

Pharmaconutrition: a new emerging paradigm

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Purpose of review

This paper highlights recent studies of interest and provides rationale for why deficiencies with the current scientific paradigm of immunonutrition has produced studies with conflicting results, and why it should be replaced with a new paradigm termed 'pharmaconutrition'.

Recent findings

Considering the overall treatment effect of immune-modulating nutrients, parenteral glutamine is recommended in patients receiving parenteral nutrition, while enteral glutamine should be considered in burn and trauma patients. Antioxidants, particularly selenium, should be considered for critically ill patients, and enteral formulas enriched with fish oils are recommended in patients with acute respiratory distress syndrome. Arginine-supplemented diets are not recommended. There are currently insufficient data to enable useful recommendations on the optimal route, timing, duration and dosage of each nutrient. The pending results of a large, rigorously designed, randomized trial, however, in which nutrients are viewed and tested as pharmacological agents, promise to clarify some of the current ambiguities and inform future practice.

Summary

This review provides insights into why the current paradigm of immunonutrition has failed to consistently demonstrate a beneficial effect of key immunomodulating nutrients, and offers a timely solution through the new paradigm of pharmaconutrition.

Keywords

antioxidants, arginine, glutamine, immunonutrition, n-3 fatty acids, nutrition support

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Introduction

During acute illness patients experience a degree of hyperinflammation, cellular immune dysfunction, oxidative stress and mitochondrial dysfunction. Depending on the severity and duration of these disturbances in metabolism, multiorgan failure and death may occur. Both as a result of this stress response and an inability to maintain a normal oral intake, patients can rapidly develop nutrient deficiencies. The relationship between nutrient deficiencies and an altered immune status is well known. Such deficiencies are common among hospitalized patients and are associated with an increased risk of developing infectious complications, organ failure, and death [1–4]. Consequently, artificial nutrition therapy, via the enteral or parenteral route, is considered an integral part of standard patient care. Over the past two decades, specific nutrients have been added to commercially available nutritional formulas in an attempt to modulate the inflammatory or immune response and affect clinical outcomes. 'Immunonutriton' and 'immune-enhancing diets' are some of the terms that have been used to describe these products. The purpose of this article is not to provide an exhaustive review of the literature on immunonutrition but to highlight recent significant

studies. We will provide rationale for why the current scientific paradigm of immunonutrition is deficient and suggest an alternative paradigm captured by the term 'pharmaconutrition'.

Immunonutrition

During the last 25 years, over 30 randomized control trials (RCTs) of immunonutrition in over 2000 critically ill and surgical patients have been completed with disparate results. These trials have utilized various combinations of nutrients, most commonly arginine, n-3 fatty acids, and nucleotides with or without glutamine and antioxidants. The poor methodological quality and small sample size included in many of these trials hamper our ability to detect significant differences in clinical endpoints. Even the largest high-quality study, involving a heterogeneous population of 597 critically ill patients [5], failed to show an effect of immunonutrition on mortality or other clinical outcomes, in both an overall and several subgroup analyses.

Attempts to resolve this controversy have been made through the completion of five separate metaanalyses,

including one by our research group [6–10]. Although results differ across these analyses, all five report that immunonutrition results in fewer infectious complications and reduced length of hospital stay, but has no effect on mortality in surgical patients. Recently, we updated our ongoing metaanalysis of studies in critically ill patients (<http://www.criticalcarenutrition.com>); the overall treatment effect was consistent with no effect on mortality [relative risk (RR) 1.06 and 95% confidence interval (CI) 0.90, 1.24] (Fig. 1), infectious complications (RR 0.95, 95% CI 0.83, 1.15), and length of hospital stay [RR standardized mean difference (SMD) -0.33, 95% CI -0.72, 0.06]. Consequently, the Canadian Clinical Practice Guidelines Committee [11] recommended that immune-enhancing diets supplemented with arginine and other nutrients should not be used in critically ill patients. This ongoing controversy surrounding the effectiveness of immunonutrition is reflected by its lack of impact on clinical practice, with less than 6% of patients in the intensive care unit receiving immunonutrition formulas [12].

