The glutamine debate in surgery and critical care

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Purpose of review
Glutamine (GLN) is a versatile amino acid, long believed to have important implications in ICU and surgical patients. An extensive body of data examining GLN supplementation of TPN demonstrated a consistent signal of improved outcomes. However, recently signals of risk have come from two large-scale multicenter trials evaluating GLN (and other nutrients) at high dose and as primary pharmaconutrients, not as supplementation to complete nutrition. These trials indicate a risk of increased mortality when GLN is given to patients in shock, renal failure, and early in acute phase of critical care.

Recent findings
Recent literature continues to confirm that low and high admission GLN levels are associated with increased ICU mortality and adverse outcomes. Further, a recent meta-analysis examined trials utilizing GLN-supplemented TPN in stabile ICU patients consistent with current clinical guidelines. This analysis showed GLN supplementation of TPN led to reduced infections, LOS and hospital mortality.

Summary
Three recent meta-analyses have confirmed traditional GLN-supplemented (or 'GLN-Complemented' – providing GLN for completeness of amino acid content) TPN is safe, reduces mortality and improves outcome in surgical and ICU patients. Patients in need of TPN, burns, trauma or malignancies should continue to benefit from supplemental GLN, administered either intravenously at less than 0.35 g/kg/day or enterally at less than 0.5 g/kg/day. Further, a large trial of EN GLN supplementation in burns is ongoing. Thus, when used per guideline recommendations, the GLN story is likely still relevant to ICU outcomes and research.

Keywords
burn injury, critical care, nutrition, parenteral nutrition

INTRODUCTION

The glutamine (GLN) debate in clinical nutrition that has continued for years is centered around the potential for this versatile amino acid to improve outcomes in critically ill, surgical, and cancer patients. GLN is the most abundant nonessential free amino acid [1] and low GLN levels have long been associated with poor outcome [2]. Thus, GLN has been labeled a 'conditionally essential' amino acid during prolonged illness, which led to the hypothesis that GLN supplementation could improve outcomes [3]. Since the 1960's industrial parenteral nutrition solutions have not included GLN for technical reasons, rendering current parenteral nutrition solutions fully incomplete. An extensive body of data examining GLN supplementation of total parenteral nutrition (TPN) demonstrated a consistent signal of improved outcomes in systematic meta-analysis data in ICU and surgical settings [4]. This led to trials of GLN used as a pharmaconutrient, often at higher doses than had been previously studied and at higher doses than recommended. Surprisingly, signals of risk came from two large-scale multicenter trials evaluating mortality utilizing a combination of high-dose intravenous/enteral GLN, the REDOXS study [5] or high-dose enteral mixture of different nutrients including GLN, the METAPLUS trial [6]. These new trials were both targeted to investigate GLN (and other nutrients) as primary pharmaconutrients, and not as supplementation to complete nutrition, such as is contained in TPN. These data show patients in early phase of sepsis, on escalating vasopressors, or in renal failure (especially without dialysis) should not get supplemental GLN. Three recent meta-analyses [7,8,9▪▪] (see Table 1) have confirmed traditional 'PN-complementation' with intravenous GLN is well

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KEY POINTS

- Glutamine 'complementation' (providing glutamine for completeness of amino acid content quite different from GLN given as a pharmaconutrient, i.e. REDOXs) of parenteral nutrition, as part of complete nutrition delivery, in surgery and critical care has a significant body of literature supporting potential benefit on patient outcomes.
- Two recent large trials of glutamine as pharmaconutrient, at larger dose, in acute phase of shock and critical illness have shown signals of risk on outcome – particularly in patients in early shock, on vasopressors, or with renal failure at admission without dialysis.
- Recent literature continues to confirm both low (<420 μmol/l) and high (>930 μmol/l) glutamine levels in ICU continue to be associated with increased mortality and poor clinical outcome.
- A recent meta-analysis focused on 'glutamine-complemented' TPN in stabile ICU patients consistent with current clinical guidelines and per package prescribing instructions confirms reduced mortality, infections, and improved clinical outcomes, consistent with other recent meta-analysis of glutamine-complemented TPN.
- Areas of future research efforts on glutamine's use in ICU and surgery to improve outcome include: use in continuous renal replacement therapy (CRRT) where glutamine losses may be high, use in oncology patients requiring TPN more than 7 days postsurgery and/or in ICU; and in burns and in trauma settings – as currently there is a large randomized trial of enteral glutamine in burn injury ongoing.

