Nutraceuticals in Critical Care Nutrition

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The importance of nutritional support in surgical patients cannot be overstated, particularly in the realm of intensive care settings. Prevention of mucosal atrophy and stimulation of the gut-associated lymphoid tissue (GALT) by early enteral feeding in postoperative surgical patients has only recently become part of our standard of care. Feeding the gut is clearly a stimulant for the immune system, and plays a key role in lower infection rates measured in patients receiving enteral as opposed to parenteral nutrition. This association between nutrition and infection has been known for centuries. The World Health Organization report in 1968 clearly defined this association and began to set goals in clinical nutrition [1]. The understanding of the gastrointestinal (GI) tract as a major component of the human immune system and a key modulator of the organism's response to stress and injury has subsequently opened the door to an exciting new field of specialized enteral preparations sometimes referred to as nutraceuticals. The recent expansion of our understanding of stress metabolism and the systemic inflammatory response has influenced critical care nutrition on two levels. First, as stated above, is the importance of the provision of enteral macronutrients, namely a patient's requirement for protein, carbohydrate, and lipids. Secondly, research in nutraceuticals seems to have focused on various combinations of micronutrients and ‘conditionally’ essential nutrients. Nutraceuticals are felt to function in cellular metabolic pathways where increased demands associated with the stress response benefit from supplementation. These nutrients may be the key to fine-tuning enteral formulas for specific clinical scenarios.

For centuries, man has sought the therapeutic benefits of naturally occurring substances as components of the human diet, acknowledging the
connection between health and nutrition. With the explosion of knowledge and analytical techniques in biochemistry and molecular biology, investigators may now pinpoint the specific role of many of these elements in human metabolism. This same knowledge has also produced a far greater understanding of the systemic response to stress, effected by severe catabolism and loss of lean body mass [2]. Historically, nutritional support in critically ill patients has sought to provide adequate calories and protein to induce nitrogen balance, preventing peripheral muscle breakdown. However, we have learned that provision of adequate protein and calories does not prevent loss of lean body mass in the critically ill patient. Our attention has therefore turned to supplementation of caloric requirements with specific nutrients designed to impact critical metabolic pathways. One of the earliest clinical studies evaluating such selective supplementation randomized burn patients to receive a modular tube feeding recipe (MTF), or one of two other enteral nutritional regimens traditionally used in this population. The MTF consisted of a high-protein, low-fat formulation enriched in n-3 fatty acids, arginine, cysteine, histidine, zinc, vitamin A, and ascorbic acid. Significant benefits were observed in MTF-fed patients who had lower infection rates and shorter length of hospital stay [3].

Since the first recognition of enteral nutrition as an immunomodulatory phenomenon, investigators have been challenged to find ‘the right mix’ for any given patient or clinical scenario. This knowledge has also essentially created a market to drive pharmaceutical research in this direction (table 1). We are now faced with the challenge of optimizing specific preparations through indepth analysis of micronutrients and their individual roles in human metabolism. A wealth of in vitro, in vivo, animal and human data has been produced in the process of examining the physiology of dietary

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<th>Table 1. Immune-modulating enteral formulas</th>
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<td>Formula</td>
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<tr>
<td>Crucial®</td>
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<td>Impact®</td>
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<td>Impact Glutamine®</td>
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<td>Impact with Fiber®</td>
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<td>Impact 1.5®</td>
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<td>Oral Impact</td>
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<td>Intensical®</td>
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<td>Optimental®</td>
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<tr>
<td>Oxepa®</td>
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<tr>
<td>Alitraq®</td>
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<td>Perative®</td>
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nucleic acids, arginine, glutamine, n-3 fatty acids, and an array of other less studied nutrients.

Arginine

Arginine, like glutamine, is classified as a nonessential amino acid in unstressed conditions since the body synthesizes adequate arginine for normal maintenance of tissue metabolism, growth and repair [4]. During major catabolic insults such as trauma or surgery, an increase in urinary nitrogen, excreted largely as urea, represents the end products of increased lean body tissue catabolism and reprioritized protein synthesis. Arginine during these stress situations becomes conditionally essential in that demand is greater than endogenous supply.

Numerous animal and human studies indicate that supplemental dietary arginine is beneficial for accelerated wound healing, enhanced immune response, and acceleration in attainment of positive nitrogen balance [5]. The exact mechanisms for these benefits are yet to be entirely understood but may in part be the result of arginine’s role as a potent anabolic hormone secretagogue. Growth hormone, glucagon, prolactin, and insulin release are all increased with supplemental arginine. Arginine is also the substrate for production of nitric oxide and citrulline by nitric oxide synthase. Nitric oxide is a ubiquitous molecule with significant roles in the maintenance of vascular tone, coagulation cascade, immunity, stimulation of angiogenesis, modulation of the effects of endotoxin, and regulation of GI tract absorptive and barrier function [6]. Nitric oxide has also been implicated as a participant in numerous disease states as diverse as sepsis, hypertension, and cirrhosis. Arginine is also the substrate for the enzyme arginase with end products urea and ornithine. Through the production of ornithine and urea, arginine promotes proliferation of fibroblasts and collagen, both essential for later stages of wound healing. Arginine and its metabolite ornithine also serve as precursors for polyamine biosynthesis. Polyamines play a pivotal role in cell division, and DNA synthesis [7]. By supplying the amidino group for creatine synthesis, arginine is important in maintaining the reserve of high-energy phosphate required for ATP generation in muscle.

In animal models arginine supplementation has been associated with improved wound healing with increased wound tensile strength and collagen deposition [5]. Animal studies using arginine supplementation have shown improved survival in burns, intraperitoneal bacterial challenge, cecal ligation and puncture, and tumor implantation models [6].

