



Summer 2011



EDITORIAL

Nutrition Support in Critical Illness — Bridging the Evidence Gap

Thomas R. Ziegler, M.D.

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The modern field of specialized nutrition support began with seminal studies showing that parenteral nutrition could stimulate growth and development in infants, as well as wound healing and convalescence in adults with the severe short bowel syndrome, who until that time had been unable to survive with enteral nutrition alone.^{1,2} Later, technical developments and recognition that malnutrition among hospitalized patients was common³ led to growth in nutrition support services. By the 1980s, the use of specialized regimens of enteral and parenteral nutrition were routine in intensive care units (ICUs) worldwide, despite little evidence from rigorous, controlled clinical trials supporting the efficacy of these interventions.^{4,5}

With time, there has been improved awareness about complications related to the use of enteral and parenteral nutrition, along with improved control of blood glucose levels and delivery of reduced caloric loads.⁴⁻⁸ The use of parenteral nutrition in ICUs has diminished markedly, given evidence that enteral nutrition may be generally superior for clinical outcomes.⁶⁻⁸ However, substantial areas of uncertainty remain (Table 1). Guidance has been based

largely on expert opinion and on data from observational and small clinical trials, rather than on rigorous comparative effectiveness research.^{6,7,9,10} The 2009 European and American-Canadian clinical practice guidelines for ICU nutrition support differ in their recommendations for the initiation of parenteral nutrition in patients who are not expected to achieve adequate nutrient intake with enteral nutrition (oral diet or tube feedings).^{9,10} European guidelines suggest that parenteral nutrition be initiated within the first few days after ICU admission,⁹ whereas American-Canadian guidelines suggest withholding parenteral nutrition for 7 days in patients without preexisting malnutrition.¹⁰

In this issue of the *Journal*, Casaer et al.¹¹ describe a large (4640 patients), multicenter, randomized trial designed to address this area of uncertainty. Patients receiving early initiation of parenteral nutrition were given intravenous dextrose (20% solution) on ICU days 1 and 2; on day 2, enteral nutrition was begun (predominantly as tube feedings) with the addition of parenteral nutrition as needed to achieve the daily caloric intake goal

“Guidance for ICU nutrition support has been based largely on expert opinion and on data from observational and small clinical trials, rather than on rigorous comparative effectiveness research.”

Nutrition Support in Critical Illness — Bridging the Evidence Gap (continued)

Table 1. Major Areas of Uncertainty in the Nutritional Support of Patients in the Intensive Care Unit (ICU).^a

Clinical effect of various durations of minimal or no feeding
Optimal timing for the initiation and duration of therapy with enteral nutrition, parenteral nutrition alone or in combination with enteral nutrition, and micronutrients (known essential vitamins, trace elements, and minerals) in enteral and parenteral nutrition
Efficacy of various doses of energy, fat, and protein in enteral and parenteral nutrition
Effect of altered essential and nonessential amino acids (including glutamine) in parenteral nutrition
Efficacy of various doses and formulations of micronutrients in enteral and parenteral nutrition
Efficacy of alternative lipids (e.g., fish oil, olive oil, structured lipids, medium-chain triglycerides, and others, alone and in combination) in enteral and parenteral nutrition
Clinical efficacy of commercially available tube feedings containing combinations of antioxidants, antiinflammatory lipids, arginine, glutamine, and nucleotides in subgroups of patients
Efficacy of longer-term enteral or parenteral nutrition (or both) as needed in the post-ICU hospital and home setting
Effect of approaches for enteral and parenteral nutrition support in specific diagnostic subgroups of patients

^a Enteral nutrition includes oral complete supplements; specific oral protein, calorie, or micronutrient supplements; and complete tube feeding formulations, and parenteral nutrition refers to complete intravenous formulations.

“Enteral nutrition includes oral complete supplements; specific oral protein, calorie, or micronutrient supplements; and complete tube feeding formulations, and parenteral nutrition refers to complete intravenous formulation.”

(according to European guidelines). The late-initiation group began intravenous dextrose (5% solution) on day 1, enteral nutrition on day 2, and parenteral nutrition after day 7 as needed to achieve the caloric goal (American–Canadian guidelines).^{6,7,10} Nutrition support after discharge from the ICU was at the discretion of the attending physicians.