tolerated, reduces mortality and LOS, and improves outcome in surgical and critically ill patients. Supplementation according to the Merriam-Webster dictionary is to deliver above needs, while completion is to render a solution or whatever 'complete'. For clarity, we suggest that in the future, addition of GLN to TPN in this traditional, guideline recommended fashion be referred to as 'GLN-Complemented' TPN as it completes the amino acid content of TPN (Glutamine 8–10% in PN is a completion. This is needed to reduce confusion as GLN is not being provided as a pharmaconutrient at supranutritional doses as was done in studies like REDOXs, but rather GLN is added to TPN for completeness of amino acid content. In veterinary medicine, and in healthy top athletes the concept of rate limiting amino acid has been known for decades. Most all enteral feeding solutions contain at least 8% of amino acids as GLN [10▪▪,11▪]. Patients in need of parenteral nutrition in perioperative or ICU setting, patients with burns, trauma or malignancies may continue to benefit from GLN-complementation when administered either intravenously at less than 0.35 g/kg/day or enterally at less than 0.5 g/kg/day [12,13]. Further, there is currently a large trial of EN GLN in burn injury ongoing (RE-ENERGIZE trial) [14▪▪]. The purpose of this review is to examine recent literature contributing to this ongoing debate and discuss the status of the 'great GLN debate' and where we may go from here to optimally and safely utilize GLN in the care of our patients and in future research.

ROLE OF GLUTAMINE DEFICIENCY IN THE GLUTAMINE DEBATE: EFFECT ON OUTCOMES AND A POSSIBLE GUIDE FOR CLINICAL CARE

It has long been debated whether GLN levels should be evaluated as a guide for GLN treatment in the research and/or clinical setting. Past data demonstrates clearly that low GLN levels are associated with increased ICU mortality [2,15]. A number of recent studies have confirmed this finding remains true in modern ICU practice. A recent small study by Costa *et al.* [16▪] demonstrated that in surgical critical care patients, GLN deficiency was commonly present at ICU admission (mean GLN level: 385.1 ± 123.1) and decreased until the third ICU day. Prevalence of GLN deficiency (<420 μmol/l) at admission was 64.3%. Baseline GLN deficiency correlated with the Simplified Acute Physiology Score II (SAPS II score; Pearson's correlation coefficient $r = -39.4\%$, $P = 0.042$), and GLN was lower in cases of blood transfusion (339.9 ± 78.8 versus 454.9 ± 148.8 μmol/l, $P = 0.013$). GLN deficiency on ICU day 3 correlated with the duration of mechanical ventilation support ($r = -65\%$, $P = 0$ 0.012) and ICU stay ($r = -66.5\%$, $P = 0.009$). GLN levels below 320 μmol/l, was observed in 25% of the patients. This lower GLN levels was associated with a higher in-hospital mortality (42.9 versus 19%; P = n.s.). Another recent study has confirmed the seminal work of the Wernerman and Rooyacker lab that both low and high GLN levels during ICU stay are associated with increased mortality [2]. Tsujimoto *et al.* [17▪] performed a study of 214 mixed critically ill patients examining the role of GLN levels in ICU outcome. The mortality rates in patients with plasma GLN less than 400 μmol/ml (low GLN group mortality 39%, 28/71) or at least 700 μmol/ml (high GLN group mortality 50%, 15/30) were significantly higher ($P < 0.05$ and $P < 0.01$, respectively) than those in patients with plasma GLN levels in normal range of 400–700 μmol/ml (normal GLN group mortality 21%, 24/113). Among

Table 1. Summary of key recent meta-analysis of glutamine complementation of complete nutrition (primarily TPN) in surgery and critical illness