The majority of human studies have included arginine in combination with other so-called ‘immune modulating’ elements making it impossible to define the specific arginine influence. While supplemental arginine has been shown to improve survival in various animal models as well as a number of in vitro
measures of immune function in animals and humans, the benefit of arginine supplementation alone needs further large scale studies to confirm its benefits in the clinical setting. Certainly the early data suggest that arginine upregulates immune function, modulates vascular flow patterns, and supports nitrogen balance [8, 9].

**Glutamine**

Glutamine is the most abundant amino acid in the body and makes up greater than 50% of the free amino acid pool [10]. Containing 5 carbons and 2 nitrogen moieties makes glutamine the major interorgan donor of nitrogen and carbon. Glutamine is now considered conditionally essential, meaning that during major catabolic insults, demand for glutamine is greater than supply. Glutamine is the primary fuel for many rapidly dividing tissues such as the small bowel mucosa and proliferating lymphocytes [11]. Glutamine has numerous metabolic roles including maintenance of acid-base status, as a precursor of urinary ammonia, as the primary fuel source for enterocytes, as fuel source for lymphocytes and macrophages, and as a precursor for nucleotides, arginine, glutathione, and glucosamine [12]. Glutamine is also a major contributor to gluconeogenesis and is the primary substrate for renal gluconeogenesis in humans. Recent reports also support a role for glutamine in decreasing peripheral insulin resistance in stress models [12]. Major surgery or trauma have been reported to cause a rapid decrease in serum and intracellular free glutamine levels. During catabolic illness glutamine uptake by the small intestine and immunologically active cells may exceed glutamine synthetic rates and release from skeletal muscle, making glutamine, like arginine, a conditionally essential amino acid [10, 13].

There is an abundance of human data regarding the use of glutamine supplementation both enterally and parenterally [4]. The majority, estimated at 70–80% of luminally supplied glutamine, is metabolized by the enterocyte, minimizing access to the systemic circulation. Clearly the target for enterally supplied glutamine is the splanchnic bed and GALT. In animal models, supplemental glutamine has been shown to enhance intestinal adaptation after massive small bowel resection [14], to attenuate intestinal and pancreatic atrophy [4], to improve survival after gut ischemia/reperfusion [15], and to prevent hepatic steatosis associated with parenteral and enteral feeding [12]. Glutamine appears to maintain GI tract mucosal thickness, maintain DNA and protein content, reduce bacteremia and mortality after chemotherapy, and reduce bacteremia and mortality following sepsis or endotoxemia [12].

In humans undergoing surgical stress, glutamine-supplemented parenteral nutrition appears to help maintain nitrogen balance and the intracellular glutamine pool in skeletal muscle [16]. A recent trauma study reported a greater than 50% decrease in pneumonia compared to an isonitrogenous,
isocaloric control population [17]. A decrease in bacteremia and sepsis was also noted. In critically ill patients, glutamine supplementation may attenuate villous atrophy and the increased intestinal mucosal permeability associated with parenteral nutrition. Intravenous glutamine supplementation in a randomized, blinded trial of 84 critically ill patients showed significant improvement in long-term mortality [18]. In another study bone marrow transplant patients were randomized in a blinded fashion to glutamine or an isonitrogenous formula, resulting in fewer infections, improved nitrogen balance, and significantly shorter mean hospital length of stay [19]. Glutamine supplementation has also been shown to aid in protecting the GI tract against chemotherapy-induced mucosal toxicity [20].

While a large volume of animal and human data support the concept that glutamine is beneficial in a variety of experimental models, the benefit of routine enteral glutamine supplementation in critically ill human patients remains somewhat controversial. Well-designed clinical trials are needed to assess whether the beneficial effects demonstrated in GI physiology, immune function and postoperative metabolism translate into a reduction in hospital stay and mortality rate.

**Nucleotides**

Nucleotides form yet another important component of immune modulation through their diverse array of function in cell metabolism. The average American diet contains 1–2 g/day of nucleotides. Nucleotides are made up of the purine and pyrimidine backbone with a ribose and one to three phosphates. As nucleotides are removed during processing for whey and casein concentrates in the production of commercial formulas, critically ill patients fed enteral formulas may in fact have inadequate supply of nucleotides. Several infant and animal models have shown that supplementation of nucleotides can decrease GI infections, increase natural killer cells, increase villous height and mucosal enzyme activity.

Nucleotides are available to the host via de novo synthesis or from salvage pathways of DNA and RNA degradation. Synthesis requires substrates of glutamine, aspartate, glycine, and formate. Activity and the contribution of the salvage pathways may vary among tissues and with phases of the cell cycle. Nucleotides serve an array of vital functions including signal transduction, regulation of enzyme activity, synthesis of macromolecular compounds such as glycogen and phospholipids, promotion of gut development and maintenance of mucosal integrity, tissue repair and cell turnover. Iwasa et al. [21] have reported various combinations of nucleotides in specific ratios to be cytoprotective, increase hepatic regrowth after partial hepatectomy, increase oxidative phosphorylation, and decrease total parenteral nutrition-induced gut permeability in a rat model.
Therefore, one may speculate that in critical illness, nucleotide requirements are elevated in the face of hypermetabolism and activated immune response. Numerous animal studies demonstrate impaired mucosal function in nucleotide-depleted diets that could be reversed by oral supply of these substrates [22]. In a model system for Crohn’s disease involving indomethacin-induced enteritis in rats, supplementation of diets with 1% yeast RNA allowed a significant improvement in ulcer healing [23]. The benefits of nucleotide supplementation appear consistent across tissues and species in relation to gut barrier and immune function.

**n-3 Fatty Acids**

The importance of fatty acid metabolism in the inflammatory and immune response has been assessed in numerous studies [24]. The typical Western diet now contains significantly more n-6 than n-3 fatty acids. In addition it is now apparent that lipid membranes are strongly influenced by dietary lipid profiles. Dietary changes in lipids have been shown to alter T-cell proliferation, cell–cell adhesive properties, plasma membrane fluidity and cytokine response to various stimuli [25].

