Vitamin and Antioxidant Supplementation: Critical Evaluation of Clinical Outcomes

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The systemic inflammatory response is a critical component of the innate immune system in man that develops in a stereotypical manner to injury, inflammation, and infection. This enormously complex set of actions, reactions, and interactions develops in large measure, when cells of the monocyte/macrophage lineage are activated by a wide variety of stimuli including endotoxin, microorganisms, antigen-antibody complexes, burn injury, trauma, cancer and many other acute and chronic diseases, to release the two principal, proximal cytokines, interleukin (IL)-1 and tumor necrosis factor (TNF), both of which stimulate the production of a third, pivotal cytokine, IL-6. Working in a cascade fashion these mediators activate many of the body systems including the immune, metabolic, hematopoietic, and cardiorespiratory systems via a number of second messengers to produce fever, tachycardia, tachypnea, hypercoagulability, fibrinolysis, as well as a plethora of other effects, but particularly leukocytosis and activation of bactericidal activity through enhanced production of reactive oxygen species. There are as well a wide variety of metabolic effects including enhanced glucose production, accelerated skeletal protein breakdown with increased net protein synthesis in visceral organs like the liver and bone marrow that lead to production of larger numbers of immune cells and acute phase proteins, and increases in resting energy expenditure. This systemic inflammatory response syndrome (SIRS) is clinically identified by generally agreed upon characteristics of increases in heart rate (>90 beats/min), rises or falls in body temperature (<36 or >38°C), changes in respiratory rate or arterial oxygen concentration when breathing room air...
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(>20 breaths/min or pO₂ <30 torr), and elevations or depressions in white blood cell counts (>12,000 or <4,000 cells/mm³ or bands >10%) [1].

In the vast majority of instances these various effects of the SIRS foster an improved outcome from acute infection, injury, or inflammation of limited duration in the previously well-nourished host. For example the invariable lowering of serum iron that occurs with inflammation limits the availability of this nutrient essential to bacterial replication for certain bacterial pathogens [2]. Providing iron to restore levels towards normal can increase morbidity and mortality in infection [3]. Similarly the reduction in serum zinc by sequestration in various tissues can serve to increase metallothionein production and serve as an essential cofactor for a variety of zinc-dependent enzymes. Increasing zinc intake in infected patients who are not zinc deficient can exacerbate the inflammatory response [4]. The anorexia, increase in sleep duration and depth, and reduction in spontaneous activity that follow a SIRS all serve to reduce energy expenditure and preserve energy reserves, while the reduction in food intake helps to avoid pathologic hyperglycemia that could result, if forced feeding to meet energy expenditure were provided in the setting of increased gluconeogenesis and insulin resistance. Hyperglycemia of >200 mg/dl occurs more than 25% of the time when total parenteral nutrition is provided at 30 kcal/kg and more than 50% of the time at 35 kcal/kg [5], levels that exceed energy expenditure in many postoperative patients [6], but are less than those found in most trauma patients [7]. Serum glucoses elevated to this level not only markedly increase the risk of infection [8], but recent evidence suggests that hyperglycemia itself activates the SIRS [9] and thereby might further aggravate inflammation.

Balancing this pro-inflammatory cascade is a so-called compensatory anti-inflammatory response syndrome (CARS) [10]. Certain of the interleukins including IL-6 are partially, while others like IL-4 and IL-10 are principally, counter inflammatory and immunosuppressive. Another cytokine, IL-1 receptor antagonist elicited by the SIRS competes with IL-1 for its receptor and has no agonist activity, although the IL-1 receptor antagonist has to be in considerable excess to block IL-1 activity effectively. Shed extracellular portions of the TNF and IL-6 receptors can serve to bind TNF and IL-6 in the serum rendering them unable to activate the intracellular signaling cascade. Certain of the eicosanoids, which are one of the most ubiquitous of the second messengers for cytokine action, such as the leukotrienes, can enhance cytokine secretion, while others like prostaglandin E₂ reduce cytokine secretion by mononuclear cells. The stimulation of the hypothalamic-pituitary-adrenal axis with the SIRS leads to enhanced cortisol production that has largely anti-inflammatory and immunosuppressive effects. More recently a new role for fetuin, a negative acute phase protein first identified more than 50 years ago, has been elucidated. Fetuin has been shown to reduce TNF production by activated macrophages [11]. Spermine, a polyamine found widely in cells, is produced by actively regenerating cells and released by
injured or dying cells. Spermine and fetuin interact to dampen the innate immune response [12] providing an additional mechanism for the diminution and resolution of the SIRS.

