgical Outcomes with Immunonutrition

The field of pharmaconutrition has opened the door to new therapies for patients in the intensive care unit (ICU). A solid body of evidence on selected nutrients, along with outcomes data and clinical guidelines, now give intensivists a blueprint for applying immunonutrition as a therapeutic approach in critical care.

From Pivotal Research to Current Recommendations

Presented by Ainsley Malone, MS, RD, LD, CNSC, a Nutrition Support Dietitian in the Pharmacy Department of Mount Carmel West Hospital in Columbus, Ohio, USA. She has assisted in the management of nutrition support therapy for critically ill patients for more than 25 years.

"In the early 1990s, immunonutrition was an emerging therapeutic entity," said Ainsley Malone, MS, RD, LD, CNSC. "At that time, 95% of ICU patients were fed parenterally, and few enteral options were available." Today robust evidence exists in the field of pharmaconutrition, and guidelines on the use of immunonutrition in critically patients are widely available, although they vary by organization (Table 1).

The early studies highlighted here produced promising results that helped lay the groundwork for the current state of immunonutrition. Since then, investigators have continued to research immunonutrition with varying results – some beneficial, some neutral and others harmful – as the field becomes increasingly complex and robust.

The benefits of immunonutrition involve stemming the cascade of responses to severe injury, trauma or infection, which begins with a hypermetabolic effect triggering catabolism and diversion of the body's protein, fat and carbohydrate reserves. As the cascade continues, decreased immunocompetence, secondary infections, multiple organ failure, and death may ensue. "Immunonutrition can play a clear role in altering that immunocompetence," Malone stated.

Supported by a medical education grant from Nestlé HealthCare Nutrition.

Immunonutrition research has focused largely on glutamine, arginine, fish oil, and nucleotides. Glutamine, a substrate for the gut, kidneys and immune cells, has potent antioxidant effects. Arginine, a secretagogue for insulin-like growth factor 1 and growth hormone, enhances T-cell proliferation, detoxifies ammonia, promotes vasodilation, and is essential to wound healing. Fish oil, rich in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), exerts an anti-inflammatory effect on multiple disease entities and enables beneficial alteration of membrane phospholipids. Nucleotides are important in the maintenance of the cellular immune response.

The first study in immunonutrition evaluated an immune-enhancing formula in patients who underwent upper gastrointestinal (GI) abdominal surgery (Daly J, et al. *Surgery*. 1992;112:56-67). Daly and colleagues randomized 85 patients to receive either the immune-enhancing formulation (containing arginine, EPA, DHA, a nucleotide, and other nutrients) or standard diet. The immune formulation was initiated on postsurgical day 1 by needle catheter jejunostomy, starting at full strength (25 mL/h); the goal (~25 kcal/kg/d) was reached by postsurgical day 3 or 4. Results showed that lymphocyte stimulation in response to concanavalin A was greater with the immune formula at day 7, and postoperative complications were significantly reduced with the immune formula compared with the control. The investigators concluded that postoperative immunonutrition significantly improved immunologic and clinical outcomes.

The second study was a two-year, multicenter, randomized trial in which trauma patients (excluding those with comorbid chronic disease, head injury or pelvic fracture) received either an immune formulation or standard enteral nutrition (Moore F, et al. *J Trauma*. 1994;37:607-615). The feedings were started at full strength (25 mL/h) within 24 hours of injury via jejunal access, and patients reached their target within 72 hours. As with the study by Daly et al, "early initiation of immunonutrition enables early goal achievement," said Malone. The immune formulation contained greater amounts of arginine, glutamine, omega-3 fatty acids, nucleic acids, and some additional antioxidants compared with the control nutrition. The results revealed that the immune formula group had significant increases in total lymphocyte, T lymphocyte, and T-helper cells versus the control group. No differences between groups occurred in the number of ventilator days, ICU days or hospital days, but the immune group had significant reductions in abdominal abscesses and multiple organ failure. The authors concluded that an "immune-enhancing enteral diet offers clinical benefits in stressed surgical patients."

In the third study, a mixed ICU patient population was randomized to either the immune or control formulation (Bower R, et al. *Crit Care Med*. 1995;23:436-449). The formula was initiated within 48 hours of the precipitating event, and the goal rate of 60 mL/h was reached within 96 hours. Although the intact protein content was the same in both formulations, the addition of arginine provided a greater nitrogen source in the immune formula, which also contained increases in omega-3 and antioxidant content. Hospital length of stay was reduced among patients stratified as septic who received the immune formulation compared with the controls. "Furthermore, patients who received an average of 850 mL daily of the study formula had a significantly shorter length of stay compared with those who did not receive that larger amount of formula," reported Malone.