The two groups were well matched at entry according to illness severity, diagnosis, demographic characteristics, and nutrition risk scores. Mortality indexes in the two groups were similar; however, the late-initiation group had a significant (6.3%) reduction in the length of stay in the ICU and slight but significant improvements in secondary outcomes (infectious complications, indexes of organ dysfunction, and length of stay in the hospital). In addition, the late initiation of parenteral nutrition was associated with a modest reduction in

total hospital costs (approximately \$1,600 per patient).

Casaer et al. incorporated an upper target for blood glucose of 110 mg per deciliter (6.1 mmol per liter), which was lower than the target of 140 to 180 mg per deciliter (7.8 to 10.0 mmol per liter) now used in most ICUs. Patients in the two study groups had similar levels of blood glucose, so this factor did not mediate the differential responses observed. Identical and complete intravenous preparations of vitamins and trace elements were given daily to all patients, with intravenous potassium, magnesium, and phosphorus to maintain blood levels. Thus, between-group differences are probably limited to effects of the macronutrients (calories, dextrose, amino acids, and lipid emulsion) in the parenteral nutrition. Weaknesses of the study include the necessarily unblinded design and the amino acid doses, which were lower than those recommended in current clinical practice guidelines.^{9,10}

Underlying mechanisms for the outcome differences between the early-initiation group and the late-initiation group are unclear, but differences in the length of stay in the ICU and hospital may be due to the increased rates of infection and associated organ dysfunction in the early-initiation group. The authors suggest that early initiation of parenteral nutrition may be associated with the suppression of autophagy, with inadequate clearance of damaged cells and microorganisms, but other unknown factors (e.g., altered immunity and biofilm characteristics) may also be involved.

Casaer et al. clearly show that the early initiation of parenteral nutrition to achieve caloric goals of approximately 25 to 30 kcal

Nutrition Support in Critical Illness — Bridging the Evidence Gap (continued)

per kilogram of body weight per day is associated with worse clinical outcomes than those in patients in whom initiation was delayed for a week. However, these data should not be overinterpreted, since between-group differences in outcome were small, rates of death in the two groups were similar, approximately 80% of the patients were not seriously malnourished at entry (nutrition risk score, ≤ 4), and 60% were admitted to the ICU after cardiac surgery. Also, patients who were readmitted to the ICU and those who were seriously malnourished or were receiving established enteral or parenteral nutrition at the time of ICU admission were excluded.

In addition, patients in the late-initiation group received early enteral nutrition and daily intravenous vitamins and trace elements before starting supplemental parenteral nutrition on day 8. The optimal requirements of micronutrients for patients in the ICU are unknown (Table 1)⁴. Nonetheless, it may be prudent to provide complete enteral or parenteral preparations of vitamins and trace elements if parenteral nutrition is delayed in patients who cannot tolerate full enteral nutrition. Intravenous micronutrient preparations are subject to periodic market shortages; thus, consultation with health professionals and societies with experience in specialized nutrition support is important (e.g., the American Society for Parenteral and Enteral Nutrition at www.nutritioncare.org).

The findings of Casaer et al. should result in renewed attention to the nutritional needs of patients in the ICU and after their discharge from the ICU, inform the use of thoughtful nutritional care in the ICU (including the judicious use of parenteral

nutrition and early use of enteral nutrition), and stimulate further study concerning the nutritional support of critically ill patients.

From the Department of Medicine, Division of Endocrinology, Metabolism and Lipids, and the Emory University Hospital Nutrition and Metabolic Support Service, Emory University School of Medicine, Atlanta, GA.

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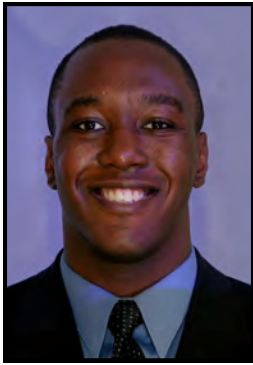


Thomas R. Ziegler, M.D.

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Arginine Therapy in Critical Illness: Is there a role?

Summary from the 2011 Spring GASPEN Meeting by Omar K. Danner, M.D.

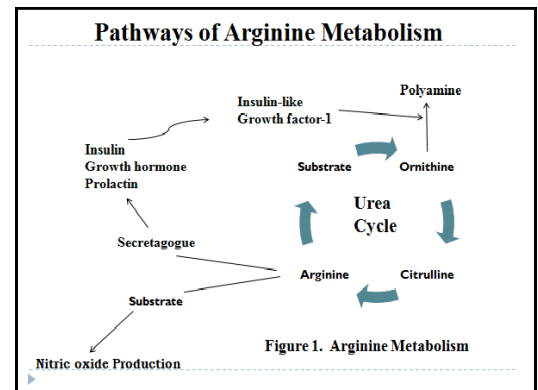


Omar K. Danner, M.D.