Thus, under most circumstances, these two systems of inflammation and counter inflammation are carefully balanced leading to inflammation, repair, and recovery without a requirement for exogenous nutritional support. However, under certain conditions, the SIRS can be potentially harmful. It has been convincingly demonstrated that IL-1, TNF, and especially IL-6 levels are directly correlated with the severity of illness as well as subsequent morbidity and mortality [13–15]. The excessive production of pro-inflammatory cytokines, due to overwhelming illness or repetitive episodes of less severe SIRS, are thought to play a prominent etiologic role in the development of multiple systems organ failure [16]. On the other hand, an excessive CARS exemplified by higher levels of IL-10 in relation to TNF can lead to heightened immunodepression and poorer outcome [17]. Therefore not only the pro-inflammatory and the anti-inflammatory components need to be well controlled, but the relationship between the two must be appropriate.

Another common pattern of the SIRS is that seen with chronic illness characteristic of end-stage liver, renal, cardiac, or pulmonary disease [18–21], other chronic illnesses like inflammatory bowel disease [22], some cancers [23], as well as certain common chronic diseases such as obesity [24], diabetes [25], and coronary artery disease [26] to name but a few. Apparently the severity of the SIRS in many of these conditions is sufficiently small as to be detected by only the most sensitive measures of cytokine activity, such as serum-soluble TNF receptor and C-reactive protein elevations, and hypoalbuminemia, but the inflammatory response is continuously stimulated leading in many instances to morbid consequences, such as protein calorie malnutrition on the one hand or accelerated atherosclerosis on the other. This then introduces another important variable in the expression of SIRS, the nutritional status of the host. Malnutrition markedly increases the morbidity and mortality of injury or infection [27, 28]. A corollary is that the severely malnourished individual fails to release pro-inflammatory cytokines in response to experimental stimuli [29, 30]. Short-term refeeding for about 1 week restores this ability [29, 30], and as well improves clinical outcome following major surgery [31].

One of the most important components of the SIRS is the production of reactive oxygen species including superoxide anion, singlet oxygen and hydroxyl and nitric oxide radicals, hypochlorous acid, and hydrogen peroxide particularly by cells of the monocyte/macrophage lineage, eosinophils, neutrophils, and endothelial cells in response to IL-1, TNF, and IL-6 stimulation [32]. These reactive oxygen species are the major mediators of damage and death to invasive microorganisms, but have the potential to damage normal and pathologic tissue as well. In the resting state the main source of reactive oxygen species is in the mitochondria. A fraction of the electrons transferred
in the respiratory chain by NADH and FADH$_2$ react directly with oxygen, producing the superoxide anion [33]. Reactive oxygen species cause the phosphorylation, ubiquitination, and degradation of I$\kappa$B and nuclear translocation of NF$\kappa$B [33]. NF$\kappa$B stimulates the production and release of TNF [9, 34], which is pro-inflammatory. The human host has a series of antioxidant systems to control these two-edged weapons, so as to maximize their putative value, while minimizing their potential for harm. These include the normal constituents that provide the bulk of antioxidant defenses including vitamin C for the intra- and extracellular fluid, vitamin E in lipid membranes, and glutathione, a tripeptide composed of glycine, cysteine, and glutamic acid, as the principal intracellular antioxidant [32, 35]. Constitutive enzyme systems, such as superoxide dismutase for conversion of superoxide to hydrogen peroxide, glutathione peroxidase and catalase for the conversion of hydrogen peroxide to water, can serve to detoxify these compounds, whereas myeloperoxidase in leukocytes convert hydrogen peroxide and chloride to the hypochlorous acid as a potent microbiocide by its ability to damage protein [32, 35]. Trace amounts of iron can facilitate the conversion of superoxide via the Fenton reaction to the hydroxyl radical, which is a potent initiator of the chain reaction of lipid peroxidation [32, 35] that can be cytodestructive through its effects on membrane lipids. The very active hydroxyl radical can also destroy DNA, inactivate proteins, and break down carbohydrates. This reemphasizes the essential importance of sequestration of iron both by specific compounds and by compartmentalization as part of the SIRS to help control these processes. Vitamin E has the ability to break this reaction of lipid peroxidation, and the principal mechanism for restoration of vitamin E is by reaction with vitamin C, which itself is regenerated by glutathione [35]. Selenium is an important cofactor for glutathione peroxidase, which accomplishes this reaction. Glutathione disulfide so produced is reduced back to glutathione by glutathione reductase, which requires NADPH as a source of reducing equivalents produced through the pentose phosphate pathway [35]. The SIRS not only markedly enhances reactive oxygen species production but accelerates antioxidant defenses as well. Glutathione and superoxide dismutase synthesis are increased by cytokine action, and iron availability is reduced by tissue sequestration in transferrin and ferritin, and hemoglobin binding by the acute phase protein, haptoglobin. Other positive acute phase proteins, such as metallothionein and ceruloplasmin, limit exposure to zinc and copper ions [36, 37]. Ceruloplasmin has superoxide dismutase-like activity as well [38].