High levels of polyunsaturated fatty acids, especially linoleic acid, have a suppressive effect on neutrophils, lymphocytes, monocytes and macrophage function in both in vitro and in vivo studies. The more specific immunosuppressive influence includes inhibition of lymphocyte proliferation, decrease in neutrophil chemotaxis and migration, impairment of the reticuloendothelial system and decrease in the bactericidal capacity. Exchange of subtypes of fatty acids limits production of arachidonic acid metabolites such as thromboxane A2, prostaglandin E2 and I2, as well as leukotriene B4, all mediators of the systemic inflammatory response and hypermetabolism in sepsis. Therefore, the effect of n-3 fatty acids likely comes from a profound alteration in the immunoregulatory process achieved by elaboration of various cytokines, interleukins, and interferons [26]. Early studies in the Eskimo population of Greenland demonstrated that their diets enriched in n-3 fatty acids conveyed lower risk of coronary artery disease, likely due to diminished platelet aggregation and thrombosis, both of which are directly influenced by platelet-activating factor release stimulated by cytokines and other products of membrane phospholipid metabolism [27]. n-3 fatty acids have been associated with and reported to decrease cardiovascular disease, inflammatory diseases, autoimmune disease, type-I diabetes, and lower the incidence of colon and breast cancer. A number of animal studies have confirmed the benefit of n-3 fatty acids in terms of a reduction in post-burn metabolic rate, mortality from infection, bacterial translocation rate, and response to lipopolysaccharide. With regard to critically ill patients, the relevance of dietary n-3 fatty acids is clear in light of their attenuation of the inflammatory
response, antithrombotic effects, prevention of overproduction of PGE-2 to stress stimuli, and depression of plasma triglyceride levels. In addition to the dietary influence in cell membrane changes, recent evidence now indicates that fatty acid ratio changes can have acute effects on platelet adhesiveness, neutrophil function, membrane stability and alteration in microvascular perfusion. An elegant study by Suchner et al. [28] defines the correlation of intravenous lipid infusion, prostaglandin-F/thromboxane B2 ratios, pulmonary hemodynamics, and gas exchange. Acute respiratory distress syndrome (ARDS) patients enrolled in this trial demonstrated worsening oxygenation and increased pulmonary shunt shortly after administering a bolus of intravenous fat emulsion. Reduced production of vasoactive mediators by elimination of n-6 fatty acids likely limits splanchnic vasoconstriction thereby modulating gut ischemia during stress, minimizing bacterial translocation, and preserving GALT integrity. In general it is felt that, in the critical care setting, increasing n-3 fatty acid levels compete with cyclooxygenase metabolism to limit the n-6 production of PGE2 and leukotrienes of the 4 series, all of which are proinflammatory and/or function to limit microvascular flow. Numerous animal studies and one very important clinical study in ARDS patients, using a formula enriched with n-3 fatty acids, reported fewer ventilator days and shorter duration of intensive care unit (ICU) stay [29].

Clinical Evidence

Since 1990 there have been 26 prospective randomized human trials investigating the effects of immunonutrition in hospitalized patients. Despite the variations in study design, the majority of the well-designed studies demonstrate a clear benefit in terms of reduced infection rates, decreased antibiotic use, and reduced ICU and hospital length of stay [30]. These studies may be best approached by categorizing each into subgroups including general ICU, GI surgery, trauma, burn, and sepsis/multiorgan system failure patients. Moore [30] examined a general ICU population of 296 patients, randomized to enteral feedings supplemented with arginine, dietary nucleotides, and fish oil (Impact®, Novartis) or a control formula, demonstrating a substantial reduction in length of hospital stay and a significant reduction in acquired infections. Five prospective randomized trials have been published limiting the study to include only trauma patients. Of these studies, four demonstrated advantages to early immune-enhancing enteral feedings in terms of incidence of systemic inflammatory response syndrome, resolution of hypermetabolism, infectious complications, length of hospital stay, incidence of intra-abdominal abscesses and multisystem organ failure.

Supplemented enteral formulas allowed comparable results in acutely burned patients as well. Similar analyses have been carried out in ‘general surgery’ patient populations, many of whom presented for resection of
GI cancer. The vast majority of these studies revealed a lower rate of postoperative infections and shorter length of hospital stay in patients given supplemented enteral formulas. Other benefits included earlier liberation from mechanical ventilation, shorter length of ICU stay, improved phagocytic ability of monocytes, and decreased IL-6 plasma concentrations. Three studies in particular were able to predict a cost savings per patient in treating fewer complications when using supplemented enteral formulations. It is likely that this result may be extrapolated to other studies when shorter length of hospital stay and decreased cost incurred by infectious complications are weighed against provision of an immune-enhancing enteral feeding [30].

There are now three meta-analyses encompassing most major prospective randomized clinical trials on supplemented enteral feeding [31–33] (table 2). Both studies published in 1999 demonstrated reduced infection rates and shorter duration of hospital stay in patients with critical illness who received enteral nutrition supplemented with key nutrients. In the meta-analysis by Beale et al. [32] of 1,482 patients in 12 trials, patients administered the supplemented enteral formula also spent significantly fewer days supported with mechanical ventilation. Heyland et al. [33] examined 2,402 patients in 22 randomized trials involving n-3 fatty acids, arginine, and nucleotide-supplemented enteral nutrient formulas. As in previous studies, immunonutrient formulas were associated with decreased infection rates and decreased length of stay. In a subset analysis, critically ill septic patients (as opposed to surgical patients) demonstrated a higher mortality rate when given supplemented formulas. Overall Impact® and Immunaid® produced lower mortality rates than in groups using other formulas. Therefore, the authors conclude that further study is necessary to identify subgroups of patients who will benefit from nutraceuticals.