Regarding current guidelines on immunonutrition, Malone cautioned that "it's important to consider the population that was studied." She noted that the 2009 Canadian clinical practice guidelines were based on a meta-analysis of studies encompassing mixed types of critically ill patients. "The meta-analysis found that diets supplemented with arginine and other nutrients in critically ill patients overall have no effect on mortality or rate of infectious complications, but they may possibly reduce hospital length of stay, ICU length of stay, and mechanical ventilation." These guidelines were updated in 2012, adding two arginine studies relating to pancreatitis patients.

According to the 2009 guidelines published jointly by the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) and the Society of Critical Care Medicine (SCCM), immune-modulating enteral formulations

Table 1.

Clinical Guideline Recommendations Across Organizations

Use of Immune-Modulating Formulations	Australia/ New Zealand 2003	ESPEN 2006	Canadian 2009/2012	SCCM 2009	A.S.P.E.N. 2009
In all ICU patients	No	Yes	No	Yes	Yes
In surgery/trauma patients	n/a	Yes	Yes	Yes	Yes

should be used in appropriate patient populations (major elective surgery, trauma, burns, head and neck cancer, mechanical ventilation), being cautious in patients with severe sepsis. The 2010 European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines identified specific populations, recommending the use of immune formulations containing arginine, nucleotides, and omega-3 fats in elective GI surgical patients. ESPEN guidelines assign an Acute Physiology and Chronic Health Evaluation (APACHE) II score to patients with mild sepsis, and state that an immune-modulating formula in patients with severe sepsis may be harmful. The Academy of Nutrition and Dietetics (AND) does not recommend these formulas in all ICU patients.

Clearly, current guidelines vary. As Malone emphasized, "The important point to remember is that we need to look closely at the population for which the guideline recommendations are made."

Fish Oil in Critical Illness: Mechanisms and Clinical Applications

Presented by Paul Wischmeyer, MD, Professor of Anesthesiology, Associate Chair of Clinical and Translational Research, and Director of Nutrition Therapy Services at the University of Colorado School of Medicine in Denver, Colorado, USA. He is also the Director of the Translational Pharmacology and PharmacoNutrition Laboratory at the University of Colorado.

Humans have evolved for many years on a Omega 3:Omega 6 ratio of approximately 1:1, unfortunately the ratios of these nutrients obtained from our diet is rapidly "devolving" to include a marked increase in Omega-6 fats and a decrease in Omega 3 fatty acids. "Twenty years ago, the Mediterranean diet offered a 2:1 ratio of Omega 6:Omega 3, which provided benefits against heart disease, but that ratio is rapidly increasing today with U.S. intakes of 18:1 now the norm," said Paul Wischmeyer, MD. This change in intake of dietary fish oil exists in many cultures worldwide, and it is of particular concern regarding patients who present to the ICU.

"There's quite an imbalance in our patients' diets, and we must consider restoring that – perhaps in part through omega-3 supplementation," Wischmeyer said, noting that such a therapeutic approach makes sense from a mechanistic standpoint. "In inflammation, proper supplementation of omega-3 fatty acid, EPA, gamma linolenic acid (GPA), and other key fatty acids that our diets were meant to contain for thousands of years may arrest the inflammatory loop and reduce the amplification that occurs in these patients."

Furthermore, researchers have discovered that omega-3 fatty acids contain key molecules, called resolvins and protectins, that resolve acute inflammation. For example, they have been shown to arrest neutrophil infiltration into the lung. "That's where the degradation of our diet has become a problem," stated Wischmeyer. "In Africa and other third world countries with more evolutionary conserved diets there is very little autoimmune disease and less heart disease mortality; these appear to be related to our new, potentially toxic, western diet."

All current guidelines for ICU patients recommend use of continuously-administered enteral fish oil supplemented formulas in patients with acute respiratory distress syndrome (ARDS). Numerous trials evaluating this supplementation as a continuous part of complete nutrition delivery demonstrate this to be safe, with no adverse events. Moreover, in pediatric patients, parenteral fish oil monotherapy has been shown to be safe and efficacious in reversing parenteral nutrition-associated liver failure, even when given for years (de Meijer VE, et al. *JPEN J Parenter Enteral Nutr*. 2009;33:541-547).

