This article explores the evolving paradigm of pharmaconutrition using antioxidant micronutrients, looking at the available evidence for antioxidant supplementation in the critically ill. In particular it discusses the protective mechanisms of action of selenite in critically ill SIRS patients and how selenium supplementation as a pharmaconutrient can be best applied.

Is Selenium Monotherapy the Cornerstone of this Strategy?

Selenium is essential for the activity of selenoenzymes such as antioxidant, immunological, and anti-inflammatory properties. Selenium is an essential trace element with antioxidant, immunological, and anti-inflammatory properties. In 2005, for the first time, a meta-analysis demonstrated that antioxidants were associated with a significant reduction in ICU mortality (risk ratio [RR], 0.65; 95% confidence interval [CI], 0.44–0.97; P=0.03) (Heyland et al. 2005). The authors further demonstrated that daily doses of selenium (higher than 500 μg) showed a tendency towards a decrease in mortality (RR, 0.52; 95% CI, 0.24–1.14; P=0.10). Four years later, the same Canadian group updated these results, showing that antioxidant supplementation was still associated with a significant reduction in mortality (RR, 0.76; 95% CI, 0.64, 0.91; P=0.002). Moreover, the specific effects of parenteral selenium on mortality were similar (RR, 0.84; 95% CI, 0.67, 1.05; P=0.13).

Most recently, an updated systematic review and meta-analysis, which aggregated 20 trials that had reported mortality as an outcome, concluded that combined antioxidant supplementation was associated with a significant reduction in mortality (RR, 0.82; 95% CI, 0.72–0.93; P=0.002) (Manzanares et al. 2012). Supplementation with antioxidant micronutrients showed a significant reduction in duration of mechanical ventilation (weighed mean difference, -0.67 days; 95% CI, -1.22, -0.13; P=0.02) and a trend towards a reduction in infections (RR, 0.88; 95% CI, 0.76, 1.02; P= 0.08). However, it was not possible to demonstrate any significant overall effect on ICU or hospital length of stay (LOS). Of practical interest is the fact that antioxidant micronutrients were associated with a significant reduction in overall mortality among patients with higher risk of death (>10% mortality in control group) (RR, 0.79; 95% CI, 0.68, 0.92; P=0.003). This finding supports the notion that patients with more severe insults and higher mitochondrial dysfunction resulting from bioenergetic failure experience the largest depletion of antioxidants (Manzanares et al. 2012). These patients may therefore exhibit a greater clinical improvement with antioxidant supplementation than less sick patients.

What Does the Most Up-to-Date Evidence Show About Antioxidant Supplementation in the Critically Ill?

When aggregated, selenium supplementation was specifically associated with a trend towards a reduction in mortality (RR, 0.89; 95% CI, 0.77–1.03; P=0.12). The seven selenium trials demonstrated a trend towards a reduction in infections (RR, 0.87; 95% CI, 0.74–1.02; P=0.08), whereas three of the trials that didn’t use selenium demonstrated no effect on infections (RR, 1.10; 95% CI, 0.60–2.04; P=0.75). Thus, parenteral selenium monotherapy, administered as a loading dose followed by a continuous infusion, may be strongly recommended to reduce mortality and infections in critically ill SIRS patients (Hardy et al. 2012).

What Do We Know About the Protective Mechanisms of Action of Selenite in Critically Ill SIRS Patients?

Although the optimal time to start antioxidant therapy has not yet been established, both experimental and clinical data support the concept that antioxidant micronutrients are more effective when initiated prior to injury or as early as possible after the insult. Selenium is an essential trace element with antioxidant, immunological, and anti-inflammatory properties. Selenium is essential for the activity of selenoenzymes such as...
Selenium Supplementation as a Pharmaconutrient for the Critically Ill: When, How and How Much?

There is enough evidence in current literature to consider antioxidant cocktails and/or parenteral selenite supplementation as monotherapy in critically ill SIRS patients. The best antioxidant cocktail approach has not yet been determined. However, we know that initiating high-dose intravenous sodium selenite (1000–2000 μg as a bolus over 30 minutes to two hours) immediately on admission to the ICU (within the first 24 hours), and thereafter as a continuous infusion at a daily dose between 500-1600 μg for up to 10 to 14 days, is a novel and successful strategy in the critically ill. This concept of pharmaconutrition, using selenium as monotherapy, is quite distinct from the routine incorporation of selenium (and other micronutrients) in standard parenteral or enteral nutrition. High-dose sodium selenite should be supplemented in the most seriously ill ICU patients, including those with severe sepsis and septic shock. High-risk cardiac surgery patients may also benefit in the near future, but more evidence from on-going clinical trials is awaited before recommendations can be made for this patient population.

What is the Future for Antioxidant Micronutrient Supplementation for Intensive Care?

The largest randomised controlled trial on antioxidants in combination with high-dose glutamine supplementation has been the Reducing Deaths due to Oxidative Stress (REDOXS) Study, which is unpublished; but it seems to have failed to demonstrate any improvement on clinical outcomes in MODS patients. In this multicentre trial, more than 1,200 patients were enrolled to receive intravenous glutamine in combination with enteral or parenteral antioxidant cocktails, including vitamins C (1500 mg), E (600 mg), b-carotene (10 mg), zinc (20 mg), and selenium (300 μg). Although this strategy was safe, it was unfortunately unable to demonstrate efficacy by improving relevant clinical outcomes, including ICU and 90 day survival, in critically ill SIRS patients.

How can we explain the unexpected REDOXS results regarding antioxidants supplementation? Perhaps the absence of an intravenous bolus of selenite as a loading dose inhibited stimulation of the protective effects of selenium as an anti-inflammatory strategy for ICU patients with organ failure. This could be considered as a methodological weakness. Furthermore, some patients received an insufficient daily dose of intravenous selenium. In fact, according to the recent metaanalysis on antioxidant micronutrients (Manzanares et al. 2012), a daily parenteral dose greater than 500 μg is necessary for better clinical outcomes. Although some patients in the REDOXS protocol received 800 μg of selenium, this was administered by either the enteral or the parenteral route, and we do not know enough about the pharmacokinetic profile of enterally administered selenium in SIRS patients. We suspect that enteral absorption in septic shock patients is unpredictable and these doses may have been insufficient.

Among the antioxidant micronutrient strategies, parenteral selenite should be the cornerstone of a pharmaconutrition approach for the critically ill. We believe, there is sufficient evidence to consider initiating high dose intravenous selenium therapy routinely in SIRS patients, immediately on admission to the ICU. Nonetheless, more research is needed to define the true role of pharmaconutrients in the prevention or treatment of cellular and tissue dysfunctions. A research strategy that combines basic investigations into the pharmacokinetic and pharmacodynamic profiles of pharmaconutrients, with well-powered prospective clinical trials for safety and efficacy, will clarify the future of pharmaconutrition in critical care medicine and clinical nutrition. This type of study would be able to further elucidate the best antioxidant micronutrient approach, including safety, tolerability, and feasibility of high-dose antioxidants in ICU patients.