Several recent reports using immune-modulating formulations preoperatively and/or pre- and postoperatively have shown significant benefit

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients</th>
<th>Number of studies</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Heys et al. [8], 1999</td>
<td>1,009</td>
<td>11</td>
<td>Decreased infection rate</td>
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<td></td>
<td></td>
<td></td>
<td>Decreased hospital stay</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No change in mortality</td>
</tr>
<tr>
<td>Beale et al. [9], 1999</td>
<td>1,482</td>
<td>12</td>
<td>Decreased infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Decreased ventilator days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Decreased hospital stay</td>
</tr>
<tr>
<td>Heyland et al. [33], 2001</td>
<td>2,419</td>
<td>22</td>
<td>Decreased infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Decreased hospital stay</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>?Mortality</td>
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in decreasing postoperative infectious complications. Of particular interest is the study by Gianotti et al. [34] giving an immune-modulating formula to well-nourished patients preoperatively with significant improvement in outcome. We are now able to examine a significant number of patients enrolled in randomized studies on immune-enhancing nutrition. From these data we are obligated to develop a new standard of care for the use of nutraceuticals in critically ill patients. We may now be able to define which patients benefit from this intervention as opposed to which patients incur higher mortality, which formula should be given, when should it be used and for what duration. Some of these issues were recently addressed at the US Summit on Immune-Enhancing Enteral Therapy held in San Diego, Calif., May, 2000. The entire proceedings were published in an attempt to clarify recommendations for use [30] (table 3).

### Table 3. Consensus recommendation from the US Summit on Immune-Enhancing Enteral Therapy

<table>
<thead>
<tr>
<th>Probable benefit</th>
<th>Expected benefit</th>
<th>No expected benefit</th>
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<tbody>
<tr>
<td>Major vascular with COPD</td>
<td>Major GI surgery</td>
<td>Resuming per os intake within 5 days</td>
</tr>
<tr>
<td>Major head and neck resection</td>
<td>Serious trauma (ISS &gt;17, ATI &gt;19)</td>
<td>In ICU only for monitoring</td>
</tr>
<tr>
<td>Severe closed head injury (Glasgow &lt;9)</td>
<td></td>
<td>Incomplete/inadequate resuscitation</td>
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<tr>
<td>Major burn (&gt;30% TBSA)</td>
<td></td>
<td></td>
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<tr>
<td>Ventilator dependent with high risk of subsequent infection</td>
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The Future of Immunonutrition

Recently a new interest has developed in certain probiotics and their importance in critical illness. Probiotics consist of live microbes that when ingested confer some benefit to the host organism as a result of microbial influence on human physiology. Rapidly evolving concepts in this field suggest that maintenance of the luminal microenvironment may prevent normally nonpathogenic species from developing mucosal adherence and invasion. These opportunistic microbes may then modulate the inflammatory and immune response. Numerous bacterial and yeast species have been described which have dramatically different effects on the GI system. In direct association with critical care management is the use of *Lactobacillus* GG to reduce antibiotic-associated diarrhea [35]. If success rates are similar in large
randomized clinical trials, the use of probiotic therapy may become the routine.

Exciting new data in the realm of probiotics were recently unveiled by Popoff et al. [36] from the University of Alberta. Recent in vitro experiments demonstrate the role of epithelial cells in modulating the immune response at the mucosal level by sampling DNA of local organisms. These investigators used both a freeze-dried culture of live probiotic bacteria, as well as purified DNA from probiotic strains to pretreat human colonic cells in culture [36]. Cells subsequently exposed to pathogenic bacteria displayed significant reductions in activation of inflammatory pathway elements. This study is the first evidence that epithelial cells perform this level of receptor-based recognition, independent of immune surveillance cells. This new concept in epithelial biology opens the door to refinement of the ingredients of the probiotic ‘cocktail’ based on membrane receptor composition and the ability to maximize the anti-inflammatory effect.

In summary, we now have a wealth of animal and human data attempting to elucidate the appropriate mix of ‘immune-modulating’ nutrients (table 4), the adequate level of nutrient required to show benefit, the appropriate timing of delivery and, most importantly, the clinical scenarios yielding the best outcome with the use of immune-modulating formulas. The basic tenets outlined above should be observed prior to any attempt at nutritional immune modulation.

What is more controversial, yet apparent from multiple clinical trials, is that the concept of immunonutrition is now not only theoretical, but can yield clinical benefit. Subtle differences in patient selection, population studies, and nutrient mix can explain the outcome differences in the relevant studies. Additional research is needed in the arena of single nutrient supplementation to better define mechanisms in humans. Continued, rigorous, critical evaluations of the data are needed as more immunonutrients and ‘nutraceuticals’ are reported for modulation of immune function. Optimizing outcomes in critical care will be the reward for tenacious pursuit of further understanding of the potential beneficial pharmacologic effects of nutraceuticals.

Table 4. Nutrients reported to have ‘immune-modulating properties’

<table>
<thead>
<tr>
<th>Nutrient</th>
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<tr>
<td>Arginine</td>
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<tr>
<td>Glutamine</td>
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<td>Sulfur amino acids</td>
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<tr>
<td>Nucleotides</td>
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<tr>
<td>n-3 fatty acids</td>
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<tr>
<td>Fiber/probiotics</td>
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<tr>
<td>Glutathione/antioxidants</td>
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<tr>
<td>Ornithine α-ketoglutarate</td>
</tr>
<tr>
<td>Probiotics</td>
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<tr>
<td>Taurine</td>
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References


**Discussion**

*Dr. Moldawer:* I started my talk with the pharmaceutical side in which we were doing drug testing, and now we should perhaps talk more about these drugs in our food. So let me put a challenge to you that the pharmaceutical industry would never consider testing 3 or 4 different drugs simultaneously in septic patients, and in fact the Food and Drug Administration (FDA) is very leery about combination therapies without biological activities with single monotherapies. So I ask you an obvious question: have we failed in this approach to really do good science and do control trials with individual nutrients first?