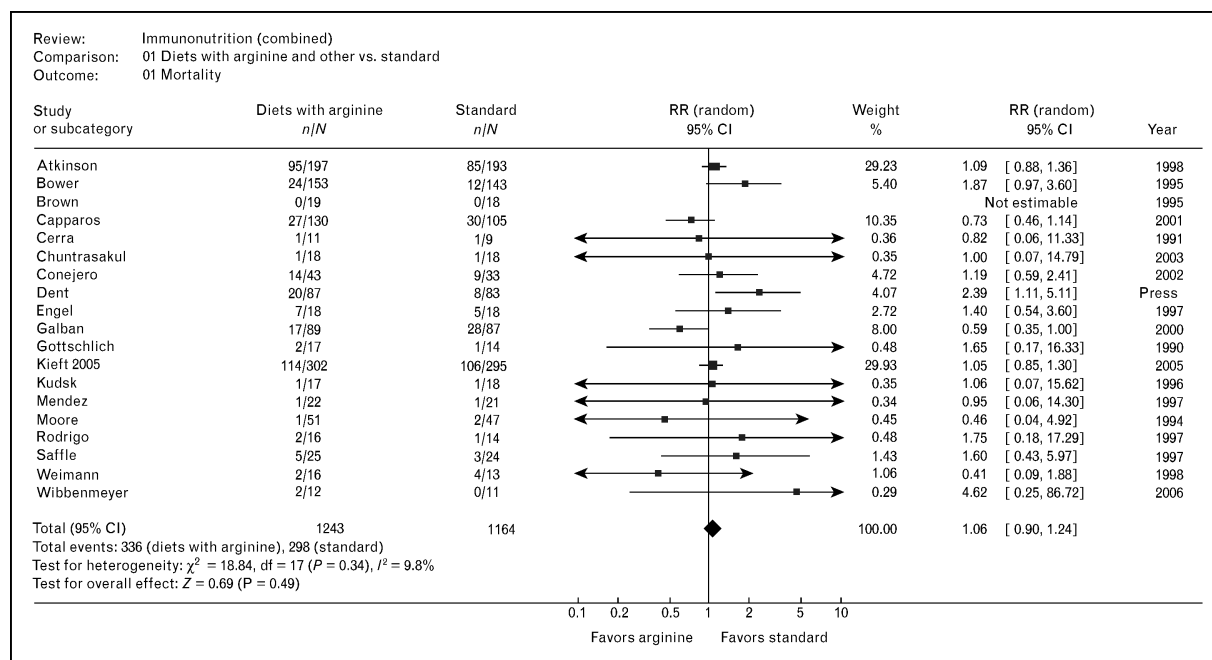
Why is it that, despite the large volume of research in this area, we are still unable to demonstrate a positive treatment effect of immunonutrition? The historical paradigm of immunonutrition has focused on delivering various nutrient combinations to a heterogeneous patient population. What is apparent from current evidence is that this paradigm is fundamentally flawed and that this

fixed mixed cocktail approach does not suit every patient. It is plausible that some of these nutrients, tested individually, may have some positive (or negative) therapeutic effects in some groups of patients, but when combined together and administered to a heterogeneous patient population, any treatment effect is lost. If our hypothesis is that the administration of nutrients in supranormal amounts has ‘pharmacological’ effects on the inflammatory response to critical illness and can improve clinical outcomes, our approach to assessing the efficacy of these nutrients should be analogous to the assessment of any pharmacological agent, with due diligence to discerning the precise dose, timing and route of administration of individual nutrients, plus their effects in select patient populations. Future studies in this area should be conducted under this new paradigm of pharmaconutrition.

