Pharmacology: An Emerging Paradigm

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“As nutrition research has advanced, we have a new problem — information explosion. It becomes challenging for the bedside practitioner to distill or synthesize the signals from this myriad of critical care nutrition research,” said Daren K. Heyland, MD, MSc, from Queens University and Kingston General Hospital in Ontario, Canada. Dr. Heyland is a member of the Canadian Critical Care Clinical Practice Guidelines Committee, which addresses nutrition in critical illness. The committee has released 17 recommendations for best practice with respect to nutrition in critical illness as well as conducting research, outlined by Dr. Heyland at the 36th Critical Care Congress (Heyland et al. J Parenter Enteral Nutr. 2003;27:355).

“We’ve generated this body of knowledge, and we’ve been active in trying to implement these ideas at the bedside in the form of cluster-randomized trials and other methods,” he said.

Immunonutrition

Immunonutrition has exciting implications for those in nutritional and critical care, but it remains controversial. Studies have shown that various nutrients have effects on the immune system, metabolism, and gastrointestinal (GI) structure and function. These nutrients have been added to commercially available products known as immunonutrition or immune-enhanced diets. Immune-enhanced diets have been tested in a number of randomized controlled trials to evaluate their impact on critically ill patients. The largest study involved 397 patients with different underlying diseases who received a high-protein formula enriched with arginine, glutamine, antioxid-

ants and omega-3 fatty acids (Krief et al. Intensive Care Med. 2005;31:524). Researchers found that these products had no effect on hospital mortality or on any other secondary end-point. Dr. Heyland’s group incorporated that study into an ongoing meta-analysis of similar arginine-supplemented products.

“After 20 years of research, after more than 20 randomized controlled trials involving more than 2,200 patients and millions of dollars, we still come up with an answer that suggests that these nutrients have no effect,” remarked Dr. Heyland. “Is the problem that the nutrients do not affect clinical outcomes, or is there a problem in our scientific approach to this problem?” He would submit that we are pursuing the wrong scientific approach to demonstrating the effect of these nutrients in critically ill patients.” He suggested changing the paradigm and focusing more on the nutrients by themselves.

Pharmacology: Which Nutrient for Which Population?

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Nutrients and Patient Populations

The impact of nutrition is greater than just nutrition or nutritional strategy. Disciplines outside critical care are starting to test the hypothesis that a specific nutrient by itself, independent of nutrition, will have a large, clinically important effect on different populations.


These cases illustrate placebo-controlled nutrient studies that are having an impact on clinically important outcomes; they are not isoenergetic, isocaloric, nutritional strategies. Historically, in the immunonutrition paradigm, elective surgical patients and critically ill patients have been exposed to a variety of nutrients to discover what works and what does not work.

Critically Ill Versus Elective Surgical Patients

The treatment effects of various nutritional strategies and nutrients are systematically different in critically ill patients versus elective surgical patients (Heyland et al. JAMA. 2001;286:944). Looking at studies of immunonutrition, there is no treatment effect from these diets in critically ill patients, but inferred cytokine activation are significantly reduced in the elective surgical patient population.

This difference in treatment effect makes sense given the underlying pathophysiology of these two patient populations. In the elective surgical patient population, cellular immunoincompetence is the issue, with cellular immune dysfunction, decreased cytokine production, and increased cytokine production. A University of Pittsburgh team has shown that the increased expression of arginase in this population leads to a depletion of arginine. In the absence of arginine, T cells do not work (Taheri et al. Clin Cancer Res. 2001;7[3 Suppl]:558).

Diets that are enriched with arginine and other substrates that may inhibit arginase restore immunocompetence and reduce the infectious complications in the elective surgical patient population. The underlying pathophysiology of critical illness is very different. The activation of white blood cells sets off a chain of events that leads to free radicals, which lead to more inflammation and continues a vicious cycle that ultimately impairs the mitochondria and their ability to utilize oxygen.

Pharmacologic nutrition attempts to evaluate nutrients that may have a positive effect on functions that support the mitochondria, leading to an improvement in patient outcomes.

