Glutamine: Where to from here?

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Introduction

• Most abundant amino acid in the body.
• Normal plasma concentration 500 – 900 μmol/l.
• De Novo synthesis ➔ skeletal muscle (50 – 80g/day)
• Exported to the splanchnic area ➔ enterocytes & immune cells.
• Conditionally essential amino acid ➔ Critical illness
  • Production not altered
  • Insufficient to keep up with demand
Rationale for Supplementation

- Low plasma Glutamine concentration (< 420 μmol/l) at time of ICU admission = independent predictor of unfavorable outcome.
  - ± ⅓ of ICU patients ➔ low plasma Gln levels

- Similar prediction for high plasma Glutamine concentration (>930 μmol/l)
  - Much smaller group of ICU patients ➔ high plasma Gln levels
  - Acute liver failure often associated with high/very high plasma Gln concentrations
  - Chronic/acute-on-chronic liver failure not accompanied by high plasma gln
  - Reported in terminal patients with multiple organ failure, not necessarily including liver failure.

Rodas et al, Clinical Science (2012) 122, 519 - 597
Wernerman, Critical Care (2014), 18:214
Rationale for Supplementation

High APACHE II or SOFA score not statistically associated with glutamine depletion

- Risk for a given patient → increased if altered plasma Gln level is present

Wernerman, Critical Care (2014), 18:214
- Included 40 RCT’s.
- Included ALL patients – surgical, critically ill and mixed
- 3170 patients in total
- Critically ill patients showed significant reduction in mortality
- Across all patient types – significant reduction in infections
- Significant reduction in hospital LOS across all patient types
- Only trials giving >0.2g/kg/day for >9 days showed significant reduction in short-term mortality, infections and LOS.
A Randomized Trial of Glutamine and Antioxidants in Critically Ill Patients

Daren Heyland, M.D., John Muscedere, M.D., Paul E. Wischmeyer, M.D., Deborah Cook, M.D., Gwynne Jones, M.D., Martin Albert, M.D., Gunnar Elke, M.D., Mette M. Berger, M.D., Ph.D., and Andrew G. Day, M.Sc., for the Canadian Critical Care Trials Group
REDOXS

– Largest RCT on Gln to date
– 1223 critically ill patients from 40 ICU’s.
– Mechanically ventilated patients with 2 or more of the following:
  – Respiratory dysfunction
  – Hypoperfusion requiring vasopressors
  – Acute renal failure
  – Low platelet count
– Randomized to receive one of four interventions
  • 30g Enteral Gln + 0.35g/kg IV Gln
  • IV and enteral anti-oxidants
  • Gln PLUS anti-oxidants
  • Placebo

Heyland et al, NEJM 2013
REDOXS

• Non-significant trend towards increased 28 day mortality in Gln group (OR 1.28 p=0.05)
• Significantly higher in-hospital and 6 month mortality in Gln group.
• Significantly increased LOS – Hospital and ICU in Gln group.

Heyland et al, NEJM 2013
REDOXs

• Criticism
  – Majority medical patients (75%)
  – High dose of glutamine administered
  – Combination enteral and IV gln
  – Timing of administration (patients in shock)
  – Majority of patients not on PN (80% EN)
  – Patients were poorly fed
    • Significant increase in mortality <½ requirements
  – Included patients with renal failure (>35% on admission)
    • Significant increase in mortality with baseline renal dysfunction (OR 2.75)
High-Protein Enteral Nutrition Enriched With Immune-Modulating Nutrients vs Standard High-Protein Enteral Nutrition and Nosocomial Infections in the ICU: A Randomized Clinical Trial

Arthur R. H. van Zanten, MD, PhD; François Sztark, MD, PhD; Udo X. Kaisers, MD, PhD; Siegfried Zielmann, MD, PhD; Thomas W. Felbinger, MD, PhD; Armin R. Sablotzki, MD, PhD; Jan J. De Waele, MD, PhD; Jean-François Timsit, MD, PhD; Marina L. H. Honing, MD, PhD; Didier Keh, MD; Jean-Louis Vincent, MD, PhD; Jean-Fabien Zazzo, MD, PhD; Harvey B. M. Fijn, MD; Laurent Petit, MD, PhD; Jean-Charles Preiser, MD, PhD; Peter J. van Horssen, PhD; Zandrie Hofman, MSc
Metaplus