Clinical outcome data reveal differing results depending on how the fish oil was administered. A meta-analysis found that continuous infusion of fish oil given as part of full nutrition in patients with ARDS was associated with an 83% reduction in organ failures and a 60% reduction in all-cause mortality at 28 days (Pontes-Arruda A, et al. *JPEN J Parenter Enteral Nutr*. 2008;32:596-605). In contrast, Rice and colleagues reported poorer outcomes, including lack of a mortality benefit and more days with diarrhea, when fish oil supplementation was administered as a bolus dose, separate from the nutritional support feeding, in patients with acute lung injury (Rice TW, et al. *JAMA*. 2011;306:1574-1581.)Moreover, in a phase II trial, no change in biomarkers of inflammation occurred following bolus administration of fish oil for treatment of acute lung injury (Stapleton R, et al. *Crit Care Med*. 2011;38:1655-1662), whereas continuous infusion has been shown to reduce these markers. "It may be that when fish oil is poured into a sick gut as a bolus dose, it is not absorbed and when coupled with inadequate complete nutrition delivery these fats may be metabolized as energy rather then exerting their anti-inflammatory effect," said Wischmeyer. "This is supported by the fact that the levels achieved in the Rice trial were considerably less then those that were achieved in previous positive trials of fish oil supplementation, given as a continuous infusion, as part of complete nutrition."

In a parenthetical discussion of protein, Wischmeyer pointed out that the control group in the multicenter study by Rice and colleagues received 20 g of protein daily which supplemented about 5 times more protein then the fish oil group. This higher protein delivery in the control group was associated with a significantly lower mortality rate. "Is it possible an extra 20 g of protein daily in underfed patients saves lives?" asked Wischmeyer. "I can report that in our international database of many thousands of ICU patients, we see that every additional 30 g of protein we give improves survival" (Alberda C, et al. *Intensive Care Med*. 2009;35:1728-1737).

Wischmeyer also noted that administration of large amounts of fish oil or other pharmaconutrients (e.g., glutamine) appears not to be effective unless the patient also receives other nutrients as part of complete nutrition delivery. "To achieve a clinical effect, other nutrients must be present around the pharmaconutrient," he said.

In addressing the use of continuous fish oil to prevent sepsis and septic shock, Wischmeyer discussed the results of a multicenter, randomized trial in Brazil involving 200 patients with signs of the systemic inflammatory response syndrome (SIRS) and prior to major organ failure (Pontes-Arruda A, et al. *Crit Care*. 2011; 15:R144). Compared with a standard, non-high fat, enteral formula, the fish oil formula reduced the development of severe sepsis, septic shock, organ failure, days of mechanical ventilation, and hospital length of stay. "These patients were not intubated and not in septic shock at enrollment," Wischmeyer said. "These results show promise for using fish oil to prevent the progression to sepsis, septic shock, and organ failure, perhaps correcting a long-standing dietary imbalance due to lack of needed Omega-3 content in the average patients diet." Clearly, this is an exciting topic that needs more multicenter randomized trials." Other evidence supports favorable outcomes with the use of parenteral fish oil in abdominal sepsis, reducing inflammation, reoperative rate, and hospital length of stay.

"More research is needed, but we have years of data regarding the safety of fish oil pharmacotherapy both enterally and intravenously," concluded Wischmeyer. "I think we should 'be afraid' of what our patients are eating, because they're fundamentally different from patients we would have cared for 100 years ago. There's a major nutrient imbalance in patients today. It's possible Mom knew that when she gave us cod liver oil. Armed with this knowledge, perhaps we can restore balance to our patients and give them what they've always needed."

The Impact of Immunonutrients on Surgical Patients

Presented by Robert G. Martindale, MD, PhD, Professor and Chief in the Division of General Surgery at Oregon Health and Sciences University in Portland, Oregon, USA.

In the perioperative setting, appropriate and timely nutrition can improve outcomes. It can reduce loss of lean body mass in stress, helping patients to ambulate sooner and perhaps prevent such complications as deep vein thrombosis, pulmonary embolism or pneumonia. Moreover, early enteral nutrient delivery in surgical patients can decrease mortality, decrease the incidence of infections and attenuate the metabolic response to surgical stress. "We also know that specific nutrients have other beneficial effects in surgical patients, including membrane stability and mucosal maintenance," said Robert G. Martindale, MD, PhD. "Clearly we have strong evidence from prospective randomized clinical trials to support the use of perioperative metabolic and immune modulating formulas."

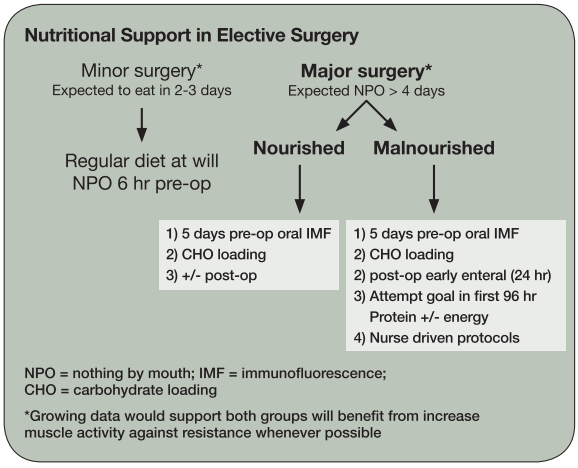

Figure 1.