Patient population

Some of the inconsistent results generated from trials of immunonutrition may stem from the fact that within a given patient over time or across different patient populations, the severity of ‘gut failure’, the degree of bacterial translocation, the degree of cellular immune dysfunction, the balance of inflammation/anti-inflammation, and the regional and systemic generation of reactive oxygen species (ROS) will vary. For example, following elective surgery, patients experience a period

Figure 1 Risk ratio (RR) and associated 95% confidence intervals (CIs) for the effect of immunonutrition on mortality in critically ill patients



n/N, number of patients that die/total number of patients in group.

of immunosuppression that increases the risk for acquired infectious morbidity and mortality. Consequently nutrients, such as arginine, that enhance cellular immune function may reduce infectious complications in the elective surgical patient. In contrast, critically ill patients experience complex and variable immune and inflammatory changes that are poorly understood. In the early stages of critical illness both the cellular defence system, which includes both innate (nonspecific) immunity and adaptive (specific) immunity, and the systemic inflammatory response are activated. A decrease in the cellular defence response occurs simultaneously with signs of hyperinflammation as early as the onset of severe sepsis [13]. Hence, for critically ill patients, nutrients that support the cellular defence system, combat oxidative stress and attenuate the inflammatory response are more likely to be of benefit.

Pharmaconutrients

Historically, nutrition has been viewed as adjunctive care and not as an active therapeutic strategy; however, the concept of pharmaconutrition is based on the impact of nutrients being greater than just the provision of nutrition alone. A deficiency of the majority of studies to date is that they have been trials of nutritional strategies; comparing standard enteral formulas to specialized formulas enriched with specific nutrients. Consequently, the quantity of the nutrients delivered is dependent on the provision of an adequate volume of enteral formula which can be problematic in hospitalized patients who often have trouble tolerating their enteral feeds. Other studies add nutrients to parenteral nutrition, which has limited application to clinical practice as parenteral nutrition is only used in a minority of patients. This makes attempts to isolate the effect of individual nutrients problematic. In accordance with the new paradigm of pharmaconutrition, the administration of key nutrients should be dissociated from the provision of parenteral or enteral nutrition so that their full dose can be delivered, either parenterally or enterally, and their therapeutic effects evaluated appropriately.

Arginine

Arginine stimulates release of growth hormone, prolactin, and insulin, and increases the number of T cells and enhances T-cell function. During catabolic disease arginine serum levels decrease due to a reduced dietary intake, increased uptake in endothelium, liver, and intestine [14], and increased metabolism, but with increasing time from the initial traumatic event and with the development of sepsis arginine levels begin to increase [15]. Depending on the underlying pathophysiology, there is an upregulation of different enzymes, and therefore, a different metabolism of arginine [16]. It can be metabolized through a family of nitric oxide synthetase

enzymes to nitrogenous compounds like nitric oxide or metabolized via arginase to urea and ornithine. An increased expression of arginase leads to a depletion of arginine and decreased T-cell activation and immunocompetence, and an increased risk of infection. Consequently, it is hypothesized that arginine supplementation may inhibit arginase and prevent these negative sequelae. The benefit of this strategy on morbidity has been demonstrated in elective surgery [10]. As highlighted previously, however, the underlying pathophysiology of critical illness is very different, and there is a signal from current studies to suggest that arginine supplementation may be associated with harm in infected or septic critically ill patients. This potential toxic effect of arginine may be due to its role as a substrate for inducible nitric oxide synthase (iNOS). iNOS is upregulated during inflammatory states resulting in an increased production of nitric oxide, contributing to impaired microcirculation and organ dysfunction. This theory is supported by a recent study of parenteral arginine supplementation in a canine model of *Escherichia coli* peritonitis [17], which reported an increased mortality and worsened shock in the supplemented groups. The administered dose, however, was multiple times higher than physiological levels and the parenteral mode of delivery would have bypassed the significant gut regulation of arginine. Nevertheless, there are three RCTs [18–20] of different arginine-supplemented diets that demonstrate excess mortality in patients with infection associated with these diets. There are no RCTs of arginine alone in critically ill patients but a preliminary observational study in humans published in abstract form [21] indicates that arginine may be given to septic patients without increasing oxidative stress or adversely affecting hemodynamic stability. Further research is required on the influence of arginine in specific populations and the genetic variability of nutrient response. In the meantime, arginine and arginine-supplemented diets are not recommended in critically ill patients.

