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Glutamine Supplementation in Parenteral Nutrition and Intensive Care Unit Patients: Are We Throwing the Baby Out With the Bathwater?

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Keywords

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An Aspirin a Day Keeps the Doctor Away? True in All?

Clinical research in many fields of medicine, including the intensive care unit (ICU), has demonstrated numerous therapies to be efficacious when targeted to patients with clear clinical or biologic need for the therapy. However, as the eternal search for the "magic bullet" therapy continues to improve outcome in all patients, we often transfer therapies that have been successful in targeted patient groups to all patients aiming for the mythical "goliath trial." This phenomenon was recently observed with aspirin therapy to reduce myocardial infarction (MI) and stroke.[1] Aspirin has unquestionably been shown to reduce subsequent vascular and cardiac events when given following a previous MI or stroke.[2] However, when given to all patients, regardless of whether they had had a previous MI or stroke, aspirin was shown to markedly increase the risk of gastrointestinal (GI) bleeding and was determined not to be ideal for *all* patients.[1] This finding did not change the fact that any years of data still demonstrated that aspirin is still clearly indicated in patients following MI or stroke, but the risk of bleeding outweighed the benefit of daily aspirin when given to patients without a clear preexisting data-driven indication. As a result, did we tell all of our patients to stop taking aspirin? Of course not! We only refined our knowledge and learned to use aspirin more safely in the right patients. Our experience in the ICU has been quite similar. This author would roughly estimate that there have been approximately 79 large trials of sepsis therapies of > 1000 patients over the past 20 years. Of these, 72 have been negative (no effect of therapy), and 6 showed harm of studied therapy. The 1 study (The Prowess Trial)[3] that showed benefit then, unfortunately, was shown not to be beneficial in 2 subsequent trials. What can we learn from this? First, when we attempt to extend successful previous trials into the "goliath" trial, we often disregard the original inclusion/exclusion criteria of the previous successful trials to include "all patients" and enroll larger numbers. This was true in the aspirin trials attempting to prove all patients should take a daily aspirin, not just those at high risk for subsequent MI or stroke. This, of course, was not successful.[1]

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Extending this to the ICU, in our large trials, we often attempt to treat all ICU patients with the same intervention, whether they are a 72-year-old with septic shock or a 23-year-old trauma patient, and expect all these quite diverse patients to benefit from one therapy—this is clearly unrealistic. Again, in the search for the "mythical magic bullet," we perform trials targeted to patients who may be well outside the previous beneficial trials target population or given to a broad spectrum of patients in whom a positive signal may be "washed out" or negated by a subgroup of patients benefiting and a subgroup of patients at risk for harm.

In their commentary "Consequences of the REDOXS and METAPLUS Trials: The End of an Era of Glutamine and Antioxidant Supplementation for Critically Ill Patients?" published in the *Journal of Parenteral and Enteral Nutrition*, van Zanten et al[4] challenge the concept of routine glutamine (GLN) supplementation in critically ill patients. Current clinical practice guidelines are called into question as being derived from "older, smaller, single-center trials." These trials are considered "underpowered to detect harm" and thus inadequate to guarantee the safety of GLN. On the other hand, the authors point to the "signal of harm" coming from 2 large-scale multicenter trials evaluating mortality that investigated different ingredients, using either a combination of high-dose intravenous (IV) and enteral nutrients (the Reducing Deaths Due to Oxidative Stress [REDOXS] study)[5] or high-dose enteral mixture of different nutrients (the METAPLUS trial).[6] These new trials were both targeted to investigate GLN (and other nutrients) as primary pharmaconutrients and not nutrition. These trials are both quite unique and unlike any of the previous trials on which our guidelines are based, since in all previous trials, GLN was given as a supplement to parental nutrition (PN). Despite this, the authors conclude that "we cannot be confident that supplemental glutamine, especially when provided as alanyl dipeptides and antioxidants, are safe, whether provided enterally or parenterally, whether high or low dose." The authors also discourage the routine administration of GLN to mechanically ventilated critically ill patients until the issue is resolved.