Systematic review [reference] (year)	Question	Number of included studies	Patient number included	Effect on overall mortality	Effect on hospital mortality	Effect on infectious complications	Effect on hospital LOS	Other key outcomes
Stehle *et al.* [9▪▪] (2017)	GLN-complemented PN use in ICU patients who administered GLN dipeptide strictly according to current clinical guidelines for GLN-use in PN as part of complete nutriton	15 RCTs	842	N/A	GLN benefit: RR 0.55, 95% CI 0.32–0.94, $P=0.03$	GLN benefit: RR 0.70, 95% CI 0.60–0.83, $P<0.00001$)	GLN benefit: −2.30 days; 95% CI 4.14–0.45, ($P=0.01$)	GLN benefit reducing: ICU LOS ($P=0.04$) Mech. Vent days ($P=0.02$)
Wischmeyer *et al.* [7] (2014)	Parenteral GLN complementation in ICU patients (doses ≤0.5 g/kg/day)	26 RCTs	2317	Trend to GLN benefit: RR 0.88, 95% CI 0.75–1.03, $P=0.10$,	GLN benefit: RR 0.68, 95% CI 0.51–0.90, $P=0.008$	Trend to GLN benefit: RR 0.86, 95% CI 0.73–1.02, $P=0.09$	GLN benefit: WMD -2.56, 95% CI −4.71 to −0.42, $P=0.02$,	Trend to GLN benefit: VAP, ICU LOS
Bollhalder *et al.* [8] (2013)	GLN-complemented PN use in surgical and ICU patients	40 RCTs	3107	N/A	GLN reduced mortality in critically ill (RR 0.71, 95% CI 0.53, 0.96, $P=0.024$)	GLN benefit overall: (RR = 0.83; 95% CI 0.72–0.95, $P=0.009$) Surgery: (RR 0.61; 95% CI 0.46–0.82;$P=0.001$).	GLN benefit overall: 2.35 days shorter (95% CI −3.68 to −1.02, $P<0.0001$)	Only trials with mean GLN admin. More than 9 days had significant benefit on short-term mortality, infections, and LOS No effect of trials giving less than 0.20 g/kg/day GLN

CI, confidence interval; GLN, glutamine; LOS, length of stay; N/A, not available; PN, parenteral nutrition; RR, relative risk; VAP, ventilator associated pneumonia; WMD, weighted mean difference.

patients with sepsis, the mortality rates of low GLN group (46%) and high GLN group (67%) were significantly higher ($P < 0.05$ or $P < 0.01$, respectively) in comparison with normal GLN group (26%). Thus, new data continues to demonstrate that low and high GLN levels during critical illness are associated with adverse outcome.

A recent trial protocol publication has described the ongoing large multicenter RE-ENERGIZE study of EN GLN in burn injury. A pilot study for this trial was performed to evaluate the feasibility and safety of GLN administration in burn injury prior to initiation of the full trial. In this RE-ENERGIZE pilot study, baseline GLN levels were measured in 18 initial patients [14▪▪]. The average plasma level of GLN level in these burn injured patients was 408 ± 146 μmol/l (below normal range of 420–700 μmol/l), demonstrating significant GLN deficiency in this group of burn patients. In this RE-ENERGIZE pilot of burn injured patients, the highest level of GLN observed in the measurement taken at baseline was within the normal range for plasma GLN level (723 μmol/l) [14▪▪]. Thus, as hypothesized, a majority of the burn patients demonstrate GLN deficiency at admit to ICU. This is quite different from what was observed in the REDOXs trial where a majority of patients were admitted with normal plasma GLN levels and these levels decreased over time in ICU [5].

It has been suggested that GLN deficiency may be the key to benefit of GLN administration. Currently, this continues to not be practical in routine clinical practice as amino acid analysis is complex, time-consuming process not available readily in most centers without significant delay in obtaining results. Our preliminary results from the REDOXs trial indicate that acute elevations of blood urea nitrogen, lactate dehydrogenase (LDH), and presence of acute renal failure are predictive of elevated GLN levels (> 930 μmol/l) and may be indicators of whom should not receive GLN as part of clinical care. Analysis of this data is currently ongoing. In summary, it is not clear that GLN level measurement prior to administrating GLN would effectively target patients likely to benefit from GLN addition to TPN or EN GLN. Further REDOXs trial analysis did not reveal that GLN administration, even at very high dose led to any 'toxic' increases of GLN in patients who had GLN levels available. This author believes the most compelling cause of the elevated GLN levels seen in a small number of REDOX patients is likely as a marker of cell death and impaired metabolism. This is likely a marker of severity of organ failure, specifically renal failure, and severe shock rather than a direct cause of harm or organ injury.

