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Using Specific Nutrients to Improve Outcome and Shorten Length of Stay in the ICU

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Fact or Fantasy?

Nutritional delivery in the critically ill population has radically evolved in the past 15 years from the concept of nutrition delivery to prevent malnutrition to the concept of nutrition therapy as a crucial element in maintaining vital organ function and modulating key processes such as immunity, inflammation, and anti-oxidant defenses. Utilising specific nutrients such as fish oils, arginine, glutamine, leucine, anti-oxidants, and nucleic acids as pharmaconutrients given at levels above that needed for "normal" metabolism has now become accepted as part of current ICU care throughout the world. The recent guidelines produced as a collaboration between the Society of Critical Care Medicine and the American Society of Critical Care Medicine describes the rationale and gives use of metabolic and immune modulating formulations a grade 'A.' This grade is supported by 15 level two studies and six level one studies (Martindale et al. 2009). Similar grade 'A' recommendations are made by the European Society of Enteral and Parenteral Nutrition (Weimann et al. 2006).

John Hunter in 1784 described in his book, "A treatise on blood, inflammation and gunshot wounds a mechanism of inflammation and a comment that "many types of injury produce a similar inflammation." Sir William Osler in 1904 has been quoted as saying "except on few occasions the patient appears to die from the body's response to infection rather than from it." These two extremely insightful comments both made over one hundred years ago describe one of the major themes in the concept of nutritional modulation of metabolism and immunity in the critically ill in 2010. Attempting to attenuate or control the metabolic response to stress and trauma at a manageable level rather than allowing the extremes of the systemic inflammatory response (SIRS) and the lows associated with compensatory anti-inflammatory response (CARS) is now the key focus in early aggressive nutritional therapy. The metabolic response to stress is well described and includes a hyperdynamic cardiac and pulmonary response, insulin resistance, hyperglycemia, accelerated protein catabolism from the muscle, poor adaptation to starvation, increased oxidative stress, and if the response goes on unabated, complex immunological changes resulting in immune suppression (Atiyeh et al. 2008). During this hyperdynamic phase of illness, surgery or trauma the loss of lean body mass continues despite delivery of adequate enteral or parenteral protein and calories. In effect, delivery of just "calories and protein" to the hyperdynamic patient is not reversing the adverse effects of ongoing loss of lean body tissue. The ideal concept of using specific nutrients to alter this hyperdynamic response was proposed in the late 1980's and has now become the standard of care for critically ill patient, traumatised and surgical patients.

The use of the fish oils (EPA and DHA) is at the centre of this pharmaconutrition evolution. Appropriate use of omega-3-FA can partially attenuate the metabolic response, reverse or stop the loss of lean body tissue, prevent oxidative injury and favourably modulate the inflammatory response (Calder 2010). Traditionally lipids were felt to be important in clinical nutrition but only as a caloric source, providing essential fatty acids and support the absorption of fat-soluble vitamins via micelle formation in the proximal small bowel. Currently specific lipids are being used to alter the metabolic response to stress by changes in cell membrane phospholipids, alterations in gene expression, modulating endothelial expression of ICAM-1, E-selectin and other endothelial receptors regulating vascular integrity and function. Additionally, EPA and DHA derivatives, including resolvins, docosatrienes, and neuroprotectins, are potent active effectors of resolution of inflammation (Mayer and Seeger 2008; Serhan 2009). Resolvins regulate polymorphonuclear neutrophil (PMN) transmigration. Docosanoids and neuroprotectins are both derived from DHA and have potent neuroprotective properties.

Neuroprotectin decreases neutrophil infiltration, proinflammatory gene signaling, and NFkB binding. Neuroprotectin D1 (NPD1) has been found to reduce neural infarct volume by half in an animal ischaemia-reperfusion model (Bazan 2005). These protective mediators are found to be highly conserved among species, from fish to mammals (Serhan and Savill 2005). With the discovery of these compounds it is acknowledged that resolution of inflammation is an active process rather than a passive time dependent process. Fish oils also have a regulatory influence on the vagus nerve. The vagus has a well know bidirectional and multi- level interaction between the central nervous system and the innate and adaptive immune system. Fish oils have recently been shown to dampen the inflammatory response mediated via the vagal fibers.