Glutamine

The amino acid glutamine has many essential metabolic functions. It plays a central role in nitrogen transport within the body, is a fuel for rapidly dividing cells (particularly lymphocytes, enterocytes, and colonocytes), is the most important substrate for renal ammoniogenesis, and is a precursor to glutathione [22]. Glutamine protects structural and functional integrity of intestinal mucosa and augments cellular immune functions, especially those associated with cell mediated immunity [22]. During severe metabolic stress (i.e. trauma, sepsis, major surgery, bone marrow transplant, chemotherapy and radiotherapy) the requirement for glutamine exceeds glutamine synthesis and supply from proteolysis, resulting in depletion of glutamine stores. Consequently, glutamine may become a conditionally essential amino

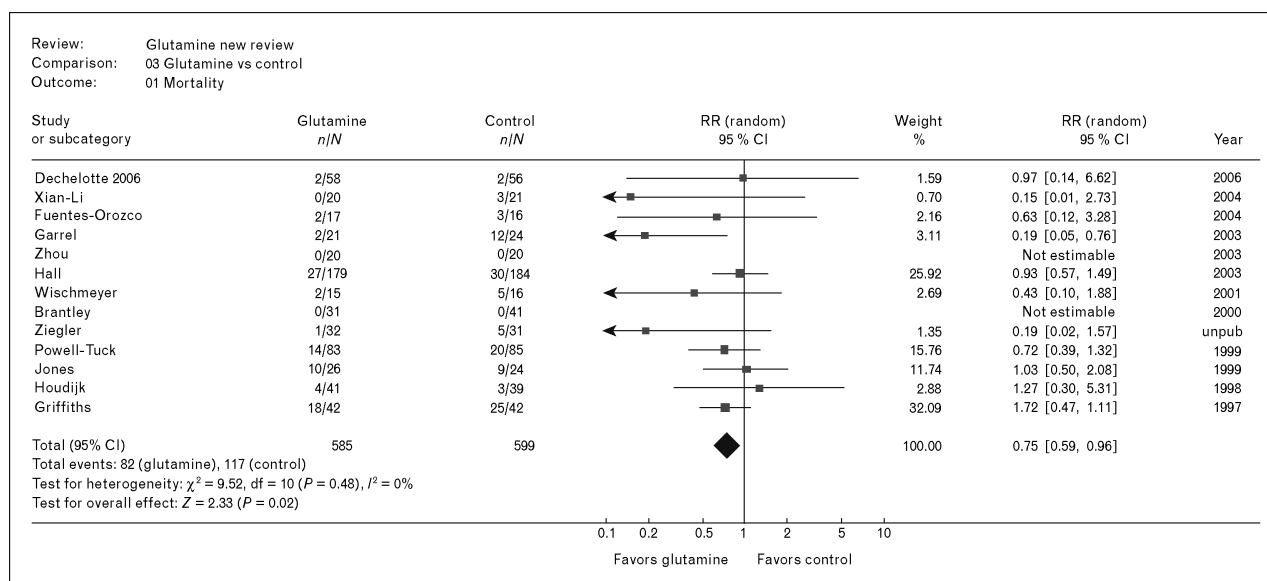
acid in these individuals [23,24]. In addition, lower levels of glutamine have been associated with immune dysfunction [25] and increased mortality [26]. Glutamine supplementation during illness may therefore enhance gut barrier and lymphocyte function, preserve lean body mass, and protect against the damaging effects of oxidative stress. Another possible biological mechanism for this positive therapeutic effect may be glutamine's ability to protect against septic shock. Heat shock protein (HSP) expression is vital to cellular and tissue protection after stress or injury, as their absence leads to increased cellular apoptosis. Recent animal and human studies have demonstrated that glutamine may enhance tissue HSP expression and reduce inflammatory cytokine release [27,28], and that these increased levels are correlated with a decreased length of hospital stay and ventilator time in critically ill patients [28]. In shock and myocardial injury reperfusion models, glutamine supplementation has been shown to reduce the occurrence of cell death or apoptosis by preventing the fall in glutathione levels, ATP/ADP ratio, NAD/NADH content, and lactate accumulation which occur during shock [28,29]. Evidence is also emerging that suggests that some of the benefit of glutamine supplementation may be as a consequence of its role as an important precursor for the endogenous synthesis of arginine through an intestinal-renal pathway involving interorgan transport of citrulline [30,31]. In addition, recent studies suggest that glutamine may reduce insulin resistance, which is another mechanism by which it may confer beneficial effects [32].