L-arginine (Arg) is one of the 20 most common naturally occurring amino acids. It was first isolated from a lupin seedling extract in 1886 by the Swiss chemist Ernst Schultze. Although it has traditionally been considered a non-essential amino acid, it is now well recognized that Arg is rapidly depleted during stress states. Therefore, it is presently considered to be a semi-essential or “conditionally essential” amino acid. However, the biosynthetic pathway does not produce sufficient Arg to meet the body's total daily need. Thus, some Arg must still be consumed through diet because the body usually does not manufacture enough. In general, most people do not need to take Arg supplements.

Although L-Arg has been discovered to have many other functions and uses in the body, one of the most important is that it has been shown to enhance cellular immunity. Arginine also plays an important role in cell division, healing of wounds, and release of hormones. Other benefits and functions attributed to L-Arg include the fact that it is a major precursor for the synthesis of nitric oxide (NO), reduces healing time of injuries (particularly bone), speeds repair time of damaged tissue and helps decrease blood pressure.

The role of arginine in immune function during critical illness has received a lot of attention over the last decade. L-Arg has been shown to be essential for T-cell proliferation. In myeloid cells, via the arginase-1 enzyme, L-Arg augments production of NO, which plays a vital role in cytotoxicity and cytostasis against pathogens and supports bacterial killing (Zhu et al. *Crit Care Clin.* 2010).



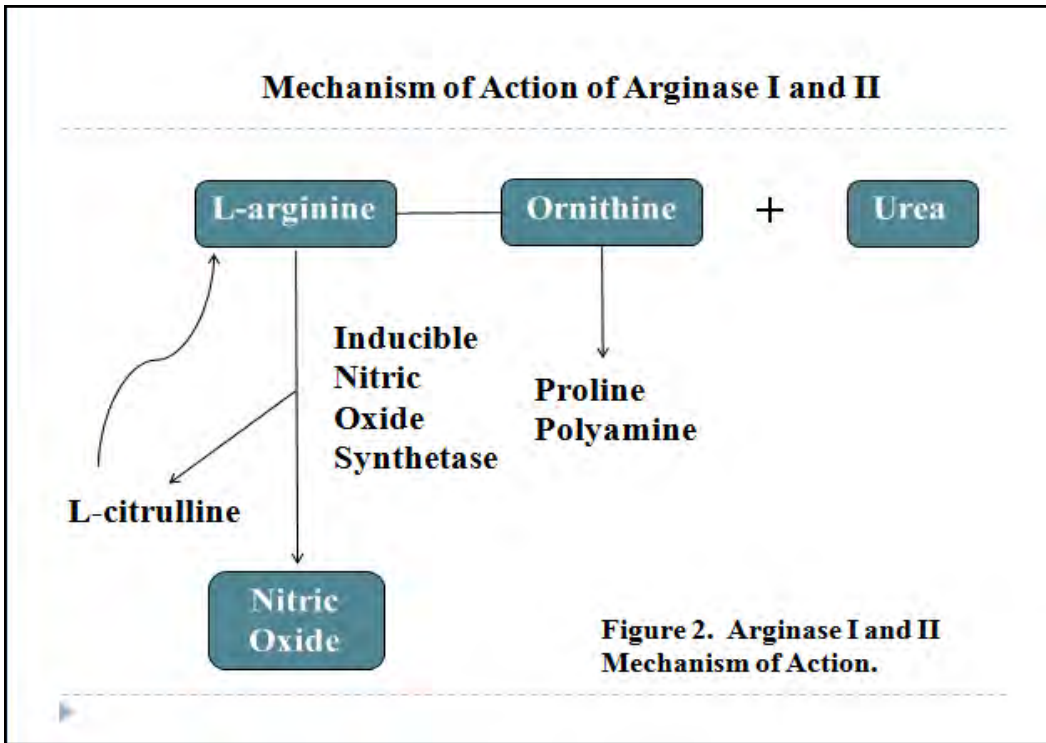
Under certain stress states, the enzymes involved in Arg metabolism are activated. For example, arginase-1 is induced in white blood cells of myeloid origin after acute trauma or surgery. Arginine levels do not only drop after trauma or surgery, they also have been shown to decrease after physical activity. The reduction occurs rapidly within minutes to hours. Decreased levels also may be observed in sepsis, with reduction proportionally to the severity of infection. Theoretically, this requires replacement during stress states.

