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Consequences of the REDOXS and MetaPlus trials: the end of an era of glutamine and antioxidant supplementation for critically ill patients?

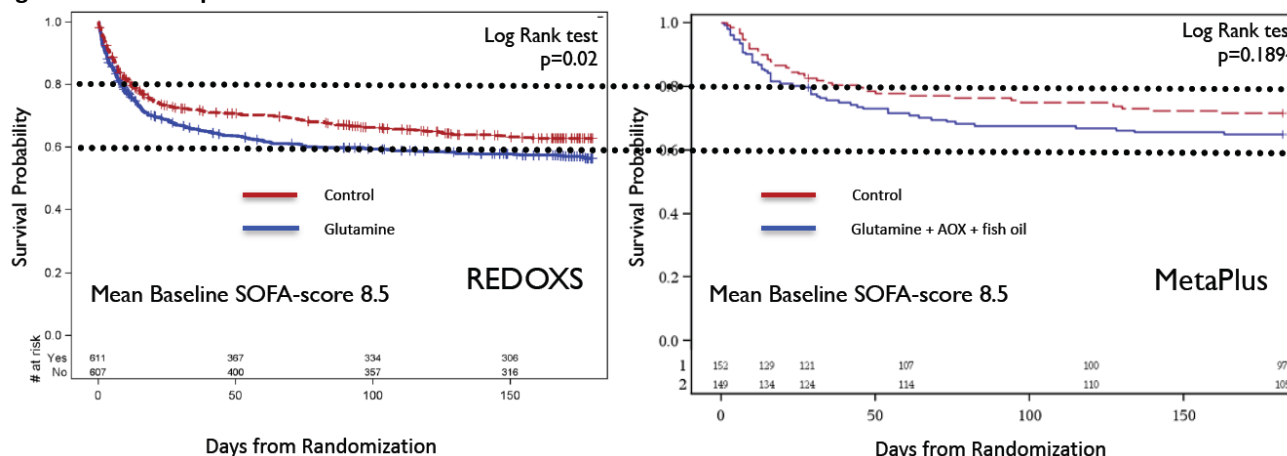
Recently, two large-scale, multicenter randomized trials studying the effect of supplemental glutamine and antioxidants in critically ill ventilated patients have been published^{1,2}. Together, the results of these 2 studies challenge current guidelines and recommendations for these special nutrients.

The REDOXS Trial was a factorial 2x2 randomized trial conducted in 40 intensive care units (ICUs) in North America and Europe¹. A total of 1223 mechanically ventilated adult patients with multi-organ failure were randomized to receive glutamine, antioxidants, both, or placebo. Consistent with a pharmacutrition approach, patients received high doses of study nutrients administered separate from artificial nutrition (intravenous glutamine supplementation [0.35 g/kg/day parenterally provided as 0.50 g/kg/day of the dipeptide alanyl-glutamine, and an additional 30 g/day of glutamine enterally, provided as 42.5 g alanyl-glutamine and glycine-glutamine dipeptides). Contrary to the study hypothesis, the primary analysis demonstrated no clinical benefit of these nutritional interventions and identified a trend toward increased mortality at 28 days (32.4% vs. 27.2%; adjusted odds ratio, 1.28; 95% confidence interval [CI], 1.00 to 1.64; P = 0.049) and a significant increase in hospital and 6 month mortality among patients who received glutamine as compared with those who did not receive glutamine. Overall, there was no effect of antioxidants on 28-day mortality (30.8%, vs. 28.8%; adjusted odds ratio, 1.09; 95% CI, 0.86 to 1.40; P = 0.48). In a *post hoc* subgroup analysis, both glutamine and antioxidants appeared most harmful in patients with baseline renal dysfunction. No subgroups suggested reduced mortality with supplements³. The adverse effects of glutamine observed in the REDOXS trial were partially attributed to the high dose of study supplements provided to these patients.

The MetaPlus trial was conducted from February 2010 through April 2012 including a 6-month follow-up period in 14 ICUs in the Netherlands, Germany, France, and Belgium. A total of 301 adult patients who were expected to be ventilated and to require enteral nutrition (EN) for more than 72 hours were randomized to the intervention feed or standard high protein EN. Consistent with attempting to supplement patients because of presumed nutrient deficiency, per 1500ml, the enriched diet contained 30 grams total glutamine (23 grams of supplemental glutamine as alanyl-glutamine dipeptides), extra antioxidants including an additional 285 mcg of selenium and an additional 7.5 grams of fish oils. The control diet was a isocaloric standard high-protein EN (Nutrison Advanced Protison, NV Nutricia, Zoetermeer). In both groups, feeds were initiated within 48 hours of ICU admission and continued during the ICU stay for a maximum of 28 days. The trial reported an intention-to-treat analysis, performed for the total population, as well as predefined medical, surgical, and trauma subpopulations.