There are a number of other nutrient compounds and metabolites that have antioxidant activity including taurine, uric acid, bilirubin, selenium, carotenoids, such as carotene and lutein (protection against singlet oxygen), and a vast array of bioflavanoids found in soy (genestein, daidzein), citrus (quercetin, naringen, tangeritin, limonin), other fruits and red wine (anthocyanins), and green tea (catechins) to name a few. The actions of most of these compounds are chemical rather than enzymatic, which would suggest
that higher intakes would provide greater activity [35]. Furthermore, to some extent their actions are interchangeable, so that the benefits of higher fruit and vegetable intake to reduce the risk of cancer or heart disease would not require a specific fruit and its constituent compounds could be administered. However, there is a very important principle, which must be recognized. Antioxidants work by terminating free radical generation by interacting with highly oxidizing agents and becoming oxidized themselves. Under certain conditions, such as very high doses and the presence of transition metals, these compounds can become pro-oxidant themselves [35]. This may be one possible reason why in the Finnish trial of β-carotene and vitamin E in lung cancer it was found that β-carotene actually increased the risk of mortality, despite confirmation of the basic hypothesis that a high intake of β-carotene-containing foods and serum levels of β-carotene at the outset reduced the risk in all groups [39].

Thus, when considering the potential effects of antioxidant supplementation in the clinical setting, concerns similar to those about the value of anticytokine therapy in critical illness must be raised. Since in most circumstances cytokine production and the SIRS are beneficial, presumably the production of reactive oxygen species and enhancement of antioxidant defenses by the SIRS would be as well. To identify at the initiation of therapy those patients likely to have an adverse outcome from an excessive pro-inflammatory response and to treat them with various anticytokine therapies that block IL-1 or TNF has been unsuccessful [40]. Whether this was due to timing of administration, duration of treatment, or the overlap of cytokine actions has not been determined, but enthusiasm for this form of therapy has waned. Similar concerns about the pharmacologic use of antioxidants are warranted for the same reasons with the additional concern that excessive doses of antioxidants may in fact have pro-oxidant effects. This, however, should not preclude the investigation of high physiologic replacement of various antioxidants for the critically ill, since deficiencies or low stores of certain of the antioxidants can reasonably be expected to be present in certain patient groups and their replacement potentially assisting in the systemic inflammatory response. For certain other patient groups accelerated catabolism might cause depletion in a clinically relevant period. Four candidate antioxidants would meet these definitions, selenium, glutathione, carotene, and vitamin E, although the latter two are included more for their ease and safety of administration than for their likelihood of deficiency or value of physiologic replacement doses.

There are in fact a very limited number of studies that test antioxidant compounds in critically ill patients. Physiologic selenium replacement in patients with severe SIRS receiving total parenteral nutrition has been studied in a randomized, prospective pilot study, based on the observation that selenium levels and glutathione peroxidase activity are lower in patients with severe illness [41]. Serum selenium levels and glutathione peroxidase activity were increased to normal levels, and the APACHE III score was significantly
reduced over that found in the control group. Hemodialysis was significantly less often required in the treatment group, and mortality was lower (52 vs. 33.5%) although not significantly so [41].