A recently updated metaanalysis (<http://www.criticalcarenutrition.com>) [33] examined the relationship between glutamine supplementation and clinical outcomes in critically ill patients, and revealed a significant reduction in mortality (RR 0.75, 95% CI 0.59, 0.96, $P=0.02$) (Fig. 2), a significant reduction in infectious complications (RR 0.79, 95% CI 0.63, 0.93, $P=0.04$), and a significant reduction in length of stay (SMD in days -4.50 , 95% CI -8.28 , -0.72 , $P=0.02$). In a subgroup analysis, it seems that the majority of the treatment effect is from parenteral glutamine in the context of parenteral nutrition studies. Based on these results, parenteral glutamine is recommended when parenteral nutrition is prescribed and enteral glutamine should be considered when enterally feeding burns and trauma patients. The role of glutamine supplementation in other critically ill patients receiving enteral feeds is unknown.

Antioxidants

Antioxidants are part of a complex endogenous defence system designed to protect tissues from the damaging effects of oxidative stress caused by excessive amounts of ROS and reactive nitrogen-oxygen species. Evidence is growing that oxidative stress is central to the underlying pathophysiology of critical illness, especially the development of organ failure. In critically ill patients, there are reduced stores of antioxidants, which have been associated with an increase in free radical generation, an augmentation of the systemic inflammatory response, subsequent cell injury, increased organ failure, and even higher mortality [34]. A systematic review

Figure 2 Risk ratio (RR) and associated 95% confidence intervals (CIs) for the effect of glutamine supplementation (enteral and parenteral) on mortality in critically ill patients



n/N, number of patients that die/total number of patients in group.