*Dr. Martindale:* I think we have failed because there is very little or no data on single nutrients in that population. It would be very nice. I think with this group we could perhaps eventually get collaborative studies going to get enough patients. The problem is money, and I think that no one would fund this kind of study with single nutrients because they are going to site the data that are already out. It would be very nice to have the data, but it is going to be very difficult to show in humans.

*Dr. Zazzo:* In the same position I will ask you why your consensus statement did not mention the available data on trace elements?

*Dr. Martindale:* Our goal really was to look at these main nutrients or products that are already out there and there was such variability. You know the trace elements in those areas were just not addressed, it was not part of our specific question. This is a very good question, it definitively needs to be addressed but it was not in that consensus.

*Dr. Cynober:* I question the fact that ornithine α-ketoglutarate was totally ignored by you, and most of the American investigators, despite various clinical studies [1–3] that have been published in the *American Journal of Clinical Nutrition, Critical
Care Medicine, and the Journal of Nutrition, which are all American journals and considered as not so bad. In addition I will especially focus on the results with ornithine α-ketoglutarate in burn patients because in my opinion 3 independent studies [4] show that this glutamine precursor improves wound healing. Taking this drug into consideration would probably have moved the ASPEN summit recommendation for burn patients from low to better level of recommendation.

Dr. Martindale: I can allude back to the fact that we used peer-reviewed literature, some of it with ornithine α-ketoglutarate, but we went back to the more clinical studies. What is available in the clinical studies that are using these formulas on the market, that was what we were looking at.

Dr. Cynober: But do you feel that wound healing is not a clinical end point in burn patients?

Dr. Martindale: No, no question but in this case we were looking very specifically. I agree, α-ketoglutarate is beneficial. I don't know where it all fits.

Dr. Rosenfeld: I have one doubt, we know the stores are decreased or the substrates are heavily mobilized. My doubt is that what you are providing improves full function, gives the cell new function or works better. Are we just restoring the normal functions or giving the starving cell the conditions to react to the situation?

Dr. Martindale: I think we are enhancing function and especially in case of arginine administration. I think the data support that T-cell function seems to be supported by arginine. So I think it is variable but in this case I believe we are helping, not just maintaining.

Dr. McClave: You tease out that group with pneumonia in the Ross study (unpublished data). What is the take-home message from that if we clearly identify somebody with pneumonia, is it the age, is it the sepsis, and we treat them differently? The second question is: if they aren't that well on admission and then we start immunonutrition and then they develop pneumonia, what do we do?

Dr. Martindale: If they have pneumonia I will not use immunonutrition, if they already have pneumonia and already are septic. That is my take-home message, and in elderly septic individuals I think we should be very careful. I think if nothing else as the whole controversy is brought up, the point is that we can't generalize, we have got to be specific. I think that nitric oxide has the ability to be a panacea or a toxic, depending on the situation.

Dr. McClave: What happens if you start them on immunonutrition and they develop pneumonia, would you stop it?

Dr. Martindale: Good question, I wouldn't stop it.

Dr. Déchelotte: I would like to comment on this point about pneumonia. If patients who have pneumonia are not to be included in a study with immunonutrition, I think it makes no sense with the major goals of immunonutrition. I think the right interpretation of these data should be that this type of immuno-enhancing diet, this type and given in this way, is not adequate for this kind of patient. I think it is a very important point to make that this word ‘immunonutrition’ is misleading because it covers a very wide field of many things, of many substrates, many combinations of substrates, differences in doses, differences in site and timing of delivery, and I think we should omit this word. Of course it is quite practical in common use, on an everyday basis, but it is very misleading, we should specify glutamine-enriched or arginine-enriched, it is actually more precise.

Dr. Martindale: I think that is a very good point and that is why I brought up the point about Optimental®, which was the formula used and has half the arginine of most of the other products. But I think you are right, should we just not use that product, and if supposedly arginine is the problem, it probably isn't because of the dose that is in there.
**Dr. Steenhout:** You just mentioned that this study was done with a product with half the dose of arginine. In your nice slide I realize that the product also contains structured lipids. So I don’t know if that is involved in this bad effect or not. But what is your opinion about structured lipids in such a formula because it is coming slowly.

**Dr. Martindale:** The question on structured lipids is again very controversial. Most people would believe that the structured lipid is beneficial, but again we don’t have enough data to confirm this.

**Dr. Heyland:** I am actually delighted to hear that. I don’t think we are too far off in our view of immunonutrition, because what I heard you say, if I am correct, is that you do not give this to sepsis patients, it is alright for elective surgical patients, and perhaps we still have some disagreement in the average critically ill nonseptic patients. Again I wonder if this point of disagreement is not based on the interpretation of the different results from the studies. I tend to focus on the intention-to-treat analysis as you know, and I think that most focus on compliance analyses. You emphasized the point that we need to get an adequate dose of the nutrients or drugs, as may be, into the patients. What do you think about the hypothesis that giving an arginine supplement-containing formula to a relatively sick intensive care unit (ICU) patient, the effect that it would have on gastrointestinal motility and creating problems with tolerating feeds so that then the sickest patients are excluded from the analysis? In this sort of secondary analysis, you are really left with imbalanced groups which you favored, in the arginine-containing group you have excluded 6 patients because they did not tolerate enteral feeds. Would you tell me what you think about that analysis?

**Dr. Martindale:** I think first we don’t have any data that a high arginine formula does decrease tolerance.

**Dr. Heyland:** In terms of nitric oxide, if you produce nitric oxide it will impair gastric emptying.

**Dr. Martindale:** But in many cases it increases blood flow.

**Dr. Heyland:** Yes, but the motility goes down. There are experimental data for that.

**Dr. Martindale:** With high levels, very high levels in it, in an already stimulated model but not in the normal patient.