Antioxidant status in critically ill patients, such as those with acute respiratory distress syndrome, is also severely compromised and evidence of oxidative stress is evident by elevated malondialdehyde levels [42]. Glutathione status is also compromised in critically ill patients and correlates with glutamine concentrations [43]. Glutamine enrichment alone or in combination with other active, but not primarily antioxidative ingredients, has been studied in a number of clinical situations with some evidence for clinical efficacy. The first studies performed were with glutamine-enriched total parenteral nutrition formulas compared to standard total parenteral nutrition in patients undergoing bone marrow transplant. Parenteral glutamine administration with total parenteral nutrition significantly reduced infections and hospital stay in 42 patients [44] with a suggestion of improved survival but not length of stay or infections in a second similar study [45]. However, oral glutamine supplementation was not effective in bone marrow transplant patients [46]. Furthermore, parenteral glutamine peptide supplementation of total parenteral nutrition did not ameliorate chemotherapy-induced toxicity [47], while oral glutamine as primarily local therapy did reduce the duration and severity of stomatitis after cytotoxic cancer chemotherapy [48]. Glutamine-enriched total parenteral nutrition, as a means of reducing the infection rate and hospital stay, was examined in 28 patients undergoing major surgery [49]. A significant reduction in hospital stay was found, but the mean stay of 22 days in the control group was substantially longer than usual clinical practice. In a larger trial of glutamine-enriched total parenteral nutrition in 168 patients requiring total parenteral nutrition, no difference in infection rate or hospital stay was seen except in a subgroup of surgical patients, but once again the stays were quite long in both groups [50]. Another study in surgical patients using the dipeptide L-alanyl-L-glutamine-supplemented parenteral nutrition also significantly reduced hospital stay, and the control group length of stay was more consistent with usual practice at 17.5 days [51]. In an intensive care unit population receiving total parenteral nutrition with and without glutamine, survival at 6 months was significantly better in the glutamine group [52]. A mechanism for this effect so long after the treatment is difficult to propose, but hospital costs per survivor were significantly reduced as well. In another critically ill intensive care unit population an enteral formula enriched with glutamine provided to very low birth weight infants significantly reduced hospital costs [53]. A study with glutamine-enriched enteral nutrition in 72 multiple trauma patients demonstrated a significant reduction in infection, but this did not translate into a significant reduction in hospital stay [54]. However, in a second study of trauma patients using a formula containing not only extra glutamine, but also arginine, n-3 fatty acids, and nucleotides, there was a significant reduction in infection rate and hospital length of stay [55]. The overall assessment of these
variable data suggests that glutamine probably provides clinical benefit, and it is reasonable to propose that this is in part due to its effect on antioxidant status. However, glutamine has a multitude of other effects that may in some or large part play a role as well as the unknown contribution of other bioactive compounds contained in the various formulas.

A study that expressly looked at glutathione and N-acetylcysteine, which is a precursor, in patients with early septic shock showed changes in peroxidative indexes, when the patients received glutathione alone with further improvement in these indexes and clinical score in the group receiving both compounds [56]. In the few clinical trials of N-acetylcysteine given alone in high doses, several studies showed shortening of the duration of lung injury [57, 58] but not mortality, and others had conflicting results [59–61]. Whether the therapy is likely to be beneficial or harmful in any particular patient or setting may be due to the prevailing conditions, as has been found with anticytokine therapy. A recent study of N-acetylcysteine in critically ill patients provides a possible mechanism for this duality of impact. These authors demonstrated that phagocytosis was enhanced, whereas the respiratory burst was diminished, by N-acetylcysteine administration [62]. The authors speculate that these two actions in concert could be beneficial for certain conditions like ischemia/reperfusion or endothelial activation, but detrimental for infection [62].