RECENT META-ANALYSIS DATA EXAMINING STRICT GUIDELINE USE OF 'GLUTAMINE COMPLEMENTATION' OF PARENTERAL NUTRITION

A recent publication of a new meta-analysis examined only clinical trials utilizing 'GLN- supplemented' TPN (or 'GLN-complemented' TPN-providing doses of GLN to ensure completeness of TPN amino acid content) in stable ICU patients strictly consistent with current clinical guidelines and package insert prescribing instructions [9▪▪]. Stringent eligibility criteria were used to select only those randomized controlled trials (RCTs) that tested the outcomes of critically ill adult patients without hepatic and/or renal failure who were hemodynamically and metabolically stabilized and who were administered GLN dipeptide strictly according to current clinical guidelines (via the parenteral route at 0.3–0.5 g/kg/day; maximum 30% of the prescribed protein delivery) in combination with adequate nutrition. This systematic analysis examined 15 clinical trials that were found to meet these study criteria. The results of this meta-analysis demonstrated that parenteral GLN dipeptide supplementation or 'complementation' significantly reduced infectious complications [relative risk (RR): 0.70, 95% CI 0.60–0.83, $P < 0.0001$], ICU length of stay (LOS) (common mean difference: −1.61 days, 95% CI −3.17 to −0.05, $P = 0.04$), hospital LOS (mean difference: −2.30 days, 95% CI −4.14 to −0.45, $P = 0.01$), and mechanical ventilation duration (mean difference: −1.56 days, 95% CI −2.88 to −0.24, $P = 0.02$). 32% (95% CI 0.60–0.83; $P = 0.0001$); ICU LOS (mean difference) −1.61 days (95% CI 3.17–0.05; $P = 0.04$); reduced hospital LOS (mean difference) −2.30 days (95% CI 4.14–0.45; $P = 0.01$); reduced mech. vent. days (mean difference) −1.56 days (95% CI −2.88 to −0.24; $P = 0.02$) versus parenteral nutrition that did not contain GLN. Most importantly, 'GLN-Complementation' of TPN was associated with a 45% mortality reduction versus GLN not being present in PN (95% CI 0.32–0.94, $P = 0.03$). Thus, three key recent meta-analyses [7,8,9▪▪] have re-affirmed that the utilization of traditional GLN-supplementation as part of parenteral nutrition (TPN) continues to be safe, show reductions in mortality and improvement of a range of patient outcomes in critical illness in surgery (see Table 1). Therefore, the ESPEN 2019 guidelines maintain the use of GLN in TPN of stabilized critically ill patients [10▪▪] to prevent GLN from being the rate limiting amino acid [11▪].

A KEY NEW GLUTAMINE TRIAL: THE RE-ENERGIZE TRIAL OF GLUTAMINE IN BURN INJURY

Burn injury leads to a catabolic and systemic inflammatory response that is likely greater than any other

insult a human can survive. This catabolic response is compounded by severe burn wound nutrient losses (including GLN), that is known to be associated to severe nutrient deficiencies [18]. As a result, over many years, a number of small clinical trials have examined the role of GLN to improve outcome in burn injury. These initial trials suggest a signal of benefit of GLN use as part of complete nutrition in burn injury [19] A recent meta-analysis of GLN use in burns patients examined six trials in 225 severely burned patients [14▪▪]. The results of this analysis demonstrated a benefit of GLN administration on patient survival (RR, 0.22, 95% CI 0.07–0.62, $P = 0.005$), lack of an effect on infection (RR, 0.78, 95% CI 0.46–1.31, $P = 0.34$, three trials) and reduction of hospital LOS (WMD: 6.06, 95% CI −9.91 to −2.20, $P = 0.002$).

Thus, based on these promising initial results our research group, led by Heyland [14▪▪], initiated the RE-ENERGIZE trial. This is an international trial described in detail in the aforementioned protocol publication. Briefly, the RE-ENERGIZE trial is a pragmatic, double-blind, multicentre randomized controlled trial targeted to enroll 1200 severe burn injured patients. Patients are randomized to either: GLN group who receive enteral L-GLN at 0.5 g/kg/day when patient is found to have a BMI less than 35 and when BMI is at least 35, patients are prescribed 0.5 g/kg/day calculated using adjusted body weight; or a control group receiving maltodextrin given in an isocalorically fashion. Given large sample size across many participating burn units, a pragmatic design is utilized. Consistent with this, standardized nutrition practices across sites are currently initiated; however, other efforts to define standards of care for additional burn care aspects are not practical and are not prescribed. As the protocol publication describes in detail [14▪▪], mortality at 6 months is the primary outcome for the RE-ENERGIZE study. Time to discharge alive from hospital is the primary secondary outcome. Quality of life via the Short Form-36 (SF-36) physical function domain of the activities of daily living and activities of daily living (instrumental), length of stay in ICU and length of stay in hospital, time on mechanical ventilation, occurrence of Gram-negative bacteremia, and mortality in hospital are also key measured outcomes. The RE-ENERGIZE trial is aggressively enrolling at this time worldwide and we look forward to the results of this key trial that will define the paradigm of GLN use in burn injury.