There were no statistically significant differences in the primary end point, incidence of new infections according to the Centers for Disease Control and Prevention (CDC) definitions between the groups: 53% (95%CI, 44%-61%) in the enriched group vs 52% (95% CI, 44%-61%) in the control group (P = .96). Secondary end points included mortality, Sequential Organ Failure Assessment (SOFA) scores, mechanical ventilation duration, ICU and hospital lengths of stay, and subtypes of infections according to CDC definitions. No statistically significant differences were observed in other end points, except that patients that received the enriched diet had increased higher 6-month mortality rate (hazard ratio of 1.57, 95%CI, 1.03-2.39, P = .04 for 6-month mortality adjusted for age and Acute Physiology and Chronic Health Evaluation II score). The 6 month survival curves in this study in fact mirrored almost exactly the 6 month survival curves from the REDOXS study (see Figure 1). Moreover, in an a priori subgroup analysis, the medical subgroup had a higher 6 month mortality (54% in the enriched group vs 35% in the control group, P = .04) whereas no differences in mortality were observed in the trauma and surgical subgroups. Admittedly, it is difficult to attribute this signal of harm to just the glutamine and antioxidants as the enriched diet included supplemental fish oils. However, given the REDOXS results, we are concerned the signal is coming from glutamine and antioxidants.

Figure 1. 6-month probabilities of survival in the REDOXS and MetaPlus studies



In contrast, there have been 2 recent meta-analyses published that continue to show a positive treatment effect of supplemental glutamine and antioxidants^{4,5}. Wischmeyer and colleagues aggregated statistically 26 RCTs of IV glutamine supplementation involving 2484 patients. Trials of EN glutamine including the REDOXS and MetaPlus trial were not included in this review. They observed that IV glutamine supplementation was associated with a trend towards a reduction of overall mortality (RR 0.88, 95% CI 0.75, 1.03, P = .10) and a significant reduction in hospital mortality (RR 0.68, 95% CI 0.51, 0.90, P = .008). In addition, IV glutamine was associated with a strong trend towards a reduction in infectious complications (RR 0.86, 95% CI 0.73, 1.02, P = .09) and ICU length of stay (LOS) (WMD - 1.91, (95% CI -4.10, 0.28, P = .09) and significant reduction in hospital LOS (WMD -2.56, 95% CI -4.71, -0.42, P = .02). However, because of a concern about 'single-center' bias⁶, these investigators went on to show that only the single center trials demonstrated a significant effect of glutamine on overall and hospital mortality and infectious outcomes with no beneficial effect observed in the multicenter trials. In another recent glutamine meta-analysis, investigators compared the treatment effect of trials conducted over the last 2 decades and demonstrated that only trials done before 2003 manifested a positive signal while more recent trials failed to demonstrate any positive treatment effect⁷. One explanation of this may be that the older studies evaluated L-glutamine whereas the more recent studies, including REDOXS and MetaPlus studied supplemental alanyl-glutamine dipeptides. Nevertheless, it would appear that only old, small, single center trials of IV glutamine, when meta-analyzed showed a positive treatment effect.

With respect to antioxidants, Manzanares and colleagues recently performed a meta-analysis of 21 RCTs of antioxidant supplementation in critically ill patients that included the results of the REDOXS study. When the results of these studies were statistically aggregated, combined antioxidants were associated with a significant reduction in mortality (risk ratio [RR]= 0.82, 95% confidence interval [CI] 0.72-0.93, P = .002); a significant reduction in duration of mechanical ventilation (weighed mean difference in days = -0.67, 95% CI -1.22,-0.13, P = .02); a trend towards a reduction in infections (RR= 0.88, 95% CI 0.76,1.02, P = .08); and no overall effect on ICU or hospital LOS. With few exceptions, most RCTs included in this systematic review were relatively small studies with a number of patients lower than 100, and thus inadequate to detect clinically important treatment effect of combined antioxidants on mortality. The signal emerges only after statistically aggregating these smaller trials.

How do we put this all together?

The signal of harm from these substrates comes from 2 large-scale, internally valid, multicenter trials that used both high dose IV and EN nutrients and a trial that used low dose EN nutrients only. In contrast, the signal of benefit seems to come from old, small, single-center trials. Small single center trials would be considered inadequate to guarantee safety as they are grossly underpowered to detect harm. These small trials, combined in meta-analyses, formed the basis of past clinical practice guidelines and now that larger scale trials with adequate power to evaluate mortality outcomes are conducted, these guidelines need to be updated. Given that our first dictum in medicine is to do no harm, we cannot be confident that supplemental glutamine and antioxidants are safe, whether provided enterally or parenterally, whether high or low dose. Until more data are available, we recommend that glutamine, especially when provided as alanyl dipeptides, and antioxidants not be routinely administered to mechanically ventilated critically ill patients.

Key messages

1. There are now 2 studies that suggest that supplemental alanyl-glutamine dipeptides and antioxidants are harmful in critically ill patient populations.
2. Evidence in support of intravenous glutamine and antioxidants comes from old, single-centered RCTs and individually are inconclusive. The positive signal is only observed in meta-analysis of these RCTs which has not been confirmed in recent, large-scale, multi-center trials.
3. More research on the safety and efficacy of glutamine, and in particular alanyl-dipeptides, and antioxidants is needed before treatment recommendations can be considered.

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