Although there has been a series of studies suggesting that vitamin E and carotene intake in pharmacological amounts can improve immune function, particularly in the elderly [63], the relevance to clinical nutrition in the hospitalized patient is uncertain. For instance to improve antioxidant status, it is far more likely to be demonstrated in a population with elevated oxidative stress. A recent trial of vitamin E therapy in doses of 200–2,000 IU/day in healthy adults with normal antioxidant levels at baseline showed no effect on three measures of lipid peroxidation [64]. However, although antioxidant levels are diminished and oxidative stress quite clearly increased by severe illness [65], reactive oxygen species can be both beneficial and harmful in the critically ill, depending on such factors as the nutritional status of the host, the severity of the illness, and the relative balance between the SIRS and the CARS. Three recent studies emphasize these points. A randomized trial of α-tocopherol in severe congestive heart failure demonstrated no impact on oxidative stress as assessed by malondialdehyde, isoprostanes, and breath ethane and pentane, and no clinical benefit [66]. A study of total parenteral nutrition containing lipid with and without supplemental α-tocopherol found no alteration in lipid peroxidation, despite the high polyunsaturated fatty acid content [67]. Finally, enteral feeding of critically ill patients with a formula supplemented by pharmacologic amounts of vitamins A, C, and E did improve low density lipoprotein resistance to stress ex vivo which were in the normal range initially but did not alter serum malondialdehyde levels or clinical outcome [68]. However in Crohn’s disease, where malnutrition is
common, serum concentrations of β-carotene, selenium, and vitamin C and the activity of glutathione peroxidase were significantly lower than controls and increased with antioxidant supplementation, but effects on clinical outcome were not evaluated, as patients were in remission [69]. In another study of vitamin E supplementation in pharmacologic amounts to a patient population characterized by a high prevalence of malnutrition and a mild to moderate SIRS, there was a significant reduction in cardiovascular endpoints and myocardial infarction [70]. There is another parallel here between the relative efficacy of anticytokine therapy and antioxidant therapy in the critically ill, as opposed to the malnourished chronically ill patient. Anticytokine therapy has not been shown to be efficacious in the former but has in chronic conditions like Crohn’s disease and rheumatoid arthritis [40]. Perhaps this will also be the case for antioxidant therapy and perhaps for the same reasons.

Thus, the data for antioxidant vitamin supplementation in critical illness do not, at present, support the pharmacologic use of these compounds, although providing them in ample amounts to restore their levels to normal in malnourished patients are probably helpful and certainly justifiable. Further study of this area is clearly indicated, but there are aspects of research design that are worth considering. Presumably the most likely patient population to benefit would be those with initial malnutrition and thus likely impairment in antioxidant status undergoing oxidative stress, such as the protein calorie-malnourished patient undergoing major abdominal surgery. In this instance, provision of antioxidants to replete patients might be expected to foster a normal systemic inflammatory response that is generally desirable with the moderate injury of major surgery. A second group would be the elderly who are known to be more likely to have diminished antioxidant status prior to the onset of acute illness for similar reasons. Finally, at some point in their clinical course, severely stressed individuals, such as those with major trauma, burns, or head injury, are likely to experience depletion of their antioxidant stores, if not adequately nourished with at least requirement levels for antioxidants along with other essential nutrients early in their illness. Perhaps the value for high physiologic to pharmacologic amounts of antioxidant nutrients in this setting would be to more rapidly replete the depleted patient, where hours may be important in restoring the normal oxidant-antioxidant balance in the critically ill. However, the use of pharmacologic doses of antioxidants with potential pro-oxidant actions to initially well-nourished patients with severe stress in the first week of injury might be expected to have as much potential for harm as for benefit.

In summary, the balance between oxidant production and antioxidant activity must be carefully balanced in critically ill patients. There is little convincing evidence that, in otherwise well-nourished individuals, more than high physiologic amounts of most dietary antioxidants are likely to improve clinical outcome with the possible exception of precursors for glutathione production. In this latter instance it may be that this pivotal intracellular
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Antioxidant is rapidly depleted, which could make it limiting for an effective systemic inflammatory response. There may be an early role as well for other antioxidants that are likely to be depleted in patients who have significant protein calorie malnutrition. In the severely stressed intensive care unit patient, the potential for harm as well as for improvement in outcome with the use of pharmacologic amounts of antioxidants suggest that formal study of their role in this setting for each potential indication will be necessary before wide clinical application is justified. It is highly unlikely that blanket provision of these double-edged swords to the critically ill will have net benefit.

References


Discussion (following the presentation, by Dr. D. Labadarios, of a summary of the manuscript prepared by Dr. Bistrian)

Dr. Griffiths: I want to comment on the issue of protein degradation. It is extremely important. For example, we don’t heal an inflamed lung without degrading and removing everything that has got into that inflamed lung, so we have to have controlled processes such as apoptosis to get rid of the inflammatory cells. That process is probably very important for single cell tissues, but muscle is a multicellular tissue. As such, we know it can break down part of its protein sources to provide fuel, but it also synthesizes proteins, for example heat shock proteins, to increase its chances of resalvaging itself once healing and repair occur. So we have a different pattern within these different tissues, which affects how we think about degradation.

