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**NIBBLE**
*Nutrition Information Byte*

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# The Role of Glutamine Supplementation in Critical Illness Given the Results of the REDOXS Study

Critically ill patients experience oxidative stress. The most seriously ill patients in the intensive care unit (ICU) have increased mediators of oxidant stress and greater incidence of multi-organ failure compared to less seriously ill patients.[1] Historically, several studies had documented that such stressed patients also have low plasma levels of key nutrients involved in antioxidant defence mechanisms and that these levels correlate inversely with their severity of illness and mortality. [2,3] In a cohort of 80 critically ill non elective surgery patients, low plasma glutamine levels <420 µmol/L were associated with significantly higher hospital mortality.[4] Selenium supplementation may improve clinical outcomes as selenium is an essential co-factor in glutathione enzymatic function, which serves as a key antioxidant.[5] Glutamine is a precursor to glutathione, and appears vital for a number of other key stress-response pathways in critical illness.[6] Meta-analyses of randomized trials suggested that glutamine and antioxidant supplementation in critically ill patients may be associated with a survival advantage.[7,8] Accordingly, we set out to evaluate whether the effect of early glutamine and antioxidant supplementation in critically ill patients with multi-organ failure would reduce 28-day mortality.[9]

In a blinded 2 x 2 factorial trial involving 40 ICUs in Canada, the United States, and Europe, we randomized 1223 critically ill, mechanically ventilated adult patients with multi-organ failure to glutamine supplementation or no glutamine and antioxidants or no antioxidants. We provided study supplements both enterally and parenterally, starting early in the disease course (as soon as possible after randomization and ≤ 24 hrs of ICU admission). High doses were used for glutamine: 0.35 g/kg/day of glutamine intravenously based on ideal body weight, provided as 0.50 g/kg/day of the dipeptide alanyl-glutamine [Dipeptiven®, Fresenius Kabi] and an additional 30 g/day of glutamine delivered enterally, provided as 42.5 g/day alanyl-glutamine and glycine-glutamine dipeptides or respective placebo. In addition, patients were randomized to receive 500 µg of selenium intravenously (selenase®, biosyn), and the following vitamins and minerals administered enterally: selenium 300 µg, zinc 20 mg, beta carotene 10 mg, vitamin E 500 mg, and vitamin C 1500 mg, or placebo. Study supplements were administered separately from standard nutrition and provided continuously for a maximum of up to 28 days. The primary outcome was 28-day mortality. The average age of patients was 63.3 years, average APACHE II score was 26.3 and 67.8% were in septic shock. In contrast to our expectations, we demonstrated increased harm associated with glutamine supplementation (Table 1).

**Table 1: Clinical Outcomes of Patients Receiving Glutamine (n= 611) vs. No Glutamine (n = 607)**

| | Glutamine | No Glutamine | P value |
|---|---|---|---|
| **Day 28 mortality** | 198 (32.4%) | 165 (27.2%) | 0.049* |
| **Day 14 mortality** | 157(25.7%) | 129 (21.3%) | 0.07 |
| **Hospital mortality** | 227(37.2%) | 188 (31.0%) | 0.02 |
| **6 month mortality** | 259 (43.7%) | 218 (37.2%) | 0.02 |

*A P value < 0.044 was required for statistical significance.

## *Where did we go wrong in our pursuit of knowledge regarding the role of glutamine in the ICU?*

The truth is, we don't know for sure but 2 comments and observations are worth noting at this point:

**1) Contrary to our original thinking, critical illness is not necessarily a glutamine deficient state.** However, we did not consistently demonstrate low plasma glutamine levels in a sub-study of 66 patients with plasma glutamine measurements in this trial. Only 31% of patients presented with low baseline glutamine (<420 µmol/L). In fact, we