In the past, some controversy has arisen around the use of the amino acid arginine in the ICU setting (Suchner et al. 2002). Arginine, despite being only semi-essential under normal physiologic conditions, plays a significant role in the intermediary metabolism of the critical care patient. L-Arginine is available from endogenous synthesis (via citrulline conversion in kidney), protein breakdown, and dietary sources (diet only contributing about 20 to 25% of total arginine supply). Arginine is a prominent intermediate in polyamine synthesis (cell growth and proliferation),

proline synthesis (wound healing and collagen synthesis), nitric oxide production (via eNOS, iNOS, nNOS), and modulator of lymphocyte proliferation and differentiation. Clearly, arginine balance and availability will affect outcomes in the critically ill patient (Zhou and Martindale 2007). The de-novo synthesis and dietary intake is commonly reduced in critical illness. While supply is decreased the cellular demand for arginine is increased. This increased demand is driven mainly by the upregulation of arginase and iNOS in the trauma, surgery and critical care setting (Morris 2009). The speculation that arginine poses a threat to the critically ill patient is mainly based on the theoretical concept that the critically ill population commonly has upregulated iNOS and that by delivering additional arginine as the substrate for upregulated iNOS would result in excess nitric oxide production with consequent vasodilation. An alternate, equally valid argument is that controlled vasodilation is beneficial in critical illness and sepsis. Shock by definition is "inadequate delivery of oxygen and nutrients to maintain normal tissue and cellular function" (Jones and Puskarich 2009). It may be that the vasodilation from arginine is an adaptive mechanism to increase delivery of oxygen to the cell (Zhou and Martindale 2007). Until recently few studies had evaluated arginine as a single agent in the critically ill and septic patient. Luiking et al. recently published an elaborate metabolic study of citrulline and arginine in septic patients. They concluded that additional arginine had no adverse effects in sepsis (Luiking et al. 2009). A study by Kao et al. evaluating arginine in sepsis concluded that, in fact, arginine may be deficient in sepsis via inadequate de-novo synthesis (Kao et al. 2009). So the theory that additional arginine delivered to the medical critically ill or septic population would be detrimental is unfounded and in fact the exact opposite may be the case. It now appears from the articles and human studies listed above that arginine may in fact be deficient in critical illness and should be supplemented.

In addition to arginine the amino acid glutamine has gained support in the critical care setting. Over the past 20 years, glutamine has been reported to offer a myriad of benefits, including maintenance of acid-base balance, primary fuel for rapidly proliferating cells (i.e., enterocytes and lymphocytes), precursor in the synthesis of endogenous antioxidant glutathione, increase levels of arginine via the ornithine pathway, reduction of insulin resistance during stress and a key substrate for gluconeogenesis (Wischmeyer 2008). Recent reports that glutamine induces heat-shock protein in numerous tissue beds is yet another beneficial effect of this versatile amino acid (Wischmeyer 2008). By enhancing the chaperone proteins, the cell protects itself from subsequent stress (Hamiel et al. 2009).

Over 50 human studies have reported the effects of combinations of metabolically active nutrients, including fish oils (DHA and EPA), arginine, glutamine, nucleic acids, and anti-oxidants with the majority showing some beneficial influence in outcome and cost effectiveness. The disease states benefiting from these metabolic modulating formulations are wide ranging and spread over several organ systems. The nutrients have been shown to lower the incidence and severity of acute lung injury and adult respiratory distress syndrome, decrease adverse cardiac events and enhance early recovery from gastrointestinal surgery and trauma. Metabolic modulating formulas also have been shown to attenuate some of the adverse metabolic effects of sepsis. Not only have these human clinical studies shown benefit in shortening hospital stay and decreasing infections, but several have also reported lower mortality rates (Macario et al. 2005; Tsekos et al. 2004; Heller et al. 2006). Although the data overwhelmingly support the use of metabolically active specific nutrients, the optimal delivery route, timing of delivery, and dosage in trauma and critical care settings will have significant influence that must be sorted out.

The concept of pharmaconutrition is now clearly accepted by most clinicians worldwide. Subsequent studies will further elaborate which ICU populations will maximally benefit. The use of fish oils, arginine, glutamine and other metabolically active nutrients is now a major part of trauma and critical care nutrition protocols as noted by the Society of Critical Care Medicine, ASPEN and ESPEN Guidelines. All three of these major societies have given an 'A' grade to the use of immune and metabolically active agents in specific populations (Martindale et al. 2009; Weimann et al. 2006). Whether nutrients are used in combination or individually, these agents should be part of the intensivist's armamentarium for improving outcome and cost effective ICU care.

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