Pharmaconutrients shown to be effective as preoperative preparation include: arginine, fish oil, nucleic acids, antioxidants, glutamine, and others. Focusing on arginine, Martindale reported on a meta-analysis of 35 articles comparing pre- and postoperative parameters in a heterogeneous surgical population that found that an arginine-supplemented diet significantly reduced overall infections and hospital length of stay (Drover J, et al. *J Am Coll Surg*. 2011;212:385-399). "The treatment effect was consistent across types of surgery, and the greatest effect was achieved when supplementation was given both before and after surgery," said Martindale.

Human studies demonstrate that use of large-dose arginine supplementation is safe and effective in improving wound healing (through increased collagen production), increased blood to poorly perfused tissues, and an increase in polyamine biosynthesis. The Safety profile is now clear even when large doses have been delivered in multiple human models including use in decreasing uterine contractions in preterm labor.

"On the other hand, the safety of arginine supplementation in patients with severe sepsis can be debated," said Martindale. One theory asserts that because arginine is a substrate for inducible nitric oxidase synthase (iNOS), the increase of iNOS may produce more nitric oxide (NO), yielding reduced vascular tone and vasodilation, resulting in hypotension and exacerbating sepsis. "This is a reasonable theory, and there may be a limited small amount of observational data to support it," Martindale said. "But a vast majority of published evidence supports a second theory, which postulates that an increase in NO is an adaptive response to enhance microcirculation and limit ischemia, coagulation and tissue injury.

Other nutrients warrant further study in critically ill and surgical populations. "There appears to be some beneficial effect with glutamine supplementation in surgical patients, but perhaps not so in the very sick ICU patient," said Martindale. More evidence is also needed regarding supplemental leucine in surgical and ICU populations. Interest in another nutritional area, probiotic supplementation, is rapidly growing. "Bacterial changes occur quickly in the ICU, so it's key to replace the patient's normal flora," stated Martindale. "Within 30 minutes of major trauma, we see virulence factors emerging in endogenous microbiome in the gut."

Martindale presented a protocol for elective surgery (Figure 1) and noted that growing data support increasing muscle uptake of protein through resistance exercise. The concept of practicing "prehabilitation" 30 days prior to surgery is key in addressing nutrition and exercises needs, but this is typically not applicable to the ICU patient. The optimal nutrition plan for the surgical patient which is supported by data includes a metabolic-modulating formulation (arginine, fish oil, and nucleic acids) ingested 5 to 7 days before surgery and carbohydrate loading with an isotonic carbohydrate solution 24 hours preoperatively. Early postoperative nutrition (i.e., started within 24 hours if possible) providing nutrient balance, high protein, fats (medium chain triglycerides, EPA/DHA, essential fatty acid), and vitamins (antioxidants in moderation; possibly vitamin D).

In summary, Martindale identified several areas of agreement about nutrition for surgical patients. Early nutritional support is better than late support, and enteral feeding is superior to parenteral feeding. Randomized placebo-controlled trials support the use of a nutritional preparation before major elective surgery. The use of immune and metabolic-modulating formulations is supported by ample literature recommending it as a standard of care in surgery. "Furthermore, as a very important point, we know that both pre- and postoperative protocols or guidelines increase nutrient delivery and improve outcomes," emphasized Martindale.

Continuing Education Self-Assessment

Maximizing Clinical and Surgical Outcomes with Immunonutrition

9. In comparison to a standard, nonfat, enteral diet, what were the effects of a continuous fish oil formula in a Brazilian study of 200 patients with signs of systemic inflammatory response syndrome?
   a. The fish oil formula reduced development of severe sepsis, septic shock, and organ failure, but had no effect on hospital length of stay.
   b. The fish oil formula reduced development of severe sepsis and septic shock, but had no effect on reduction of organ failure.
   c. The fish oil reduced development of severe sepsis, septic shock, days on mechanical ventilation, and hospital length of stay.
   d. The fish oil formula reduced organ failure and days on mechanical ventilation, but had no effect on development of severe sepsis or septic shock.

10. Which of the following was reported in a meta-analysis of 35 studies evaluating arginine supplementation in surgical patients?
   a. Arginine supplementation was more effective in patients following upper gastrointestinal abdominal surgery than after other types of surgery.
   b. Hospital length of stay, but not incidence of infections, was significantly reduced with arginine supplementation.
   c. The greatest effect of arginine supplementation occurred when it was administered both before and after surgery.
   d. Although arginine supplementation appears to increase free flap blood flow, it had no effect on reducing the risk of flap loss.