CONCLUSION

As stated, three recent meta-analyses have confirmed traditional GLN-complemented TPN is safe, reduces mortality and improves outcome in ICU patients when used via package insert and guideline parameters [7,8,9▪▪] (see Table 1). Currently available TPN amino acid mixtures inexplicably continue to be incomplete and only contain 19 amino acids. The conspicuous omission of GLN has previously been only because of stability issues of GLN in solution, which has long been addressed by stable dipeptide formulations. It seems at the very least, TPN solutions should contain basic nutritional levels of GLN, as we would think to exclude one of the other amino acids in routine parenteral nutrition formulations. Further, GLN complementation of parenteral nutrition at nutritional doses (and as part of complete nutrition) has been shown to be safe and to largely improve outcomes over many years. Patients in need of TPN, burns, trauma or malignancies, may continue to benefit from GLN, administered either intravenously at less than 0.35 g/kg/day or enterally at less than 0.5 g/kg/day.

Clearly, there are patients who should not receive GLN, beyond perhaps basal TPN levels (which are largely yet to be created) and that which occurs in enteral nutrition formulas as part of enteral nutrition protein content. As defined by the REDOXs trial outcomes [20] the patient groups who should not receive GLN currently include: patients in early phase of sepsis and septic shock; patients with hemodynamic instability with increasing doses of vasopressors; patients in renal failure (especially without dialysis or continuous renal replacement therapy).

Key future directions for GLN research are summarized in Table 2. These include potential randomized controlled trials of GLN-supplementation as part of TPN or enteral nutrition at doses less than 0.5 5 g/kg/day of total GLN in patients undergoing CRRT. CRRT is known to deplete GLN and other amino acids and results from the REDOXs trial indicate an interesting dichotomy with regard to

Table 2. Potential future research questions for use of glutamine in clinical setting

(1) Role of GLN-complementation in continuous renal replacement therapy (CRRT)? – especially when prolonged: due to ongoing glutamine losses
(2) Role of GLN-complementation TPN in postsurgical cancer patients requiring prolonged TPN (>7 days) in ICU or during hospital stay? – due to potential increased GLN deficiency in oncology patients
(3) Role of GLN-complementation in burn and trauma patients? – RE-Energize trial ongoing
(4) Mechanism of elevated GLN levels in ICU patients and potential role of untreated admission renal failure in potential for risk with GLN administration?

GLN, glutamine.

renal failure. Subgroup analysis reveals GLN administration in early renal failure increased 28-day mortality in patients with admission renal dysfunction who did not receive dialysis [OR for mortality (95% CI): 3.9 (1.7–9.0)] [21]. Interestingly, this mortality risk was potentially reversed when patients with admission renal failure received dialysis during ICU [OR for mortality (95% CI): 0.4 (0.2–1.2)]. This data may hypothesize that patients with admission renal failure undergoing early CRRT may benefit from GLN administration. Significant additional research is needed to test this hypothesis. It appears the significant risk that occurs with early renal failure from GLN administration may be ameliorated by dialysis (likely CRRT) treatment and indicate a need for GLN administration, possibly because of ongoing GLN loss from CRRT.

Other areas of research that need to be explored is the specific role of GLN-supplemented TPN in postsurgical cancer patients requiring prolonged TPN (>7 days) in ICU or during hospital stay. A number of key positive trials of GLN supplementation of parenteral nutrition in the ICU involved significant numbers of oncology patients who are likely to have the lowest GLN levels because of depletion by cancer or tumor (i.e. Dechelotte *et al.* [22]). If the GLN deficiency hypothesis that GLN-deficient patients are most likely to benefit from GLN supplementation is correct, then one could hypothesize oncology patients would be most likely to benefit. Interestingly, these patients were specifically excluded from the recent negative GLND trial of GLN-supplemented TPN in the surgical ICU [23]. Specifically, patients in this trial were excluded if they had a 'current malignancy requiring surgery as the study qualifying operation or receiving an active regimen of chemotherapy and/or radiotherapy to treat a previously diagnosed malignancy'. Thus, this patient group demands further investigation as they are most likely to benefit from GLN administration once stabilized in ICU or postoperatively.

Finally, the role of GLN needs to be explored in burn and trauma patients. As described, a large trial of EN GLN supplementation in burns is ongoing. Significant benefit was also observed in the seminal Houdijk *et al.* trial of oral GLN supplementation in trauma patients published in *The Lancet* [24]. This data has not been studied in a more definitive, multicenter fashion in trauma patients.

Thus, it seems the GLN story in surgery, cancer, and critical illness should and will continue. Current data indicates whenever GLN is used appropriately in the right patients, at the right dose, and at the right time, the GLN story is still relevant to patient outcomes! Further large clinical trial and mechanistic translational research is ongoing and much more is needed in a range of areas and patients for the next chapter of the GLN story to be written.

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