DISCLAIMER: These guidelines were prepared by the Department of Surgical Education, Orlando Regional Medical Center. They are intended to serve as a general statement regarding appropriate patient care practices based upon the available medical literature and clinical expertise at the time of development. They should not be considered to be accepted protocol or policy, nor are intended to replace clinical judgment or dictate care of individual patients.

Immune Enhancing Nutrition in the Intensive Care Unit

SUMMARY

The early institution of enteral nutrition has been shown to benefit severely injured patients in the critical care setting. In addition, the use of immune enhancing nutrition (IEN) which includes standard enteral formula supplemented with glutamine, arginine, omega-3 fatty acids and antioxidants has been investigated in critical care patients and results have been controversial. Recently, the Society of Critical Care Medicine (SCCM) in conjunction with the American Society of Parenteral and Enteral Nutrition (ASPEN) published guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient. In selecting the appropriate enteral formulation for the critically ill patient, the clinician must first decide if the patient is a candidate for a specialty immune-modulating formulation. In certain populations, research has shown that patients receiving IEN have a greater decrease in infectious complications than those patients receiving standard formulas. Strong data supporting IEN exists for the head and neck cancer as well as upper gastro-intestinal cancer populations. A number of meta-analyses and prospective clinical studies show a decrease in infectious complications in the surgical ICU population, but at this point in time there is insufficient data to support a Level 1 recommendation. There is, however, conclusive evidence showing no effect on mortality with the use of IEN in the surgical ICU. Data on the use of IEN in the trauma and burn populations is conflicting and more research is needed, but there is no strong evidence that its use would cause harm. There may be some increased risk with the use of arginine-containing formulas in patients who are severely septic and for this reason caution must be employed, but in mild to moderate sepsis these formulations have been found to be safe.

RECOMMENDATIONS

- **Level 1**
  - **Use of immune enhancing nutrition – IEN (standard enteral formula supplemented with glutamine, arginine, omega-3 fatty acids and antioxidants) should be employed in surgical patients with head and neck cancer as well as upper gastrointestinal cancer to decrease the incidence of major infectious complications.**
- **Level 2**
  - **Use of IEN is recommended for surgical ICU patients to decrease the risk of major infectious complications.**
  - **Immune modulating formulations containing arginine are safe for use in mild to moderate sepsis, but caution should be employed if used in severe sepsis.**
  - **Patients with ARDS and severe acute lung injury (ALI) should be placed on an enteral formulation characterized by an anti-inflammatory lipid profile and anti-oxidants.**
- **Level 3**
  - **To receive optimal therapeutic benefit from IEN, at least 50-65% of goal energy requirements should be delivered.**

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

INTRODUCTION

A large body of data suggests that adding pharmaconutrients to enteral formulations provides even further benefits on patient outcome than use of standard formulations alone (1). Studies from basic science have provided a rationale for the mechanism of the beneficial effects seen clinically. Such findings include the discovery of specialized immune (myeloid suppressor) cells, whose role is to regulate the availability of arginine, necessary for normal T lymphocyte function. These myeloid suppressor cells are capable of causing states of severe arginine deficiency which impact production of nitric oxide and negatively affect microcirculation. Immune-modulating diets containing arginine and ω-3 fatty acids appear to overcome the regulatory effect of myeloid suppressor cells. Agents such as RNA nucleotides increase total lymphocyte count, lymphocyte proliferation, and thymus function. In a dynamic fashion, the ω-3 fatty acids eicosapentaenoic acid (EPA) and docosohexaenoic acid (DHA) displace ω -6 fatty acids from the cell membranes of immune cells. This effect reduces systemic inflammation through the production of alternative biologically less active prostaglandins and leukotrienes. EPA and DHA (fish oils) have also been shown to down-regulate expression of nuclear factor-kappa B (NFκB), intracellular adhesion molecule 1 (ICAM-1), and E-selectin, which in effect decreases neutrophil attachment and transepithelial migration to modulate systemic and local inflammation. In addition, EPA and DHA help to stabilize the myocardium and lower the incidence of cardiac arrhythmias, decrease incidence of acute respiratory distress syndrome (ARDS), and reduce the likelihood of sepsis. Glutamine, considered a conditionally essential amino acid, exerts a myriad of beneficial effects on antioxidant defenses, immune function, production of heat shock proteins, and nitrogen retention. Addition of agents such as selenium, ascorbic acid (vitamin C), and vitamin E provides further antioxidant protection (2).

Multiple meta-analyses have shown that use of immune-modulating formulations during critical illness is associated with significant reductions in duration of mechanical ventilation, infectious morbidity, and hospital length of stay compared to use of standard enteral formulations. These same 5 meta-analyses showed no overall impact on mortality from use of immune-modulating formulations (3-5).