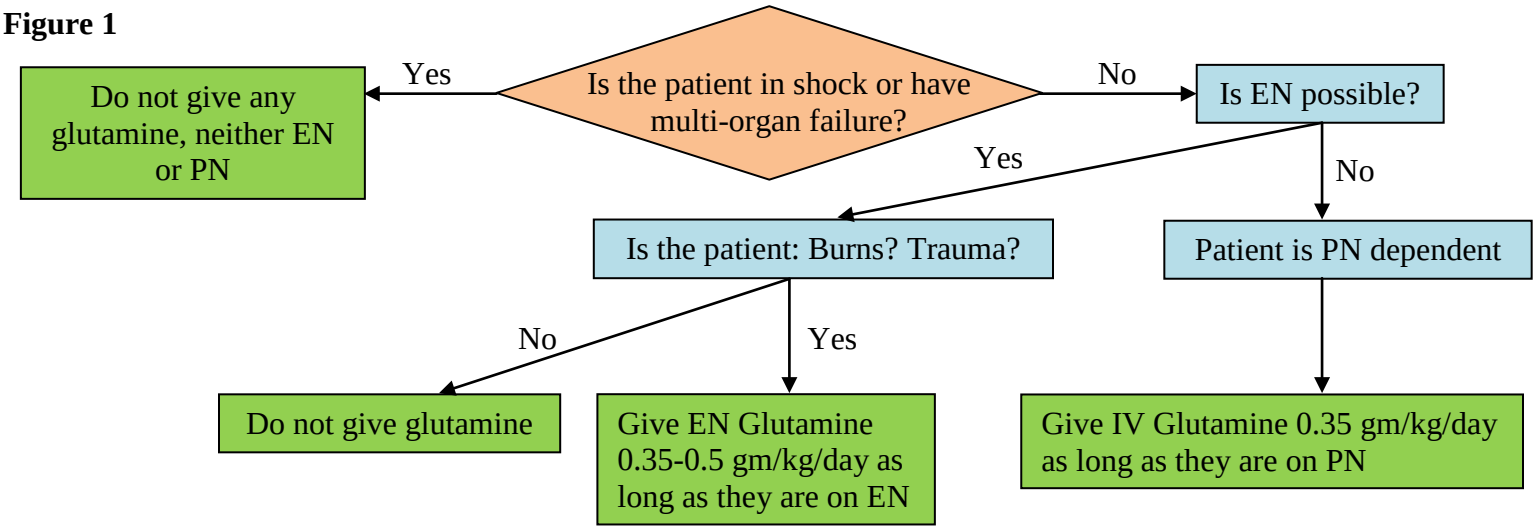
observed supra-normal levels of plasma glutamine at baseline (pre-treatment) in 15% of patients, a phenomenon only recently described by Rodas and colleagues.[10] These investigators described elevated baseline levels of glutamine in the plasma of 174 critically ill patients with multi-organ failure and a value of >930 µmol/L was actually associated with increased mortality.

**2) We built the case for glutamine supplementation by using meta-analysis of RCTs of PN supplemented with glutamine and then migrated to a different patient population (critically ill patients with multi-organ failure) as opposed to patients studied in these previously published RCTs.** We hypothesized that sicker patients with organ dysfunction were more likely to have lower plasma glutamine levels and worse clinical outcomes, and would therefore benefit the most from nutrient supplementation. However, this did not turn out to be the case. The meta-analysis included less severely ill patients receiving glutamine along with nutrition (mostly PN). The REDOXS patients were fed mostly enterally, only reaching 50% of energy and protein target.

## *So, where does that leave us with respect to the role of glutamine in the ICU?*

For sure, **any patient with multi-organ failure in the ICU should not receive glutamine regardless if on PN or not** (based on the REDOXS study). For ICU patients not in multi-organ failure and receiving PN, there is still a large body of literature summarized in a meta-analysis in our updated 2013 Clinical Practice Guidelines on our website (www.criticalcarenutrition.com) showing a beneficial treatment effect of IV glutamine (0.35 gram/kg/day). For patients not in multi-organ failure and with a burns or trauma admission diagnosis, consideration can be given to providing glutamine enterally (0.3-0.5 g/kg/day) but this is based on weak data from small studies.[11] Accordingly, we propose a *revised/updated* treatment algorithm represented in Figure 1. Future research should define whether a baseline measurement of plasma glutamine is required to guide exogenous glutamine administration depending on whether the patient admitted to your ICU has low plasma glutamine levels or not.

**Figure 1**





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