- Multi-centre RCT
- 301 Adult patients
- Expected to be ventilated and require nutrition support for >72 hours
- Randomized to receive HP or HPIM enteral nutrition
- Subgroups:
  - Medical, surgical, trauma patients

Van Zanten, JAMA 2014
Metaplus

- Treatment group received Enteral Gln 0.3 – 0.5g/kg with other immune modulating nutrients (Omega 3 FA’s and antioxidants)

- Results:
  - No significant difference in incidence of new infections
  - Significant increase in 6mnth mortality in the medical IMHP group
  - No significant difference in mechanical ventilation or LOS

- Adjusting for age and APACHE II score ➔ significantly higher 6mnth mortality in IMHP vs HP group

Van Zanten, JAMA 2014
4.1.c Composition of EN: Glutamine

2015 Recommendation: Based on 3 level 1 and 8 level 2 studies, we recommend that enteral glutamine **NOT be used in critically ill patients**.

2015 Discussion: The committee reviewed the aggregated results with the inclusion of 1 new small study in burns (Pattenshetti 2014) and a large study in mixed ICU patients including trauma patients in which the glutamine was given in addition to antioxidants and fish oils (van Zanten 2014). It was noted that there was no effect on hospital mortality, except in the small subgroup of burn patients in which enteral glutamine was associated with a significant reduction in mortality and a trend towards a reduction in infections. Since the data on trauma patients was not available from some studies, it was hard to elucidate a treatment effect in this subgroup. There was a significant reduction in hospital length of stay data overall and in burn patients but the data points were sparse with large confidence intervals. The cost and feasibility considerations were favourable despite potential limitations in acquiring the product. However, the committee was concerned about the higher mortality seen in patients receiving EN glutamine in the large van Zanten study, particularly in the subgroup of medical patients. It was also noted in our meta analyses that much of the benefit of enteral glutamine may be attributed to "small-study effects (1). Given this and the previously mentioned harm associated with glutamine in patients with shock and multi-organ failure in the REDOXS study, it was decided to downgrade the recommendation to enteral glutamine **NOT being used in all critically ill patients**. We noted the positive treatment effect in the studies of burns patients; however, the committee did not want to not make a separate recommendation in burn patients until the results of the multicentre RE-ENERGIZE Study in burns patients are available.
9.4 Composition of Parenteral Nutrition: Glutamine Supplementation

Recommendation:
Based on 4 level 1 studies and 13 level 2 studies, when parenteral nutrition is prescribed to critically ill patients, parenteral supplementation with glutamine, where available, is strongly recommended. There are insufficient data to generate recommendations for intravenous glutamine in critically ill patients receiving enteral nutrition.
2013 Recommendation: Based on 9 level 1 studies and 19 level 2 studies, when parenteral nutrition is prescribed to critically ill patients, parenteral supplementation with glutamine should be considered. However, we strongly recommend that glutamine NOT be used in critically ill patients with shock and multi-organ failure (refer to section 9.4 b Combined Parenteral and Enteral Glutamine. There are insufficient data to generate recommendations for intravenous glutamine in critically ill patients receiving enteral nutrition.

2013 Discussion:
It was noted that with the addition of 11 new trials (Tian 2006, Zhang 2007, Ozguliekin 2008, Yang 2008, Eroglu 2009, Perez-Barcena 2010, Andrews 2011, Cekman 2011, Grau 2011, Wernerman 2011 & Ziegler 2012), there were weaker signals for a reduction in overall mortality & infectious complications and yet a strong treatment effect of IV supplemented glutamine on hospital mortality and ICU and hospital length of stay remained.  It was further noted that a few large scale multicenter randomized trials of IV glutamine had failed to demonstrate a convincing positive effect (Andrews 2011, Wernerman 2011, Ziegler 2012). The committee agreed that the REDOXS study (Heyland 2012), which uses combined EN and PN glutamine supplementation at high doses, should not be included in this section due to its different intervention and patient population (shock and multi-organ failure patients). However, it was felt that the results of this 1200 patient multicentre trial, which suggested a significant safety concern, could not be ignored. Coupled with a diminished signal of benefit and a potential increase in harm, the committee downgraded the recommendation for IV glutamine to “should be considered.”
9.4b Combined Parenteral and Enteral Glutamine Supplementation