Arginine can be replaced by two principle routes, parenterally or enterally. Although the normal intake of Arg is typically 3 to 5 grams per day, demands are increased during stress states and supraphysiologic quantities of 15 to 30 grams per day are recommended. The principle aim is to restore the nutritional deficiency (Ocha et al. *Nutr Clin Prac.* 2004).

However, it was demonstrated by Gomez-Jimenez in 1995 that septic shock is associated with greatly increased NO production with deleterious consequences. Therefore, Arg replacement during pro-inflammatory states, such as sepsis, SIRS, ARDS, and septic shock has been called into question by

“Arginine is considered a nonessential amino acid that may become conditionally essential during metabolic stress. Thus, some arginine must still be consumed through diet as the body usually does not produce enough of this nutrient.”

Arginine Therapy in Critical Illness: Is there a role? (continued)



several researchers. In fact, a trend towards harm has been demonstrated in several meta-analyses, including the study by Heyland in 2004.

In conclusion, arginine therapy during critical illness and hypermetabolic states remains controversial. Although enteral immunonutrition with arginine has been shown to be beneficial in trauma and post-surgical patients, it is associated with an increased mortality rate in subsets of critically ill patients with SIRS and other pro-inflammatory states. Therefore, outside of well-controlled clinical trials, it is recommended that Arg-enhanced enteral formulas and parenteral Arg should not be used in hypermetabolic, critically ill patients. However, immunomodulating enteral therapy still holds great potential for prevention of the infectious consequences and the development of Arginine Deficiency Syndrome. Further study will be necessary to clarify the proper role and timing of arginine supplementation in critical illness.

“Arginine plays an important role in the regulation of immune function via its effects on T-cell proliferation and differentiation, wound healing, and is a precursor for nitric oxide production.”

Nutrition Support in Critically Ill Patients with Acute Pancreatitis

Ashley DePriest, Graduate Coordinated Program Student
Georgia State University, Division of Nutrition, Atlanta, GA

Pancreatitis, an inflammation of the pancreas, can be an acute case or chronic condition. In acute pancreatitis, symptoms include abdominal pain that radiates to the back, which can be worse after eating, nausea, vomiting, and tenderness when the abdomen is touched.¹ Symptoms of chronic pancreatitis include upper abdominal pain, indigestion, unintended weight loss, and steatorrhea. Complications from pancreatitis can include breathing problems due to chemical changes in the body, diabetes, infection, kidney failure, malnutrition, pancreatic cancer, and pseudocysts.

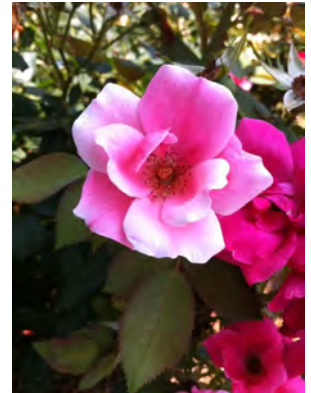
The inability to eat is a major problem when a patient is admitted to the ICU with pancreatitis and can sometimes lead to malnutrition. For many years, it has been common practice to allow the pancreas to “rest” before initiating feeding of any kind. This was also common practice to prevent the severe vomiting and diarrhea that often accompanied the condition. The latest research indicates that early nutrition support may improve outcomes in ICU patients with acute pancreatitis.²⁻⁸

In a systematic review of nutrition support in acute pancreatitis patients, it was found that enteral nutrition (EN) initiated within 24-72 hours of onset of symptoms was associated with a reduced risk of mortality.⁴ However EN was not associated with a lower risk of infection, compared to no nutrition support.²⁻⁴ Parenteral nutrition (PN) initiated within the first 24-72 hours of onset of symptoms also showed a significant reduction in mortality compared to no nutrition support.⁴ Finally, EN compared to PN

had no difference in mortality; however EN was associated with a significant reduction in complications from infection.⁴ Overall, EN is associated with reduced mortality, reduced multiple organ failure as well as reduced systemic infection rates.^{2,3}

An area of research needing further investigation is the timing of initiation of nutrition support. In the past, it has been protocol to wait 5-7 days to feed the patient. Typically this has coincided with the timing of the patient’s ability to tolerate oral intake without vomiting and diarrhea. However, current studies are now examining initiating feeding within 24-72 hours of the onset of symptoms. While a number of studies looked at 72 hours as an acceptable feeding onset time, others have assessed within 24 hours. There were some positive outcomes to earlier than 72 hours nutrition support initiation, but not enough to support it fully. Feeding onset earlier than 24 hours was shown to improve blood glucose control, but this early EN initiation also indicated higher overall complication rates than with early TPN.^{5,6} More studies need to be conducted in order to improve and specify this recommendation.