**Dr. Heyland:** I am not talking about normal patients.

**Dr. Martindale:** You are talking about surgical and not immediate postoperative patients, so they are already induced.

**Dr. Heyland:** They are already induced. There is some form of information going on in the patients so you are probably producing nitric oxide.

**Dr. Martindale:** I think we get around that by the fact that we attempt gastric feeding and if unsuccessful we go to jejunal feeding, and as you know we can feed fairly sick patients very carefully in the jejunum if we watch them very closely. I am one of the bigger advocates of early feeding, but I also think that we have gone too far with our attempts to feed earlier. In fact that was the title of my talk at the ASPEN symposium, have we pushed too long and pushed too hard trying to use the gut? Maybe we should say alright there are some patients we can’t feed and back off a little bit. So I think in that case we would enhance visceral blood flow, which may help us in the gastrointestinal tract. But you are all right, gastric emptying is a little bit of a problem but if we are intolerant then we use the gastrointestinal tract.

**Dr. Heyland:** Certainly in the future we are going to design better trials, from the gut we should be putting the tubes in the small bowels to deliver adequate nutrients or drugs.

**Dr. Martindale:** I personally like jejunal feeding for the sicker patients anyway.

**Dr. Heyland:** I think it biases the analysis and therefore the interpretation thereof if you are systematically excluding those patients who don’t get fed enough because there is an interaction between the arginine, gastric emptying, tolerance, and outcome.
*Dr. Martindale:* I think your first statement I was omitting the septic patients, I wouldn't omit all the septic patients, I would omit the septic patients with severe pneumonia and the elderly, those patients I would say.

*Dr. Heyland:* I guess we still disagree with that.

*Dr. Labadarios:* You did say that we should look at these nutrients as drugs, but if we did that the chances are excellent that they would never really appear on the market because they have never been investigated the way a drug normally is investigated. So I think we have to be careful about what we consider to be a drug. Coming back to the question of pneumonia, do you think we are in an area here where in trying to treat a disease we are likely to be creating another disease, which is not necessarily a complication of the present disease? For instance, if you look at another field of nutrition. There is little doubt about the validity of vitamin A being an immunoenhancing nutrient in high doses, but we have now realized that one of the side effects of these high doses of vitamin A supplements may be an increased risk for respiratory infections. It actually goes further because we have some data from Mozambique which show that it may not be advisable to treat children with cerebral malaria with high doses of vitamin A because if you follow the survivors for 2 years, as we have done, you find a tendency in these vitamin A-supplemented children to develop mental deficits. So quality-of-life aspects may arise from improved survival rates [5].

Do you think that we may be dealing with a situation like this? Have we got data to know what we are doing really?

*Dr. Martindale:* No, we don't have the data but I think that it would be a pretty big jump to say that the minor modifications we are making are going to produce a new problem. Now you are right in that select population, but I think we need to go back through and look at these under specific situations, and then look at the long term. We have the Griffiths data at 6 months talking about glutamine over a very short period making a difference at 6 months. We should go back now and look at the 6-month and the 1-year outcome of some of the immunonutrient studies.

*Dr. Kudsk:* This is the first time I have seen the Ross data. A question I would like to ask you, what is the pneumonia data, a post hoc analysis? If it is a post hoc analysis, it comes under all the other criticism of all studies that do post hoc analyses. It has to be tested, because if it was pre hoc then it should have been powered to show a difference in mortality in pneumonia and I suspect it wasn't.

*Dr. Martindale:* This was the intermediate analysis which went and looked at the data and said let's stop because we have a problem. I think the problem was the randomization, we would not have seen it if we had easily randomized pneumonia. These patients had pneumonia when they got the nutrient.

*Dr. Ribeiro:* Most of the studies were made with the first-generation immune-stimulant formulas. What about these newest formulas, named immune-modulating formulas, that have just emerged on the market?

*Dr. Martindale:* You are all right, this is the first-generation and 90% of the studies we have seen today were done with one product or two. I think there are minor changes in the new ones, in fact if anything they are coming down on some nutrients and going up on others, but they are not coming out very fast. The changes are not being made very fast. I think the newer ones, the second-generation, will have more trace minerals, will have a different absorption, will probably combine with probiotics or at least the prebiotics, not for all patients but some. When I think back to modulating formula there is a basic core in a modulating formula and it may be transition over time: in the first week treated, change from one and switch to a second, and change it over time, so very expensive.

*Dr. Maiorova:* You demonstrated the influence of several nutrients on immunological functions, but at the same time you showed several theoretic aspects.
Is it possible that using some amino acids, for example arginine, glutamine, influences the activity of drug-metabolizing enzymes, for example cytochromes and others, and does it influence the drug metabolism of patients in the ICUs or overall? What is your opinion?

Dr. Martindale: Certainly any nutrient, or as we would like to use it at a drug level, would clearly induce enzyme systems, we have not seen problems with toxicity in the liver with these products. Again that is why I think the FDA allows these things to be placed on the market with very low testing because they are classified as medical foods under the idea that they are generally recognized as safe, and so in most cases they are safe. I think where we can get into trouble is if we start displacing drugs from albumin binding and changing levels of drug. But in that case we haven’t seen that problem, we haven’t seen changes in drug metabolism.

Dr. Maiorova: Because I am interested in several drugs that have a very narrow therapeutic index, when their metabolism is altered we see some toxicity. I mean for example drugs used in cancer therapy.

Dr. Martindale: I have no data on the cancer therapy.