Arginine

Arginine stimulates hormonal release and can be metabolized through a family of nitric oxide synthetase enzymes to nitric oxide, which is crucial for survival. The University of Pittsburgh team found that, depending on the underlying pathophysiology, there is a different expression of these enzymes and, therefore, a different metabolism of arginine.

There is a delicate balance of nitric oxide that must be present in critically ill patients. Using nonselective nitric oxide synthetase inhibitors, nitric oxide production can be abolished, which would increase mortality in critically ill patients. In disease states where inducible nitric oxide synthase (iNOS) is up-regulated, nitric oxide production is excessive and can cause harm in terms of hemodynamic stability, immunologic dysfunction and nonspecific cytotoxicity. Hydrocortisone can push the nitric oxide response and inflammatory response and improve the survival of critically ill septic patients. Unfortunately, by giving arginine, an immune dysregulation occurs and causes more harm than good.

There are three randomized controlled trials using different arginine products with various patient populations. All show excess mortality in the critically ill infected or septic patient population (Bower et al. Crit Care Med. 1995;23:1436; Crit Care Med. 2003;30: A17 [abstract]; Bertolini et al. Intensive Care Med. 2003;29:634). The Canadian Critical Care Clinical Practice Guidelines Committee suggested that products containing arginine not be used. There is possible harm in some populations. The products certainly are more costly and, overall, they lack a treatment effect, explained Dr. Heyland.

Glutamine

People with critical illness have decreased glutamine levels. Patients who come into their critical illness with a low plasma glutamine level have the worst outcome, and these low levels are associated with increased mortality.

“By providing glutamine, I may enhance the barrier function of the gastrointestinal tract and may enhance lymphocyte function. This can reduce infectious complications,” said Dr. Heyland. Glutamine as a nitrogen donor also may lead to preservation of tissue. Animal research shows how glutamine may enhance expression of heat shock protein and enhance improvement in...
physiological outcomes.

The *Intensive Care Medicine* study demonstrated that glutamine could induce heat shock protein expression in critically ill patients, levels of which correlated with decreased length of hospital stay and ventilator time.

Three randomized controlled trials of enteral glutamine have shown improvement in the permeability of the GI tract, a decrease in endotoxin levels and a reduction in Gram-negative infections, translating into important reductions in hospital length of stay. A reduction in mortality also is associated with enteral glutamine provision in the burn population.

“When the Canadian Critical Care Clinical Practice Guidelines Committee looked across all the randomized controlled trials using meta-analyses, we found a significant reduction, almost 20%, in infectious complications associated with glutamine supplementation. When we looked at the same set of studies using mortality, we found a 25% risk reduction in mortality associated with a single nutrient administration in critically ill patients,” reported Dr. Heyland (Heyland et al. *J Parenter Enteral Nutr*. 2003;27:355).

The guidelines committee recommendation for glutamine administration now states that those using parenteral nutrition should supplement it with parenteral glutamine to optimize patient outcomes. For the majority of the heterogeneous critically ill patients on enteral nutritional, the role of parenteral glutamine is unclear.

**Antioxidants**

In critically ill conditions, Dr. Heyland has found the levels of these various substrates to be low. A number of studies show that the low levels of endogenous antioxidants are associated with complications for critically ill patients – increased inflammation, increased lipid peroxidation, increased organ failure, and increased mortality.

“Across all of these studies, when we meta-analyze them, we come up with a very large and very precise estimate of treatment effect – a 30% reduction in mortality associated with antioxidant supplementation, with a P value that is statistically significant,” said Dr. Heyland.

The investigators decided to follow up on selenium as the key driver for treatment effect. “The later analysis showed no real difference among the studies that employed selenium as a part of their cocktail,” continued Dr. Heyland. “However, it achieves greater statistical significance because it has been used more frequently and, therefore, provides a more precise treatment effect.”