The most common issue with early (<72 hours after onset of symptoms) initiation of EN is systemic infection. While this is already a problem for most patients with pancreatitis, it seems to be elevated when early EN is initiated.⁷ One study suggested that the prophylactic use of antibiotic therapy is beneficial in preventing infections and complications from infections.⁷ However, this issue has been highly debated and is not



Nutrition Support in Acute Pancreatitis (continued)



currently recommended by many physicians or organizations. The proactive use of antibiotics to prevent infections in pancreatitis patients is another area that needs more extensive research.

While it is now commonly accepted that EN is safer and provides better outcomes for patients with acute pancreatitis, it is still controversial as to the benefits of different placements of tubes. It may seem inherent that placement below the jejunum would be beneficial due to the decrease in pancreatic stimulation; there has been no research that suggests this fact. Nasojejunal tubes have been compared to nasogastric tubes and have shown no significant difference in outcomes including infection rates and mortality.⁸

According to current research, it is beneficial for patients admitted to the ICU with pancreatitis to begin enteral feeding within 72 hours of the onset of symptoms.²⁻⁷ Enteral feeding improves mortality rates, lowers infection rates and has overall better outcomes in patients when compared to parenteral nutrition.^{2-4,6,7} More research is needed to determine a specific timeframe for initiation of enteral feeding as well as to provide indications for enteral tube placements. For now it seems that below the jejunum is appropriate and does not have any contraindications.⁸

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Editor's Commentary



Evidence-based practice is defined as a “systematic process of integrating the best (research) evidence and using these research findings as the basis for clinical decisions” (Sackett et al., 2000). Evidence-based guidelines enable clinicians to help translate scientific information into practical recommendations necessary to help bring about change.

Our esteemed colleague, Glen Bergman, MMSc, RD, LD, CNSD, said it best in his Fall 2010 newsletter contribution: “Change within a facility often affords us the opportunity for reviewing current clinical practice and implementing new guidelines.” Glen’s facility has undergone several changes, a process that has opened the window for introducing guidelines, and comparing current practice to that of the national practice recommendations as established by American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.), as well as the American Dietetic Association’s Evidence Analysis Library (EAL). Your facility may have incorporated multiple changes in response to the publication of the clinical practice guidelines, or may still be evaluating what areas of clinical practice that are in need of revision. In any case, it is useful to document the extent to which the guidelines have influenced clinical practice in your hospital or institution, and which areas you would like to target for further change.” At G.A.S.P.E.N., we are interested in our member’s input. “Please consider sharing your experience in the implementation of the latest guidelines (e.g., A.S.P.E.N. Clinical Guidelines, Standards, and Safe Practices) at your facility; as we and our patients, may all benefit from your information.” — Glen Bergman, MMSc, RD, LD, CNSD



To Barbara Hopkins, MMSc, RD, LD, Clinical Assistant Professor at Georgia State University. Barb inspired me to become a better writer and taught me Nutrition & Metabolism, Medical Nutrition Therapy, and also about life!

Glen Bergman, MMSc, RD, LD, CNSD is a Clinical Nutrition Specialist in the Nutrition and Metabolic Support Service at Emory University Hospital in Atlanta, GA. Glen is also a past president of G.A.S.P.E.N.

“I have been impressed with the urgency of doing. Knowing is not enough; we must apply. Being willing is not enough; we must do.” — Leonardo da Vinci

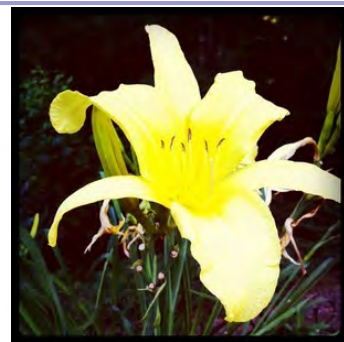
Heather M. Zhou, RD, LD

Heather M. Zhou, RD, LD

Editor-in-Chief, Newsletter
GaspEditor@gmail.com

Chapter News

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