Dr. McClain: You could make a couple of postulates on the pneumonia patients, one would be that the alveolar macrophages were too jazzed up and released tons of tumor necrosis factor and every body got inflammatory respiratory distress syndrome and died, or you could say that they could not kill and so you just got over whelming sepsis. Has anybody looked at these patients carefully to try and separate that out?

Dr. Martindale: No. We can get the Ross data, which has been looked at now as part of the abstract which should be presented at the Society for Critical Care Medicine, but as far as individual patients are concerned, we can’t really see any major difference, we haven’t looked at individuals.

Dr. Nitenberg: I have been working in that field for many years and I am more and more confused about the conclusions. If we try to go back to the real world again and if we accept your conclusions, I don’t say that I accept but suppose that we accept your conclusions, let’s say that first for surgical patients, and I think that is the strongest evidence that we have presently, we can use immune-enhancing diets preoperatively and possibly postoperatively, but what type of immune-enhancing diet could I use in my hospital? If you look carefully at the results the only immune-enhancing diet that has been proven to be efficient in this case is Impact®. If you pick up Impact® you have no results. So the only thing I can say is in our hospital for surgical patients I can try to use Impact®, nothing more, and I don’t know what is efficient in Impact®. Second point, in multiple trauma patients it is more confusing because to my knowledge there are the studies from Dr. Kudsk and Dr. Moore which have been made with Immun-Aid® if I remember well, which is another nutrition mix, but there are also the remarkable results from the Houdijk study which was made with something which is very closed to Alitraq® and which is only rich in glutamine and may be a little source of antioxidants I think. So in that case what do I have to recommend, I don’t know. What is more amazing, you say that in septic patients, I do agree with that, but in very severe ICU patients we don’t know. Unfortunately there is only one study by Galban that may prove that Impact® is efficient in septic patients and perhaps in pneumonia patients, and your conclusion does not, certainly not immune-enhancing diets in pneumonia patients. So finally what do I chose and why?

Dr. Martindale: I think in the Galban study, as you know only the mild and moderate septic patients would benefit from it, the severely septic patients would not. So I think that it is reasonable to say severe sepsis, as we have talked about it earlier, those are the patients for whom we really have to know what we are doing, nutritionally as well as metabolically. So I think that is part of the key, with severe sepsis you just have to be careful. The rest of it, you ask what should we give. I think
the data are there and I think we have to say we can give Impact®, we can give some similar products. I give what the data would support.

Dr. Berger: I probably have a silly question but it is my lack of knowledge of American products which is behind this. I have been amazed that many control studies in America have been done using Vivonex®, which is an elemental diet. I haven’t seen this myself, but I was told yesterday by 3 different American persons that in Vivonex® there is an amazingly large proportion of glutamine, or an enriched proportion, higher than any other standard enteral diet. How can we then compare, how can we interpret the trials where actually the control group was a glutamine group?

Dr. Martindale: I don’t know that any of these studies up there today use Vivonex® as control.

Dr. Moore: Can I respond, because it is our study that used Vivonex®.

Dr. Martindale: The first one.

Dr. Moore: If you go back into the history of Vivonex®, it was actually created by a pharmaceutical company. Before they went and promoted it in the ICU they said we are going to test this like a drug, and that is the reason why all those studies were done with Vivonex®. They did not want to market it unless they had data. Over about 10 years we did 3 prospective randomized trials that showed whether you gave Vivonex® without anything or Vivonex® with total parenteral nutrition (TPN) or Vivonex® with delayed TPN you get a better outcome with Vivonex®. Therefore we went on to design the Immun-Aid® study and Dr. Kudsk was in the discussion. It was hard for us to take Vivonex® and spike it with something to make it isonitrogenous. So we said this is our standard of care with the plans that Dr. Kudsk was going to do the follow-up study and make an isonitrogenous diet and compare it. Then we did the Vivonex® versus Immun-Aid study and showed improved outcomes. Dr. Kudsk did the isonitrogenous isocaloric versus the Immun-Aid® and showed the same results. His patients were a little sicker.

Dr. Martindale: I would even go back a little further than that, Vivonex® was originally made for the space program as an elemental diet. The idea was that they didn’t want the astronauts having a stool in space so give them a pure elemental diet, and in fact the Air Force troops that they studied went from 1 stool/day to 1 stool/week.

Dr. Moore: It is kind of funny.

Dr. Martindale: They didn’t know the benefit of glutamine at the time of formula creation. The reason they put glutamine in there was because of the taste because literally the troops would not drink it without something to cover the taste. When they realized that glutamine was tasteless they put in more glutamine just because of the taste issue. Tang was developed to cover the taste.

Dr. Moore: Once they figured out that there was some pharmacological fact and that something was happening, ...,

Dr. Martindale: They sold it.

Dr. Moore: They ran with that for a long time, so I always said glutamine, I don’t want to believe that. Maybe there is something with the glutamine.

Dr. Berger: Does it mean that the enteral Vivonex® studies against TPN are actually glutamine against nothing?

Dr. Martindale: They do. The original Vivonex® had less glutamine than the current Vivonex®.

Dr. McClain: It just depends on which part of the animal you are looking at. For somebody studying liver disease like myself, when I want to make patients choline-deficient or if I want to make them deficient in methionine, I give them Vivonex®. So it is probably the worse thing to give somebody with liver disease or somebody in the ICU.

Dr. Déchelotte: I would like to come back to the pragmatic remark by Dr. Nitenberg. We have to make decisions together with our hospital administration. We have to make
decisions on what product will be referenced or not in our hospital and for which patients. We made the decision 2 years ago that there wouldn't be any immune-enhancing diet. Last year we made the decision that Impact® would be taken only for heavy surgery in cancer patients, only, and we made the decision based on the available data in our hospital together with our colleagues that it should not be used for septic ICU patients. I think the new data from the Ross study (unpublished data) that you showed today, which I am very disappointed but also delighted to see, provide additional evidence from the previous meta-analyses that in severe ICU patients, septic or not, we should not routinely use Impact® which is at the present time the only nutrient diet that has been tested in this kind of patient. There are no studies with the other arginine-enriched compounds available in Europe. So we need to withhold from using these diets at the time.