Table 13. Meta-Analyses Reported Comparing Immune-Modulating Enteral Formulations to Standard Enteral Formulations

Author	Population	No. of Studies Included	General Conclusions (Effect of Immune-Modulating vs Standard Enteral Formulations)
Heys et al, 1999[181]	Medical, surgical critical illness, cancer (n = 1009)	11	Decreased infection (OR = 0.47, 95% CI 0.32-0.70, $P < .05$) Decreased length of stay (WMD = 2.5, 95% CI 4.0-1.0, $P < .05$) No change in mortality (OR = 1.77, 95% CI 1.00-3.12, P = NS)
Beale et al, 1999[182]	Medical, surgical trauma, sepsis, major surgery (n = 1482)	12	Decreased infection (RR = 0.67, 95% CI 0.50-0.89, P = .006) Decreased ventilator days (WMD = 2.6, 95% CI 0.1-5.1, P = .04) Decreased length of stay (WMD = 2.9, 95% CI 1.4-4.4, P = .0002) No change in mortality (RR = 1.05, 95% CI 0.78-1.41, P = NS)
Heyland et al, 2001[210]	Medical, surgical critical illness, major surgery (n = 2419)	22	Decreased infection (RR = 0.66, 95% CI 0.54-0.80, $P < .05$) Decreased length of stay (WMD = 3.33, 95% CI 5.63-1.02, $P < .05$) No change in mortality (RR = 1.10, 95% CI 0.93-1.31, P = NS)
Montejo et al, 2003[211]	Critical illness (n = 1270)	26	Decreased abdominal abscess (OR = 0.26, 95% CI 0.12-0.55, P = .005) Decreased bacteremia (OR = 0.45, 95% CI 0.35-0.84, P = .0002) Decreased pneumonia (OR = 0.54, 95% CI 0.35-0.84, P = .007) Decreased ventilator days (WMD = 2.25, 95% CI 0.5-3.9, P = .009) Decreased length of stay (WMD = 3.4, 95% CI 4.0-2.7, $P < .0001$) No change in mortality (OR = 1.10, 95% CI 0.85-1.42, P = NS)
Waitzberg et al, 2006[212]	Elective surgery (n = 2305)	17	Decreased infection (RR = 0.49, 95% CI 0.42-0.58, $P > .0001$) Decreased length of stay (WMD = 3.1, 95% CI 3.9-2.3, $P < .05$) Decreased anastomotic leaks (RR = 0.56, 95% CI 0.37-0.83, P = .004) No change in mortality (RR = 0.72, 95% CI 0.39-1.31, P = NS)

WMD, weighted mean difference; RR, relative risk; CI, confidence intervals; OR, odds ratio; NS, not significant.

The beneficial outcome effects of the immune-modulating formulations are more uniformly seen in patients undergoing major surgery than in critically ill patients on mechanical ventilation. This influence is

even more pronounced when the formulation is given in the preoperative period. By differentiating studies done in surgical ICUs from those done in medical ICUs, Heyland et al showed that the greatest beneficial effect was seen in surgery patients with significant reductions in infectious morbidity (RR = 0.53; 95% CI 0.42-0.68; $P \leq .05$) and hospital length of stay (WMD = –0.76; 95% CI– 1.14 to –0.37; $P < .05$). In contrast, aggregating the data from studies in medical ICU patients showed no effect on infections (RR = 0.96; 95% CI 0.77-1.20; *P* = NS) but a similar reduction in hospital length of stay (WMD = –0.47; 95% CI– 0.93 to –0.01; $P = .047$). (6)

In certain populations, research has shown that patients receiving IEN have a greater decrease in infectious complications than those patients receiving standard formulas. Strong data supporting IEN exists for the head and neck cancer as well as upper gastro-intestinal cancer populations (7,8).

It has been hypothesized that there may be some increased risk with the use of arginine-containing formulations in medical ICU patients who are severely septic. Based on one level I report, one prospective randomized unblinded study using a control group receiving PN, and a third study published in abstract form only, use of arginine-containing formulations resulted in greater mortality than standard EN and PN formulations. Two of the 3 studies reporting a potential adverse effect had comparatively lower levels of arginine supplementation. The mechanism proposed for this adverse effect was that in severe sepsis, arginine may be converted to nitric oxide contributing to hemodynamic instability. This concept is contradicted by several other reports. One of these studies showed that infusion of arginine directly into the venous circulation of septic medical and surgical ICU patients caused no hemodynamic stability. Three other studies showed that clinical outcome was better and mortality was *reduced* in moderately septic ICU patients with use of an arginine-containing formulation (compared to a standard enteral formulation). Upon review of this controversy, the Guidelines Committee felt that immune-modulating formulations containing arginine were safe enough to use in mild to moderate sepsis, but that caution should be employed if utilized in patients with severe sepsis (3).