Dr. Heymsfield: A recent paper in the New England Journal of Medicine [1] showed that propanolol seemed to improve the outcome measures in children with
severe burn injury. This runs counter to the idea that some of these responses are adaptive. How can you explain that?

Dr. Labadarios: I found the results of the propranolol study rather interesting. I think it is very curious that you could give growth hormone and double the mortality, but when you give \( \beta \) blockade you obtain exactly the opposite result. There may be a problem here of an acute situation versus a chronic situation. The pediatric burns patients in that study were only admitted to the specific unit about 1 month after the accident, and they had repeated supportive therapy in terms of grafts and so on. Also their adrenergic responses were not blunted really severely – their heart rate was only decreased by 20%, and we know that their mean arterial pressure, and by inference their oxygenation, was maintained, because if it fell the investigators reduced the dose. So one wonders whether we are not talking about two different kinds of circumstance. This brings to mind some work I did in London at King’s College Hospital, when I often puzzled over the outcome of viral hepatitis. Some people developed fulminant hepatic failure and died within 2 weeks, some people recovered in 6 or 8 weeks, and some went on to develop chronic active hepatitis in the case of hepatitis B. Isn’t this something we should be considering in the context of what we have been talking about? Obviously the approach to these three different types of outcomes must be totally different.

Dr. Soeters: Maybe this is where Dr. Grimble’s talk comes in. Why do 4% of patients develop chronic active hepatitis? Most people recover and very few get an acute fulminant form. Is there a genetic influence here?

Dr. Grimble: If I may answer that question indirectly, I think we are dealing here with a bell-shaped response curve. At one extreme we have the patients who die quickly, and I think those patients do exist, but at the other extreme we have the malnourished elderly patient who has difficulty in mounting a systemic inflammatory response and also gets overwhelming infections. We need to be able to define the middle ground, where it is a beneficial response. I think one of the things that defines that bell-shaped response is the genotype of the individual, and we need to map out those limits. At the moment, we are still acting with a degree of uncertainty within quite a broad range of response types.

Dr. Mills: My question is for Dr. Labadarios. I understand his view that we have to be cautious and responsible about vitamin supplementation, but a large part of the population is taking supplements already. Should we be asking them to stop the supplements, or should we be asking them to take their supplements in complete formulations – in other words not \( \beta \)-carotene by itself but with vitamin E, C, zinc, and selenium? If we wait for the research we are going to be left behind.

Dr. Labadarios: I don’t really have an answer to that question, except to say that what evidence we have is highly specific in terms of an effect, and we should really only act according to specific indications. In terms of public health policy – especially for antioxidants, and vitamin E in particular – we don’t have sufficient data to recommend a daily supplement.

Dr. Meguid: The question is still a valid one though. Throughout the USA there is an uncontrolled study, which is ongoing. Everybody is taking supplements in an uncontrolled environment. Even academic institutions such as Johns Hopkins, Stanford and Harvard, in their nutritional newsletters to the general public are intimating that patients should take a variety of supplements. Hence a public policy stand is urgently needed.

Dr. Labadarios: I agree with that. I would say that if you have to give advice it is that one should not exceed two or three times the recommended allowances. The new dietary reference intakes provide cutoffs, which should not be exceeded from a safety point of view.
Dr. Meguid: If I may add a footnote: The question as to the quantity of vitamins and minerals to give to pregnant women is a separate issue. Also, how much and what type of vitamins, especially antioxidants, to give to astronauts, who are exposed to increased radiation, remains an unanswered question.

Dr. El-Maraghi: I wanted to comment on kwashiorkor. There have been exhaustive studies on kwashiorkor and nutritional rehabilitation from this form of malnutrition. It has been found that affected infants have panhypoelectrolytemia, mainly of potassium, and unless you attend to this problem, whatever other nutritional interventions you advocate will be of little use. Even when such infants have proper dietary rehabilitation, their mortality is still high. It is worth mentioning also that, apart from deficient growth hormone production, they also have multiple endocrine deficiencies, including thyroid and adrenal deficits.

Dr. Carpentier: To summarize, I think we could say that you, and certainly many people in the audience, believe that part of the acute phase is beneficial and is critical for survival up to a certain point. The fact that it may sometimes be exaggerated does not mean that no nutritional support should be provided during that period, but rather that certain aspects of the response could and should be modulated. We need to know what these are, and further study is clearly important.

Reference