Timely Nutritional Support: Thoughts for the Future

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The common characteristic of the past 3 days has been the high quality of the presentations, the intensity of the ensuing discussions, fueled by speakers and delegates alike, the many take-home messages for our practices and the inevitable, but crucial in workshops of this nature, sobering questions that remain in need of urgent answers in the field we addressed. Even the most encompassing of summaries of such an intensive workshop would understandably fail to do justice to the many aspects of all the contributions made. Nevertheless, in concluding the proceedings, we deemed it appropriate to integrate and summarize some of the key issues of the Workshop in five sections.

Inflammation and Nutrition

Fundamental as the liberation of proinflammatory cytokines in relation to the acute phase response would appear to be in mediating the known nutrient release from host tissues, in creating a hostile environment for invading microorganisms, but favorable for the recovery of the host as well as in improving antioxidant defenses, it is increasingly realized that their release is under the control of genes, and their action is modulated by specific nutrients. Clearly there is some kind of cytokine genotype that influences the inflammatory drive in terms of disease process, and ultimately determines a given clinical outcome. For instance, in certain individuals the production of tumor necrosis factor-$\alpha$ is clearly modified and, in some genotypes, influences the clinical outcome of sepsis. Future research in this
domain will undoubtedly elucidate the underlying mechanism(s) determining an adverse or beneficial outcome of a specific therapeutic modality in a given individual. These concepts typify the nature of the extraordinary challenges we are faced with in our attempts to improve the current understanding of these intimately integrated relationships and the role of specific nutrients in influencing clinical outcomes. In this regard, the introduction in the workshop on the ‘nutrigenomic’ approach would imply that the practice of nutritional support will increasingly, borrow from the principles of pharmaceutics, if we are to better understand our current practices and how they can be employed to the maximum benefit of our patients.

With regard to antioxidant defenses, it would appear that plasma antioxidant concentrations are less important than their fluxes at the cellular level. Nevertheless, there remains the urgent need to fully understand their many interactions, as we clearly know only part of the global picture. Furthermore, ‘new’ players have entered the inflammation scene in the shape of lipoproteins, and their apparently important role would seem to clearly indicate a new area of intensive research in the future.

**Host Resistance**

The second part of our summary relates to the use of specific nutrients for the improvement of host resistance. Indeed, to quote our speaker, the gut is ‘a free radical time bomb’, and the fuse is lit by inflammatory bowel disease (IBD). It is generally accepted that the gut is an overabundant producer of activated leukocytes and of increased concentrations of inflammatory cytokines. The reported increase in the n-6/n-3 ratio during relapse of IBD underscores the need to better define the role pre- and probiotics may play in the frequency and severity of relapse of the disease. However, caution has been called for, especially in immunocompromised patients and in infants.

The workshop also highlighted the potential toxicity of oxygen, the tension of which in tissues would appear to drive their behavior, when exposed to hormones, nutrients, and most of the reactive oxygen species. To exemplify the concept, the data presented indicated that, while the prevalence of cardiac cell death was fairly stable during an ischaemic period, the time of reperfusion was associated with a major increase in cell death. One might be forgiven for thinking that nutrition is getting closer to philosophy, since one could interpret these findings as showing that one starts to die, while being resuscitated! On a more serious note, however, it would appear that early preventive intervention is probably going to change the management of severe disease in the future.

Of great interest, we were told that the endothelium constitutes about 1–1.5 kg of cellular mass. We were also told that incorporation of n-3 essential fatty acids (EFA) in membrane phospholipids may decrease the level of cell reactivity to various stimuli. The potential for n-3 EFA to prevent cardiac
arrhythmias and sudden death from ventricular fibrillation in overexercised dogs was convincingly shown to be prevented by pretreatment with an intravenous infusion of n-3 EFA. This may open new areas for investigation in patients suffering from myocardial infarction or benefiting from coronary revascularization. Of interest, n-3 EFA incorporation in cell membranes also appeared to protect tissue microperfusion and to improve the function of grafted organs. This of course has to be verified in humans.

Another point of great interest in the workshop is the reported increase in splanchnic extraction of protein in elderly people. These findings may, in time, contribute to the better understanding of factors predisposing elderly people to sarcopenia. In addition, the reversal of sarcopenia was shown in the elderly who were receiving protein in the form of specific protein supplements, given as sequential boluses instead of the usual 3 daily meals. This concept, known as chronobiology of protein, is certainly very promising in the management of aging-related sarcopenia, when coupled with the promotion of physical exercise.

With respect to vitamins and trace elements, there was general consensus that these micronutrients play a critical role, not only for growth but also for immune function and clinical outcomes. The role of selenium in improving brain function, especially in the ratio of clear-headed/confused, elated/depressed, composed/anxious, confident/unsure, is intriguing and must await better definition. It is also remarkable that, at a time when enteral feeding is the generally accepted first choice of nutritional support, the little that we know about the action(s) of vitamins and trace elements in the acute setting is derived mainly after parenteral rather than after enteral administration. Furthermore, we desperately need more information on the role and use of these micronutrients in specific clinical situations. In this regard, we have been warned by some of the best-known experts in the field that it is very difficult to recommend dosages of these nutrients, considering the diversity of the clinical conditions we are faced with in our patients. Certainly, in cases of acute stress, before increasing the dose of any or all of these micronutrients, one should be very careful regarding the benefit-risk ratio of such a decision.