Beneficial Effects of GLN in the ICU Have Been Proven in Numerous Clinical Trials

As with aspirin, we now know the proper dose of GLN is likely vital to its safety and efficacy. When trials of aspirin are evaluated, data indicate that higher doses are not more effective in reducing the risk of MI or stroke, but higher doses of aspirin are associated with more bleeding complications.[7] Similarly, studies such as REDOXS have made us aware that high-dose IV and enteral GLN given at twice or more the recommended (previously shown to be safe) dose could potentially increase risk when given to unique groups of high-risk patients. These are all patient groups in which GLN has traditionally been contraindicated. Specifically, many of the patients studied in these trials have always been contraindicated to receive GLN based on federally approved package insert instructions and pharmaceutical dossiers. In addition to many patients in both trials receiving GLN outside its approved mode of administration, many patients also did not receive adequate nutrition support. In all previous studies of GLN-supplemented PN, patients received GLN as part of full nutrition support. Despite this, the commentary by van Zanten et al[4] chooses to ignore over 20 years' worth of randomized controlled trial (RCT) data repeatedly showing that GLN, when given

to patients with appropriate clinical indications at approved doses, reduces mortality, infectious complications, and ICU/hospital length of stay.[8] This is a signal that has stood the test of time, even holding true in recent meta-analysis.[9] Benefits of IV GLN supplementation, such as alanyl-glutamine (Ala-GLN) dipeptide on infections and mortality, have been confirmed in not only single-center but also larger multicenter RCTs. Déchelotte et al[10] included 114 patients from 16 ICUs in France admitted for multiple trauma, complicated surgery, or pancreatitis. The most common enrollment diagnosis was surgery for GI malignancy. Ala-GLN–supplemented PN (0.5 g/kg body weight [BW]/d) was associated with significantly lower incidence of complicated outcomes, mainly due to a reduced infection rate. Moreover, hyperglycemia and insulin-requiring patients were less frequent in the Ala-GLN group. Furthermore, in one of the largest multicentric RCTs of GLN-supplemented PN, Wernerman et al[11] studied 413 ICU patients receiving PN and/or EN recruited from 11 Scandinavian centers. This trial demonstrated a 29% reduction in ICU mortality following administration of 0.283 g glutamine/kg BW/d provided as IV Ala-GLN vs placebo.

A 2011 American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) position paper on IV GLN supplementation clearly stated that “parenteral glutamine administration is associated with a decrease in infectious complications, decrease in hospital length of stay, and possibly a decrease in mortality in critically ill postoperative or ventilator dependent patients requiring parenteral nutrition (PN).”[12] Two recent meta-analyses have confirmed that supplementing PN with IV GLN is safe, reduces mortality, and improves outcome. Wischmeyer et al[9] included 26 studies with 2317 patients evaluating only IV GLN in ICU patients; another 3 studies evaluated the combination of GLN with enteral nutrition (EN). Significant reductions of hospital mortality and hospital length of stay (LOS) could be demonstrated. Likewise, also the meta-analysis by Bollhalder et al,[13] combining the data from 40 RCTs in 3107 surgical and critically ill patients, revealed a significant reduction in mortality in the critically ill and significantly reduced infection risk and hospital LOS in all patients. When higher doses of supplemented GLN were studied (>0.3 g/kg/d Ala-GLN), short-term mortality, infections, and LOS were significantly reduced. Based on 9 level 1 and 19 level 2 studies, Wischmeyer et al[9] concluded, “When PN is prescribed to ICU patients, parenteral supplementation with GLN should be considered.”

As claimed by van Zanten et al,[4] it seems that trials showing positive treatment effects in these meta-analyses were merely small, single-center trials of IV GLN published more than 10 years ago. Yet, as outlined above, this is not correct and does not accurately reflect the actual data, design, or size of the aforementioned positive GLN-supplemented PN trials: all these “traditional” GLN supplementation trials were conducted in well-selected groups of patients in need of PN, importantly excluding patients with renal and liver failure in accordance with the approved use and indication for IV GLN. Clearly, GLN was not given independently of nutrition support, and supplementation was not started directly at ICU admission. Instead, the following cardinal differences are as follows: GLN was (1) administered later during the ICU stay following hemodynamic and metabolic stabilization when patients were not in shock, (2) given at lower doses (0.3–0.5 g/kg/BW/d) in accordance with prescribing guidelines and package insert instructions, and (3) was given parenterally and not combined with enteral GLN administration.[9] It is also key to note that

most patients in these studies had cancer and thus might have particularly benefited from GLN supplementation, given increased rates of GLN deficiency in oncology patients (see Table 1).[14]

GLN Trials Show No Increased Risk of Death Prior to Patients Previously Contraindicated to Receive GLN Included