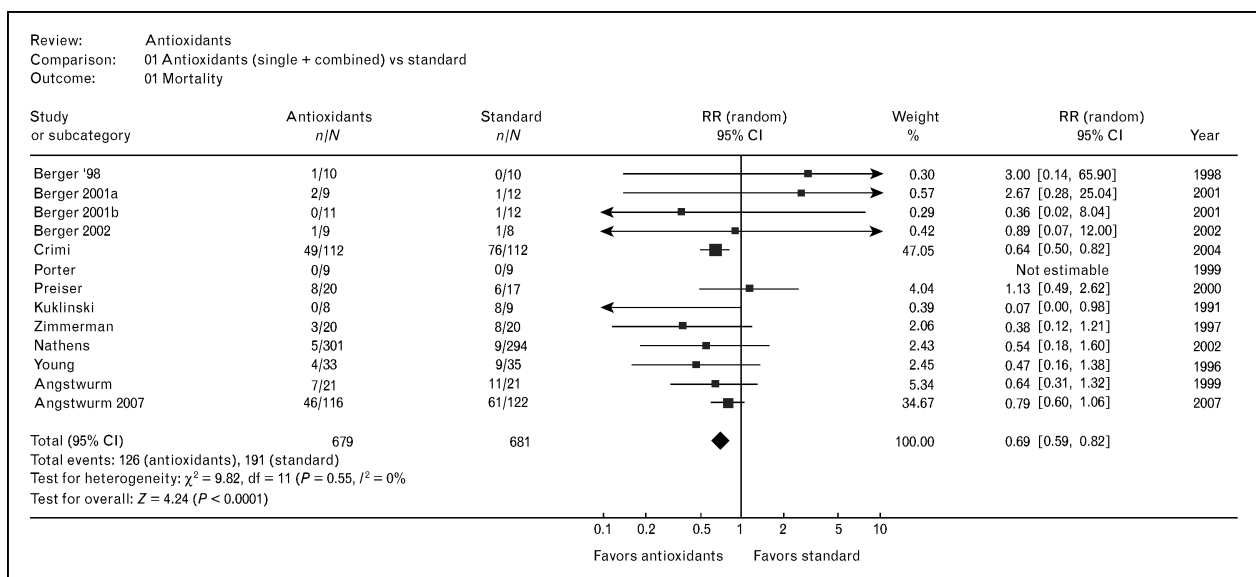
(<http://www.criticalcarenutrition.com>) [35] examining trials of antioxidant supplementation in critically ill patients has recently been conducted. Thirteen studies were identified, most studied the effects of selenium either alone or in combination with other trace elements and vitamins while others looked at the effects of zinc and vitamins A, C and E. When the results of all the trials were aggregated, overall antioxidants were associated with a significant reduction in mortality (RR 0.69, 95% CI 0.59, 0.82, $P \leq 0.0001$) (Fig. 3), but had no effect on infectious complications (RR 0.90, 95% CI 0.65, 1.24, $P = 0.51$), or ICU length of stay (SMD in days -0.10 , 95% CI $-0.46, 0.26$, $P = 0.56$) in critically ill patients. A recent large, multicenter RCT [36**] of high-dose selenium supplementation in 249 patients with severe systemic inflammatory response syndrome, sepsis, and septic shock demonstrated a large, but not significant, reduction in mortality [odds ratio (OR) 0.66, 95% CI 0.39, 1.10, $P = 0.109$]. A greater treatment effect, however, was detected in patients with high normal levels of selenium compared with normal levels of selenium, indicating that selenium is having an effect beyond restoring a deficiency. Thus antioxidant strategies, particularly selenium, should be considered for critically ill patients.

n-3 fatty acids

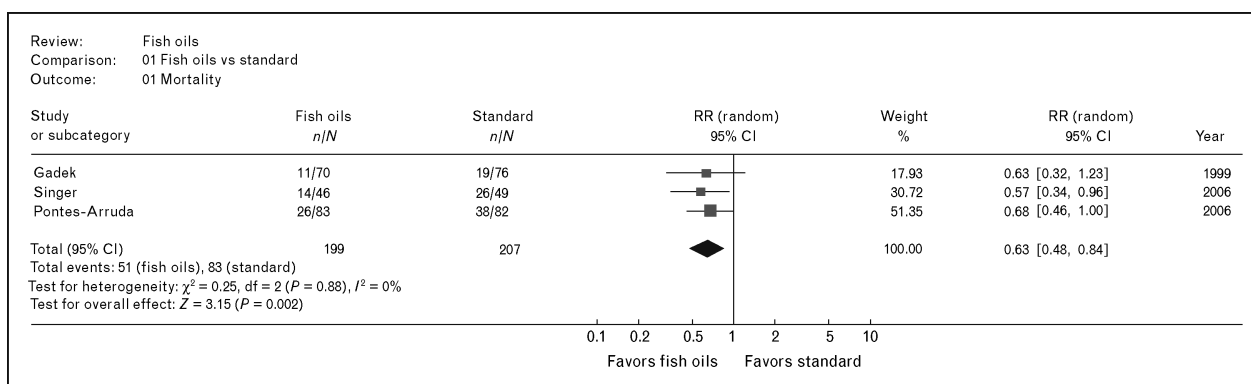
The biological effects of n-3 fatty acids or fish oils during illness is related to their ready incorporation into inflammatory cell membrane phospholipids, often at the expense of n-6 arachidonic acid. Consequently, n-3 fatty acids antagonize the production of proinflammatory eicosanoids from n-6 arachidonic acid (e.g. leukotriene B₄,