Dr. Martindale: I think you made a good statement that you sit down with the colleagues and say are we using it and make the decision. I have to say I don't know that there is a huge difference between them if they are made with the same amount of nutrients, if they put similar arginine, similar n-3 fats from a similar source, I can't say there is going to be a huge difference between them. Now it may well be that going from 6 to 16 g/1,000 cal may make a difference. But remember that the mortality was in the group that had less arginine. Half the arginine of the Impact® is where the mortality was. So to say that we should not use Impact® for the same argument you are making, to say that we should not use a high arginine formula and there we can't really make that statement either.

Dr. Déchelotte: I agree that we should not use any arginine-enriched diet at the present time for very severe ICU patients because we don't have the rationale to make the difference in comparison to a standard product.

Dr. Martindale: But that product has very little more than a normal diet, than a normal standard formula, not much more. The standard formula has about 5.5 g and this one has about 7.5 as opposed to 14, so there is very little difference between that and the standard formula. So to say that 2 g for a 1,000 cal made all the difference, I can't make that jump.

Dr. Déchelotte: If I may go to another point again with glutamine and arginine. All these data that you showed are done with arginine-enriched diets and you are well aware of the Immun-Aid® papers with arginine plus glutamine which are positive and the Dutch paper on trauma patients. So I think there is a great difference. At the present time there are limited studies with enriched glutamine diets, but most of them are either equivalent to control or better than control. None of them show any increased morbidity or mortality in comparison to control, which is a big difference to arginine-enriched diets.

Dr. Martindale: And even to make it more confusing, in the US we now have got Impact® with glutamine, and so it is even more confusing.

Dr. Zazzo: Let us go back to the dosage recommendation in the consensus statement. The consensus said 1.2–1.5 liters/day. That is right?

Dr. Martindale: Over that by the 5-day period, try to get it to about 50% of caloric goal.

Dr. Zazzo: When we consider the few studies in elective surgery, before surgery, it is 1 liter/day during a week.

Dr. Martindale: 5 days to a week.

Dr. Zazzo: Yes, but 1 liter. How do you explain this discrepancy between elective surgery and the conclusions.

Dr. Martindale: I think there is a big difference. One is going to have the metabolic stress, the metabolic demands are down and the rate of metabolism has changed significantly. If you can preload prior to the insult, I think that is the key. I think this
is sort of like carbo loading for a marathon run. We can change the membrane concentration of the n-3 fat.

**Dr. Zazzo:** This is only hypothesis, we have no data to recommend more or less?

**Dr. Martindale:** No, I can only go from the Braga and Gianotti data, and there are several others now, as you saw there are several papers now on the pre- or perioperative period. To me the most fascinating data are in the well-nourished population. Giving it for 1 week or 5 days preoperatively, 1 liter/day shows a positive outcome equivalent to giving it pre- and postoperatively. As you know the Heslin data used an immune-enhancing formula and they showed no benefit. Part of the problem there was most of those patients had albumin of >35g/l on entry for surgery and they showed no benefit. This is a very nice set up because if you can give it to the patient for 1 week preoperatively between admission and setting the patient up for surgery that can make a significant difference in a large number of patients. But again, how much to give, would 2 liters be better, would 500 cm³ be enough, we don't know.

**Dr. Tepaske:** There is a recently published Spanish study about multifibers compared to an isonitrogenous control which only showed some differences in infections in 1 versus 9 patients I believe. I am coming back to the septic patients and also looking from a nutritional and especially clinical point of view. First of all I am interested if I can feed or not feed the patients enterally, and I know if I can feed them enterally they are in the bad group, high morbidity, high mortality, I think there is no discussion about that. But then there is a second choice to make. If I can feed them nasogastrically with a tube, what do I have to choose? In my opinion there is the Bauer study and the Atkinson study showing that the best is immunonutrition. Do you agree with that?

**Dr. Martindale:** I feed septic patients with immunonutrients, so I go from there. The question is are they sick enough so that it is difficult to feed them enterally? I think you made that point very well. But I still use it in septic patients. Now I am a little more cautious if I am called for a consultation and the patient has got pneumonia, is on the ventilator, an elderly patient, but in general I would use immunonutrients in septic patients.

**Dr. de Bandt:** Haven't we overlooked the question of micronutrients in this situation? I don't know the specific requirements of pneumonia patients, but if we go back to basic biochemistry the toxicity of nitric oxide is not due to nitric oxide per se but to its reaction with superoxide anion, leading in the situation of an excess of superoxide anion to the toxic peroxynitrite anion. So if you prevent excessive superoxide anion production you enable a beneficial effect of nitric oxide which is the control of NF-κB and the activation of transcription systems such as expression of cytokines. So is there a problem in this field, have we not overlooked this question?

**Dr. Martindale:** You make a very good point. I am not sure that we have overlooked the question. I think that the reactions that are going on inside the cell are so compartmentalized that it is going to be very difficult to sort out whether it is going as a substrate for arginase versus nitric oxide synthetase, and I think that is compartmentalized and upregulated or downregulated depending on what is going on in the cell. I think that is why we see such a variation in outcome and we are overlooking it. But when we block nitric oxide synthetase we still see benefits in some cases, so it may not be nitric oxide production, but also we may get the benefit of vasodilatation.

**Dr. De Bandt:** If we take the example that Dr. Cynober gave this morning we have an increased mortality in a simple model of lipopolysaccharide toxicity when L-nitro-arginine methyl ester is administrated. When you block nitric oxide you have a dramatic increase in mortality. So it is not so simple.

**Dr. Martindale:** No it is clearly not simple.
References