NEW SECTION in 2013

Recommendation: Based on one level 1 study, we strongly recommend that high dose combined parenteral and enteral glutamine supplementation NOT be used in critically ill patients with shock and multi-organ failure.

Discussion: The committee agreed that due to the unique methodology of the REDOXS trial (Heyland, 2013), in which combined parenteral and enteral glutamine supplementation was provided, this study not be included with other studies of parenteral glutamine supplementation in section 9.4a. The committee noted the large multicentre nature of this trial in which there was an increase in mortality across all time points with the use of high dose glutamine supplementation in severely ill patients with at least two organ failures.
9.4a Composition of Parenteral Nutrition: Glutamine Supplementation

2015 Recommendation: Based on 31 studies (10 level 1 studies and 21 level 2 studies), when parenteral nutrition is prescribed to critically ill patients, we recommend parenteral supplementation with glutamine NOT be used. There are insufficient data on the use of intravenous glutamine in critically ill patients receiving enteral nutrition but given the safety concerns we also recommend intravenous glutamine not be used in enterally fed critically ill patients.

2015 Discussion: The committee noted that with the inclusion of 3 new trials (Perez Barcena 2014, Grîntescu 2014 and Carrol 2004), the effect on overall mortality and infections did not change since the last update and there is still only a trend for reduction in these outcomes. Of the 6 multicentre studies (Andrews 2011, Wernerman 2011, Ziegler 2012, Grau 2011, Dechelotte 2006, Perez Barcena 2014), 4 failed to show a strong positive effect on mortality or infections. The positive signals for reduction in ICU, hospital LOS and mechanical ventilation were noted to have significant statistical heterogeneity. The use of free glutamine (L-glutamine) vs dipeptides (L-alanyl-L-glutamine) did not alter the effect on mortality, infections or LOS and the same was true for isonitrogenous vs. non-isonitrogenous studies. The committee was concerned about the signals of harm for the use of combined intravenous and enteral glutamine in critically ill patients with shock and organ failure from the REDOXS study and the higher mortality seen in medical patients and an increase in 6 month mortality in patients receiving enteral glutamine in the large van Zanten study. Furthermore, the difficulty in accurately distinguishing the timing when a non septic patient may become septic was acknowledged, it was therefore recommended that intravenous glutamine not be used in the critically ill population. Considering this and the minimal data in burns and trauma patients, the committee chose not to make a recommendation in these specific ICU populations.
9.4b Combined Parenteral and Enteral Glutamine Supplementation

2015 Recommendation: Based on one level 1 study and 1 level 2 study, we recommend that high dose combined parenteral and enteral glutamine supplementation NOT be used in critically ill patients

2015 Discussion: The committee noted the inclusion of one single centre study in septic, malnourished ICU patients in which patients were given a total of 30 grams of glutamine via the enteral and parenteral route (Koskal 2014). When the data from this study was combined with the earlier study (Heyland 2014), there was no effect on mechanical ventilation. The lack of reporting of other clinical outcomes in this study was acknowledged as was the lower dose of administered glutamine compared to the Heyland 2014 study. The committee agreed that the increase of mortality seen across all time points with the use of high dose combined glutamine supplementation in the multicentre study of severely ill patients with at least two organ failures was still a concern, and hence the recommendation against the use of combined enteral and parenteral glutamine was not changed.
Do we know more about Gln?