thromboxane A₂, prostaglandin E₂), and are precursors for less inflammatory eicosanoids (e.g. thromboxane A₃, prostaglandin E₃, leukotriene B₅) resulting in anti-inflammatory effects. Studies of parenteral supplementation of n-3 fatty acids alone have reported mixed results. A prospective, open-label, multicenter study of 661 patients receiving parenteral nutrition with n-3 fatty acids for more than 3 days [37*] reported a reduction in hospital mortality as predicted by Simplified Acute Physiology Score II, and found that dose of fish oil was correlated with ICU and hospital length of stay and mortality. As there was no direct comparison group, these results need to be confirmed or refuted in the context of an RCT. In a randomized double-blind multicenter trial of 256 patients, total parenteral nutrition enriched with fish oils [38*] had no effect on postoperative mortality, morbidity, and ICU length of stay after major abdominal surgery. A significantly shorter length of hospital stay and higher plasma levels of eicosapentaenoic acid, leukotriene B₅, and antioxidant, however, were detected in the group that received fish oils. Three RCTs of enteral supplementation of fish oil in patients with acute respiratory distress syndrome (ARDS) have utilized enteral formulas that were also enriched with other key nutrients (borage oil and antioxidants) [39,40,41*]. A recent metaanalysis aggregating the results of these three studies (<http://www.criticalcarenutrition.com>; Fig. 4) demonstrated that enteral formula enriched with fish oils significantly reduces mortality (RR 0.63, 95% CI 0.48, 0.84, $P = 0.002$) and ventilator days (SMD in days -1.61 , 95% CI $-3.20, -0.02$, $P = 0.05$), and tended to reduce ICU length of stay (SMD in days -1.65 , 95% CI $-3.41, 0.10$, $P = 0.06$). Thus,

Figure 3 Risk ratio (RR) and associated 95% confidence intervals (CIs) for the effect of antioxidant supplementation on mortality in critically ill patients



n/N, number of patients that die/total number of patients in group.

Figure 4 Risk ratio (RR) and associated 95% confidence intervals (CIs) for the effect of enteral formulas enriched with fish oils, borage oils and antioxidants on mortality in patients with acute respiratory distress syndrome

n/N, number of patients that die/total number of patients in group.

enteral formulas with fish oils, borage oils, and antioxidants are recommended in patients with ARDS.

Nutrient administration: route, timing, duration and dosage

Under the new paradigm of pharmaconutrition, when nutrients are treated as pharmacological agents rather than as part of a nutritional strategy, there is a need for greater attention to elucidating the most efficacious route, timing, duration and dosage of nutrient administration. From a review of the studies to date, conducted under the paradigm of immunonutrition, there are insufficient data to enable useful recommendations on mode of delivery. A subgroup analysis of the metaanalysis of studies of glutamine supplementation [33] suggests that parenteral nutrition may confer greater benefits. As the hypothesized mechanism of action of many of these immunomodulating nutrients is via the gastrointestinal tract, however, it makes intuitive sense that the enteral route may be preferred. As there are no trials published to date comparing enteral and parenteral delivery of glutamine or other pharmaconutrients, we remain uncertain as to which is the most efficacious route. With our growing knowledge of the pathophysiology and nutrient–gene interactions in different disease states, in the future we will have a better understanding of the optimal timing and duration of delivering a nutrient intervention. Emerging evidence suggests that oxidative stress leading to mitochondrial dysfunction may become irreversible within 6–24 h [42] and is irreversible 48 h [43] after the onset of severe sepsis. Therefore, it appears the sooner the nutrients are provided after insult, the more likely they are to have a treatment effect.