Recent studies have shown that dietary fatty acids can reduce the severity of inflammatory injury in patients with sepsis and /or ARDS. The supplementation of nutritional formulas with a combination of EPA, GLA and antioxidants can favorably reduce an elevated inflammatory response while promoting vasodilation and oxygen delivery.(9) A meta-analysis was published by Pontes-Arruda in 2009 which combined three major published studies evaluating the effects of an EPA/GLA diet on outcomes such as mortality, ventilator time, ICU and hospital LOS as well as development of new organ failures. Significant reductions were seen in all outcomes studied. (10) As recent as 2011, Pontes-Arruda published in *Critical Care* his results of a prospective, multicenter, randomized, double-blinded, controlled trial comparing the effects of feeding patients with early sepsis a diet including enteral nutrition enriched with EPA, GLA and antioxidants to those of a standard isonitrogenous and isocaloric control diet. He hypothesized that treatment with EPA/GLA could have an effective role in reducing the progression towards severe sepsis/septic shock and new organ failures. His intention-to-treat analysis demonstrated that patients fed the EPA/GLA diet developed less severe sepsis and/or septic shock than patients fed the control diet (26.3% vs 50.9% respectively). (11) These studies and their results are contradicted in one study which criticizes the design of previous studies in terms of sample size and inclusion of only patients who tolerated full-enteral nutrition. The OMEGA trial sought to test the effects of enteral supplementation of omega-3 fatty acids, GLA and antioxidants on clinical outcomes in patients with ALI using a twice-daily bolus administration that would allow inclusion of patients unable to tolerate continuous full feedings. (12) It was hypothesized that enteral supplementation with these nutrients would reduce inflammatory mediators and improve primary outcome of ventilator free days and other clinical outcomes in patients with ALI. This study was stopped early for futility when the test group had fewer ventilator-free and ICU-free days and the 60-day hospital mortality was 26.6% vs 16.3% in control group -concluding that supplementation with these nutrients did not improve the primary end point of ventilator-free days or other clinical outcomes in patients with acute lung injury and may be harmful. (12) The current recommendations from ASPEN/SCCM Guidelines for Provision and Assessment of Nutrition Support Therapy 2009 gives the use of EPA/GLA and antioxidants in patients with ARDS and severe acute lung injury a Grade A recommendation. (3)

Multiple enteral formulations are marketed as being immune-modulating, but vary considerably in their makeup and dosage of individual components. Few studies have addressed the individual pharmaconutrients, their specific effects, or their proper dosing. Many studies on this topic have been criticized for the heterogeneity, performed in a wide range of ICU patient populations, with a variety of experimental and commercial formulations.. It is not clear whether the data from published studies and these subsequent recommendations can be extrapolated to use of formulations that have not been formally evaluated. Based on the strength and uniformity of the data in surgery patients, the Guidelines Committee felt that a grade A recommendation was warranted for use of these formulations in the surgical ICU. The reduced signal strength and heterogeneity of the data in nonoperative critically ill patients in a medical ICU was felt to warrant a grade B recommendation.

For any patient who does not meet the criteria mentioned above, there is a decreased likelihood that use of immune-modulating formulations will change outcome. In this situation, the added cost of these specialty formulations cannot be justified and therefore standard enteral formulations should be used (4).

REFERENCES

1. Moore FA, Moore EE, Jones TN. TEN versus TPN following major abdominal trauma reduced septic morbidity. J Trauma 1989; 29:916-923
2. Todd SR, Gonzales EA, Turner K, Kozar RA. Update on post injury nutrition. Curr Opin Crit Care 2008; 14:690-695
3. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine and American Society of Parenteral and Enteral Nutrition: Executive Summary. Martindale RG, McClave SA, Vanek VW, McCarthy M, et al. Crit Care Med 2009; 37:1757-1760
4. Consensus recommendations from the US summit on immune enhancing enteral therapy. *JPEN J Parenteral Enteral Nutr*. 2001; 25:S61-S62
5. Heys SD, Walker LG, Smith I, Eremin O. Enteral nutritional supplementation with key nutrients in patients with critical illness and cancer: a meta-analysis of randomized controlled clinical trials. Ann Surg 1999; 229:467-477.
6. Heyland DK, Dhaliwal R, Drover JW, et al. Canadian Critical Care clinical practice guidelines for nutrition support in mechanically ventilated critically ill adult patients. JPEN 2003; 27:355-373
7. de Luis DA, Izada O, Cuellar L, Terroba MC, Aller R. Randomized clinical trial with an enteral arginine-enhancing formula in early post-surgical head and neck cancer patients. Eur J Clin Nutr 2004; 58:1505-1508.
8. Snyderman CH, Kachman K, Molseed L, et al. Reduced postoperative infections with an immune-enhancing nutritional supplement. Laryngoscope 1999; 109:915-921.
9. Pacht, Eric et al. Enteral nutrition with eicosapentaenoic acid, alpha-lenoleic acid, and antioxidants reduces alveolar inflammatory mediatory and protein influx in patients with acute respiratory distress syndrome. Critical Care Medicine 2003. Vol. 31, No. 2.
10. Pontes-Arruda A, DeMichele SJ, Seth A, Singer P: The use of an inflammation-modulating diet in patients with acute lung injury or acute respiratory distress syndrome: a meta-analysis of outcome data. JPEN 2008, 32:596-605.
11. Pontes-Arruda A, Martins FL, et al: Enteral nutrition with eicosapentaenoic acid, alpha-linoleic acid and antioxidants in the early treatment of sepsis: results from a multicenter, prospective, randomized, double-blinded, controlled study: the INTERSEPT study. Critical Care 2011, 15:R144.