The newer trials (REDOXS, METAPLUS) used glutamine in a substantially different and unique manner (Table 1). We hoped to push the boundaries of GLN use from that of a nutrient to that of a drug (or pharmaconutrient), given completely independent of nutrition delivery. It was an ambitious and promising endeavor we believed would open up many more patients to potentially benefit from GLN. Unfortunately, GLN used as a drug in septic shock and multiorgan failure (MOF) was not successful. To this point, in the REDOXS study, the enrollment of severely critically ill patients with MOF was a mandatory inclusion criterion. These patients have almost universally been excluded in the “traditional” GLN supplementation of PN studies. More than 90% of patients had shock, a general contraindication against any form of clinical nutrition, including GLN in most previous trials. In REDOXS, by design, these patients were given nutrition products, including GLN —importantly before resolution of shock. GLN was given enterally and parenterally at a total dose of approximately 50 g/d total GLN, corresponding to 0.6–0.8 g/kg BW. Notably, this is the largest dose ever given in a clinical trial and corresponds to twice the total daily dose currently recommended by European and American (European Society for Clinical Nutrition and Metabolism [ESPEN] and A.S.P.E.N.) nutrition guidelines.[12,15] Of crucial importance, IV Ala-GLN was not given in accordance with its approved use and indication as it was given without adequate calories and dissociated from nutrition. In addition, the amount of enterally administered GLN might also have been a problem in the REDOXS study. Intensified intestinal nutrition burden might induce local splanchnic vasodilation, being harmful during shock due to worsened systemic perfusion. Conversely, if poor gut perfusion was induced by severe shock and vasopressor use prior to adequate resuscitation, early enteral feeding may have precipitated increased gut oxygen demand and gut ischemia. These considerations are clearly supported by the results of a post hoc analysis of treatment effects examined within subgroups defined by baseline patient characteristics: 28-day mortality was significantly increased in the GLN-supplemented group vs those not receiving GLN in patients with a baseline Sequential Organ Failure Assessment (SOFA) score >10 (P = .02) and receiving <33% of their prescribed caloric intake (P = .029),[16] with a trend to worse outcome in patients with shock (P = .051).

Most important, more than one-third of the REDOXS study patients had severe renal dysfunction at baseline, a clear contraindication against the use of IV Ala-GLN. As an investigator who participated in the design of this study, it should be stated we did not observe any toxicity in our pilot dosing trial, which included patients with renal failure.[17] Furthermore, we had hoped that most patients with early renal failure would receive early continuous veno-venous hemofiltration (CVVH), reducing any possible risk from Ala-GLN administration. However, this was not the case, with significant delays in CVVH initiation, often 5 days or more occurring in the actual practice of the trial. Accordingly, in the

subgroup analysis, much of the harm related to GLN administration occurred in the early renal failure group, as reflected by increased 28-day mortality in patients with renal dysfunction at study enrollment (odds ratio [OR], 2.75; 95% confidence interval [CI], 1.5–5; $P = .028$ GLN vs no GLN). This effect was even more pronounced in patients previously not having received dialysis.[16] Interestingly, this risk may be attenuated or reversed when patients evolve renal failure later in their ICU stay and receive dialysis as treatment later in the stay. This group showed a non–statistically significant reduction in mortality risk when GLN was given. Much more research would be needed to confirm this finding. What we should learn from these findings is that high-dose GLN in severe renal failure represents a significant risk factor for mortality. The etiology of this risk is currently unclear but is being actively explored in our laboratory. It appears to be a risk that occurs with early renal failure and may be ameliorated by dialysis treatment. Thus, it is crucial to define the “at-risk” patients among those with renal insufficiency before starting GLN supplementation. Commonly used parameters of renal function include high plasma creatinine (>171 mmol/L or a rise in creatinine >80 mmol/L from baseline) and low urinary volume (<500 mL/24 hours or <80 mL/last 24 hours). Alternatively, creatinine clearance (<25 mL/min), as indicated in the Ala-GLN package insert, might serve as a suitable guiding exclusion criterion. In the future, to adequately predict risk, it might be appropriate to consider further renal markers such as neutrophil gelatinase associated lipocalin (NGAL) or interleukin-18 (IL-18).

It has been suggested that GLN deficiency may be key to the benefit of GLN administration. In REDOXS, approximately 30% of ICU patients showed low plasma glutamine levels (<420 μmol/L). In all past investigations, this deficiency has been related to significantly higher hospital mortality.[18] Likewise, high plasma glutamine levels at ICU admission exceeding 930 μmol/L may also predict unfavorable prognosis. An evaluation per diagnosis group revealed that particularly high plasma GLN concentrations (outliers) were measured in the most severely ill patients with sepsis, respiratory insufficiency, and acute pancreatitis,[19] whereas among all patients, “normal” plasma glutamine levels between 400 and 900 μmol/L represented an advantage with regard to survival.[19] In REDOXS, only 9% of patients showed high plasma GLN levels at ICU admission, and these patients were not excluded from the evaluation as these levels were not known to the authors during the trial prior to initial clinical data evaluation, and only a subgroup of patients had GLN levels available at trial completion. It is not clear that measuring GLN levels prior to GLN administration would actually target those likely to benefit from GLN; further analysis from the REDOXS trial did not demonstrate that GLN administration led to “toxic” elevations of GLN in patients studied. This author believes the most likely hypothesis given the data we have now is the increased GLN levels seen in the REDOXS study may be more a marker of organ failure and severe shock than an effector of harm.