The optimum dose of pharmaconutrients is unknown. The results of subgroup metaanalyses suggest that

studies using a higher than median dose of selenium (500–1000 $\mu\text{g}/\text{day}$) or glutamine is associated with a trend towards or significant reduction in mortality (RR 0.52, 95% CI 0.24, 1.14, $P = 0.10$ and RR 0.71, 95% CI 0.51, 0.99, respectively), whereas studies using a lower dose of selenium or glutamine had no effect on mortality (RR 1.47, 95% CI 0.20, 10.78, $P = 0.7$ and RR 1.02, 95% CI 0.52, 1.2.01, respectively) [30,32]. Extremely high doses, however, may be associated with toxic effects [44]; therefore, further research is required to define the optimal dose of key nutrients.

Accordingly, to investigate the maximum tolerable dose of glutamine and antioxidants, we recently completed a phase I, single-center, open-label, dose-escalating study involving 28 critically ill patients [45]. We discovered that as we escalated the dose of glutamine to an optimal dose of 0.35 g/kg/day parenterally plus 30 g/day enterally, and the dose of selenium to 500 $\mu\text{g}/\text{day}$ parenterally plus 300 $\mu\text{g}/\text{day}$ enterally, we observed a greater reduction in markers of oxidative stress, greater preservation of glutathione levels, and an improvement in an indirect marker of mitochondrial function with no apparent adverse effect on organ function. The results of this dosing study suggest that glutamine and antioxidant supplementation at high doses is safe and may positively affect biological endpoints. A large, multicenter, double-blind RCT in 1200 mechanically ventilated critically ill patients [46] is now underway to test the therapeutic effects of these high doses of glutamine and antioxidants. The Reducing Deaths due to Oxidative Stress (REDOXS) study embraces a novel study design in which the parenteral and enteral study nutrients are dissociated from nutrition, and thus the REDOXS study represents an important paradigm shift from immunonutrition to pharmaconutrition. The first results of this landmark study are expected in 2009.

Conclusion

Despite a quarter of a century of time, money and resources invested in immunonutrition it has failed to live up to its promise to improve patient outcomes. The strength of inference we can make for single nutrients from current evidence is limited by small studies of poor methodological design in which nutrients were combined and administered to a heterogeneous patient population. While immunonutrition continues to be a topical issue, generating numerous narrative reviews and ongoing debates in the medical literature, its translation into clinical practice has been negligible. We argue that continuing to conduct studies under this current paradigm of immunonutrition will only add to the controversy. Moving forward under the new paradigm of pharmaconutrition, with a focus on single nutrients dissociated from nutrition, tested in homogenous patient populations in large, rigorously designed RCTs powered to detect differences in mortality, as illustrated by the REDOXs study, will finally start to provide us with solutions to the many long unanswered questions.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 260–261).

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- A prospective randomized double blind multicenter trial of patients undergoing major abdominal surgery who received postoperative parenteral nutrition with or without n-3 fatty acid. The authors report no effect on mortality, morbidity, and ICU length of stay but note a significant reduction in hospital length of stay.
- 39** Gadek JE, DeMichele SJ, Karlstad MD, *et al.* Effect of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in patients with acute respiratory distress syndrome. *Enteral Nutrition in ARDS Study Group*. *Crit Care Med* 1999; 27:1409–1420.
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- A novel paper that encapsulates the paradigm of pharmaconutrition by describing the background and protocol for a large, multicenter randomized trial that aims to evaluate the effect of both glutamine and antioxidant supplementation in 1200 critically ill patients.