- Non-medical critically ill patients
- Severe Acute Pancreatitis patients
- Elective Surgery patients
- Burns patients
- Trauma patients
- Optimal/harmful dose
- Combination Enteral and IV Gln
The effect of glutamine therapy on outcomes in critically ill patients: a meta-analysis of randomized controlled trials

Qi-Hong Chen¹, Yi Yang¹, Hong-Li He¹, Jian-Feng Xie¹, Shi-Xia Cai¹, Ai-Ran Liu¹, Hua-Ling Wang² and Hai-Bo Qiu¹*
Chen 2014

- Meta-analysis
- 18 RCT – including REDOXS
- Subgroup analysis performed:
  - Patient population (Medical, Surgical, Mixed)
  - Gln dosage (>0.5g/kg, 0.3 – 0.5g/kg, <0.3g/kg)
  - Mode of nutrition support (EN, PN, EN+PN)
- Influence on mortality and new infections
# Patient population - Mortality

Non-significant trend for reduction in mortality in Surgical ICU patients (23%)

**Figure 4** A subgroup meta-analysis of the effect of glutamine in specific patient populations on the mortality rate (fixed effects modes).

Chen et al, Crit Care 2014
Significant increase in mortality associated with dose >0.5g/kg

Figure 6 A subgroup meta-analysis of the different dosages of glutamine on mortality in critically ill patients (fixed effects modes).

Chen et al, Crit Care 2014
Patient population – New infections

30% Significant reduction in new infections in Surgical Group

Figure 9 A subgroup meta-analysis of the effect of glutamine in specific patient populations on the acquisition of new infections in critically ill patients (random effects modes).

Chen et al, Crit Care 2014
Significant reduction in new infections in patients receiving PN.
Parenteral glutamine supplementation in critical illness: a systematic review

Paul E Wischmeyer¹, Rupinder Dhaliwal², Michele McCall³, Thomas R Ziegler⁴ and Daren K Heyland²,⁵
Wischmeyer 2014

- 26 RCT
- Did not include REDOXS
- Parenteral Gln supplementation
- Critically ill patients
32% significant reduction in hospital mortality

Wischmeyer et al, Crit Care 2014
Significant reduction in Hospital LOS
2.56 days

Wischmeyer et al, Crit Care 2014
Original article

Glutamine supplementation in acute pancreatitis: A meta-analysis of randomized controlled trials

Varsha Asrani a,b, Wai Keat Chang a, Zhiyong Dong c, Gil Hardy d, John A. Windsor a, Maxim S. Petrov a,*
Asrani 2013

• Meta-analysis
• 12 RCT
• Regardless of route on nutrition support or glutamine administration
Mortality

70% significant reduction in mortality

Asrani et al, Pancreatology 2013
42% significant reduction in infectious complications

Fig. 4. Forest plots of pooled estimates of glutamine supplementation on infectious complications in acute pancreatitis.
Intravenous glutamine for severe acute pancreatitis: A meta-analysis

Xin Zhong, Cui-Ping Liang, Shu Gong
Zhong 2013

- 4 RCT (n=190)
- Only RCT with IV gln dipeptide included
74% significant reduction in Mortality
**Hospital LOS**

Significant reduction in hospital LOS

4.85 days

Zhong et al, WJCCM 2013
59% significant reduction in rate of complications
Data from CCPG 2015 – Enteral gln in Burn patients

81% significant reduction in hospital mortality
Data from CCPG 2015 – Enteral gln in Burn patients

Figure 8. Hospital LOS, burns subgroup analysis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>EN Glutamine</th>
<th>Control</th>
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<td>Total (95% CI)</td>
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Heterogeneity: $\tau^2 = 14.70$; $Chi^2 = 4.19$, df = 2 ($P = 0.12$); $I^2 = 52\%$

Test for overall effect: $Z = 3.04$ ($P = 0.002$)

**Significant reduction in Hospital LOS**

9.16 days
Conclusion

• Effect of Gln supplementation differs according to:
  – Patient population
  – Mode of delivery
  – Gln dose
  – Mode of nutrition support

• Critically ill patient populations that will likely benefit
  – Surgical ICU population
  – Severe acute pancreatitis
  – Burns
  – Trauma

• Do not:
  – Exceed 0.5g/kg/day – IV/Enteral/Combination
  – Use in patients with MOF, especially renal or liver failure
  – Use in the absence of sufficient nutrition support
  – Think twice in medical ICU populations
Questions