The Importance of Timing

It was said that nutritional intervention should be early, before a vicious circle is initiated. Acknowledging that starvation is universally lethal and occurs sooner in the presence of the illness without appropriate nutrition support, the timing of the latter is generally accepted to be of crucial importance. In trauma patients and patients with acute respiratory distress syndrome, we were told that the use of early enteral nutrition (namely, initiation within 24 and 72 h after admission) is supported by the data presented, although
this is not the case for total parenteral nutrition. Important as this principle may be, one should bear in mind that studies in this domain are generally considered to be statistically underpowered for a conclusive and generally applicable recommendation, in view of the complexity of the presenting pathology, individuality and the high mortality in these clinical settings. The evidence presented and the subsequent discussion that followed would appear to support the premise that the sicker the patient is, the less likely it is for the patient to derive benefit from nutrition support. This scenario is by no means a reflection on the inefficiency of nutrition support, but rather on the severity of the insult and our inability to survive insults beyond a defined severity. This is especially true during the very early period of critical illness. It would appear that during this period – in other words the first few days – the type of nutritional support that can be provided may not afford significant benefit to the patient, though the data by no means suggest that doing nothing is any better. Nevertheless, the possibility of doing harm, when in fact the aim is to afford benefit, should not be overlooked and should be made part of one’s approach to the management of these patients.

Another point of interest, which is likely to develop further in the near future, was the presentations indicating that growth factors, cytokines, glutamine, and butyrate all seem to improve nutrient absorption, though this remains to be confirmed. One, of course, should also not forget the originality of the practice offered here in South Africa of successfully feeding short bowel syndrome patients with breast milk or colostrum. Such a practice makes perfect sense on the basis of our current knowledge of growth factors, milks being known to contain a plentiful amount of these compounds. What the potential effect(s) of these factors in adults with this syndrome would be is a matter of speculation, but very well worth investigating further.

**Options for Nutritional Intervention**

Clearly, myths, impressions and beliefs are not always true. There can be little doubt that gut starvation reduces gut absorptive capacity and defenses, and causes liver intoxication. There can equally be little doubt, and there was general consensus on this issue, that, in cases of gut failure, enteral nutrition is associated with serious risk to the patient. The consensus does by no means imply that enteral nutrition should not be used in critical illness, but rather its administration should be decided upon according to clear indications, with great care and close monitoring, as well as on a case-by-case approach.

It was interesting to have noted during the proceedings that the terms ‘immunonutrition’ and ‘immunomodulation’ appeared to be used interchangeably. Apart from the demonstrated need to standardize terminology, both terms refer to the therapeutic reduction in the intensity of the acute inflammatory response or to the enhancement of immune protective mechanisms.
Overall, it seems clear that early intervention may positively contribute to reduce tissue lesions, and ultimately reduce the prevalence of the systemic inflammatory response syndrome and multiple organ failure.

The risk-benefit ratio is a function of disease severity and we should bear this in mind. Trying to modulate the immune or the inflammatory status of our patients has been shown to be useful in trauma, cancer surgery, and in a few other situations, but not in every clinical setting. That is logical – when you practice medicine, your education over many years tells you that you need to adapt a treatment to a condition, and we do not see why nutrition should escape this general rule. So, even though we find it a little odd, the concept of the ‘best mixed fixed specific formula’ that was proposed is an interesting one.

Significant changes in body composition are the sine qua non of any illness, especially critical illness. The fascinating data presented emphasized the use of such data in predicting clinical outcomes, and the emerging association of body composition with the genotype. In practical terms, body composition integrates nutritional changes over time, as exemplified in children during growth, but also in adults during refeeding after disease, or in the presence of malnutrition. There remains the urgent need, however, to establish appropriate body composition measurements which would provide more objective assessment and monitoring of the efficacy of nutritional support in the short term. Nevertheless, and since function correlates with total or organ energy expenditure, it is fascinating that with modern technology the energy expenditure of individual organs can be measured. Of course, there are limitations to these techniques with the currently available equipment. In relation to the acute phase response and its impact on nitrogen metabolism, inactivity in the presence of inflammation was clearly related to altered cell transport and metabolism, as well as to atrophy and contractile failure. Of special interest, though, were the findings that bouts of exercise actually increased myofibril transcription and/or translation rates, which ultimately increased the number and efficiency of the mitochondria. It was, perhaps, premature to have hoped that there would have been consensus on the role and beneficial use, if any, of ergogenic aids during critical illness, suffice it to say that no one questioned the marked benefits of early mobilization.

Finally, on this section of the proceedings, the confirmation that protein-energy malnutrition is still present in around 50% of patients admitted to hospital was truly disheartening, not only because of the human suffering ‘in the midst of plenty, but also because protein-energy malnutrition has serious cost implications. The latter were reported to be associated with direct health cost increases of about 70% and global costs increases of about 300%. Renewed and intensified efforts, therefore, would appear to be essential in promoting the known and well-documented cost-effectiveness of nutritional support in the correct clinical settings, as well as the minimal additional cost and the substantial savings its proper implementation can accrue.
The Future of Nutritional Care

Optimized fetal nutrition and the ‘nutrigenomic approach’ in relation to cellular energetic homeostasis, these are concepts that promise to shape our tomorrow in terms of prevention and management of our patients.

We are privileged in that we have had so many issues to think about, not only concerning nutritional support, but also the type of care we are offering our patients. There have been many, and indeed most welcome, differences of opinion, and on many occasions, when everyone appeared to be looking in the same direction, someone spoke up for a different view and pleaded for caution. This, undoubtedly, is the best basis and guarantee for the good science of tomorrow.

We would like to sincerely thank all the speakers, moderators, and delegates for their enthusiastic participation in the workshop proceedings, as well as for their acumen and capacity to identify and consider what is important and what is not.