A recent study in *Critical Care Medicine* described a large, multicenter trial of high-dose selenium in critically ill septic patients. It showed a large reduction in mortality that was not quite statistically significant (Angstwurm et al. *Crit Care Med*. 2007;35:118). However, there was still a large treatment effect in the patients who had a high normal or supernormal level of selenium. “This isn’t just about replating a nutrient to a normal level, but yet there’s additive therapeutic effects in getting the levels even higher, consistent with this concept that these nutrients are having pharmacological properties and they’re not simply just restoring the nutrient deficiency,” stated Dr. Heyland.

**Fish Oils**

Three randomized controlled trials of patients with lung injury on diets not only enriched with fish oils, but also with borage oil and antioxidants, showed that these substrates quickly are incorporated into plasma membranes and have an effect on inflammatory cytokines and on the oxygenation status of patients. Gadek et al. *Crit Care Med*. 1999;27:1409; Singer et al. *Crit Care Med*. 2006;34:1033; Pontes-Arruda et al. *Crit Care Med*. 2006;34:2325). That translates into a significant reduction in ventilation days, intensive care unit (ICU) days, and, in one study, a trend towards reduction in ICU mortality.

**The REDOX Study**

“I’ve used these meta-analyses tools to try and define which of these nutrients is most likely to have a positive effect in the average critically ill patient receiving enteral nutrition. That has led us to the concept of the Reducing Deaths from Oxidative Stress (REDOX) Study,” explained Dr. Heyland. “We looked at the effect of glutamine supplementation and antioxidant supplementation on 28-day mortality in the sickest of the critically ill patients with acute induced organ dysfunction.”

In developing the REDOX® Study design, researchers needed to solve an important problem related to optimal dose of these specialized nutrients. They borrowed from the pharmacology literature by attempting to understand what effect different doses have and what are the maximal tolerable doses.

The nutrients were considered to be pharmacological agents.

The purpose of this dosing study was to assess the safety of high-dose substrate, not to prove efficacy. The study illustrated the concept of pharmaco-nutrition and thinking of nutrients as drugs while trying to sort out these dosing questions.

“We sequentially exposed patients to escalating doses of these substrates and tracked their function or resolution to see if there is any sign of harm,” Dr. Heyland illustrated. “If there was no sign of harm in each group, then we moved to the next group and gave more substrate. Our primary endpoint was changing the SOFA (sequential organ failure assessment) score over time. We also measured some of the plasma levels of these substrates and some of the intermediate biological measures that gave us an insight into how these mechanisms might be working” (Heyland et al. *J Parenter Enteral Nutr*. 2007;31:109).

“The higher the measure of T bars, the more oxidative stress there is. With escalating doses of glutamine, we did not create a pro-oxidative condition. Rather, we saw a resolution of the oxidative stress,” according to Dr. Heyland.

For patients to survive, they needed to recover their mitochondrial ratio, their ability to cope and produce respiratory chain proteins at the mitochondrial level. Non-survivors never recovered the ability to replicate their mitochondrial DNA. The main inference from this research is that the high doses of these substrates appear to be safe. They are not associated with any worsening organ failure and, in fact, there may be some beneficial physiological effects. There also was greater preservation of glutathione-reduced oxidative stress and improved mitochondrial function.

**Conclusion**

To move forward and really understand the effect of nutrients in individual patient populations, the nutrients must be disassociated from the nutritional products and tested in isolation in large-scale studies.

“Several meta-analyses of several substrates suggest that these nutrients are actually modulating disease processes and are associated with large mortality effects in critically ill patients. I think we need to change the way we think about nutrition and think of it as therapy. We should be concerned with the timeliness of its administration, so it is administered early in the course of critical illness to modulate the disease response to optimize the patient outcome,” concluded Dr. Heyland.

**Continuing Education Self-Assessment**

**Pharmacology: An Emerging Paradigm**

9. Which of the following is true about glutamine and the critically ill patient?
   a. It may enhance heat shock proteins.
   b. People with critical illness have decreased glutamine levels.
   c. It is recommended that if parenteral nutrition is used, it should be supplemented with parenteral glutamine to optimize patient outcomes.
   d. All of the above.

10. There is a 30% reduction in mortality associated with antioxidant supplementation in critically ill patients.
   a. True
   b. False