An additional intentional confounder in the REDOXS and METAPLUS studies was that GLN was mixed with other pharmaconutrients, such as fish oil, vitamins, or selenium. This mixture may have created negative interactions, particularly in the Meta-Plus trial, as our laboratory has shown that the combination of these nutrients may modify or block the potential beneficial effects of the individual nutrients, particularly GLN’s beneficial effects.[20]

Are We “Throwing the Baby Out With the Bathwater”?

In fact, unfortunately it appears with the REDOXS study that we have made quite a number of “goliath” errors: we disregarded many of the previously established inclusion and exclusion criteria used in the previously successful trials of GLN-supplemented PN, as well as the approved mode of administration in trying to improve outcome in sepsis and MOF—a true “goliath task.” We used large pharmacological doses of supplemental enteral and parenteral GLN dipeptides together with other pharmacologically active nutrients. The results underscore that GLN dipeptides should not be given in high doses (>0.5 g GLN/kg BW/d), dissociated from complete and adequate nutrition, and earlier than 48 hours post-ICU admission. Patients with severe renal dysfunction at admission, especially without dialysis, and those with MOF and severe unresuscitated shock requiring significant vasopressor support should be excluded from GLN supplementation. REDOXS was undertaken with the best of intentions to attempt to improve outcomes in a large group of patients early in the ICU by using GLN as a drug, much like when fish oil was separated from nutrition and other nutrients and failed to improve acute respiratory distress syndrome[21]—in opposition with previous trials. Our attempts to create “drugs” from these nutrients have been unsuccessful.

Yet, the failure of this “goliath task,” much like the failure of daily aspirin to benefit all patients at all doses, does not imply that these results should now negate 20 years of previous successful research in an entirely different patient population, using a different dose, and given as part of complete nutrition therapy. This would mean “throwing the baby out with the bathwater,” ignoring all other positive trials in other patient groups, especially PN patients without renal failure or shock and including critically ill patients with stabilized MOF. GLN still saves lives—this has been demonstrated in thousands of patients over many years. We continue to perform GLN trials in specific populations (ie, RE-ENERGIZE trial in burn patients), and this author strongly believes the “right” patients (eg, patients in need of PN, patients with burns, trauma, or malignancies) will continue to benefit from supplemental GLN, administered either intravenously at a dose of 0.35 g/kg BW/d as GLN dipeptides or enterally at a dose of 0.5 g/kg BW/d.[12] The most important finding of our new data from these “goliath” trials is that it actually may finally teach us how to give GLN more safely and in a more targeted way at the right dose, to the right patients, at the right time.

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Table 1

Differences Between Traditional Parenteral GLN Supplementation Trials and the REDOXS Trial.

Trial Characteristic	Traditional Parenteral GLN Supplementation Trials	REDOXS Study
Nutrition delivery	Only patients requiring full PN support	No nutrition support required—patients received poor nutrition delivery overall (~50% of goal kcal)
GLN role	Only as supplement to full PN	Separate pharmaconutrient—given independent of nutrition
Timing of GLN administration	Typically later in ICU care—after resolution of shock	Within 24 hours of ICU admittance—almost all patients in shock and in MOF
Presence of organ failure	Renal and liver failure almost universally excluded—per package insert. MOF typically excluded.	All patients with MOF as per inclusion criteria. One-third of patients with renal failure.
GLN dose	0.3–0.5 g/kg/d Ala-GLN intravenously	30 g/d enterally; 0.5 g/kg/d IV Ala-GLN Total GLN: 0.6–0.8 g/kg/d
Combined EN/PN	No	Yes
Patient type	Trials often included many surgical oncology patients (based on trials' inclusion data and as cancer is reported to be the most common indication for PN[22])	Majority not surgical oncology patients

Ala-GLN, alanyl-glutamine; EN, enteral nutrition; GLN, glutamine; ICU, intensive care unit; MOF, multiorgan failure; PN, parenteral nutrition; REDOXS, Reducing Deaths Due to Oxidative Stress trial.