

Asia Pacific Focus Group Parenteral Nutrition **Glutamine, where do we go from here?**

A high-level scientific forum, the Asia Pacific Focus Group Parenteral Nutrition, was convened in Hong Kong on 8 Nov 2013, to discuss the most current updates regarding the use of IV glutamine in critical care nutrition. Prof. Paul Wischmeyer, an internationally-renowned clinician and researcher from the US, presented a highly interactive discussion on “Glutamine, where do we go from here” with an expert panel composed of health professionals from eight Asian countries, who were invited based on their professional expertise in nutrition therapy in critical illness, and continued commitment to improving the standards of such in their respective countries, coordinated by Prof. Xu Yuan (CSCCM - CSPEN), Mr. Mohammad Jahit Shukri (PENSMA), and Dr. Jesus Fernando Inciong (PhilSPEN) and sponsored by Fresenius Kabi Asia Pacific.

Goal

To optimize patient outcomes in critical illness through the best standards of glutamine use

Objectives

- To review the indications, global guidelines and existing evidence for glutamine use;
- To understand the latest updates regarding use of glutamine in critical illness in medical and surgical patients in the light of recent publications, particularly the REDOXS trial;
- To identify patient factors most appropriate for glutamine therapy; and
- To clarify clinical settings where caution is advised in glutamine use.

Background

Glutamine (Gln) is a conditionally essential amino acid. It is synthesized in the body, but becomes deficient during catabolic stress, such as: during critical illness, after major surgery, and following extreme exercise. In this situation, depleted glutamine levels can result in immune dysfunction that is associated with higher mortality in critically ill patients. Indeed, low glutamine levels have been associated with illness and injury, but beneficial outcomes were reported with glutamine supplementation in studies by Morlion et al, Goeters et al, Dechelotte et al, and Houdijk et al. (1–4)

This can be explained on the basis of the cellular and organ benefits of glutamine, described by Kelly and Wischmeyer (5):

- Enhanced heat shock protein and inflammatory cytokine attenuation through NF- κ B;
- Reduced translocation of enteric bacteria or endotoxins through maintenance of intestinal mucosal barrier;
- Elimination of translocating bacteria through maintenance of lymphocyte function;
- Control of NO formation through hexosamine synthesis;
- Preserved cellular energetics- Increased ATP content through reversal of cytopathic hypoxia;
- Enhanced insulin sensitivity;
- Decreased free radical availability through glutathione synthesis.

Current status of glutamine utilization in clinical practice

Based on the current evidence to date, the patient profiles/ clinical conditions where IV glutamine has been shown to be beneficial are the following:

A. Patients undergoing major surgery for cancer

- Post-operative PN + IV-Gln is beneficial vs std PN after major surgery for GI cancer (1,6–9) as presented in the meta-analysis by Novak et al where the glutamine dose was 0.2-0.35 g/kg bw/day dipeptide (10)
- IV-Glutamine in PN for abdominal surgery – meta-analysis (11)
 - Improved nitrogen balance (CI[2.95, 13.7], p=0.002)
 - Reduced infectious morbidity (CI[0.06, 0.93], p=0.04)
 - Shortened hospital LOS (CI[-5.26, -1.84], p<0.00001)
- Impact of glutamine dipeptide on surgical outcomes – meta-analysis (12)
 - Reduced hospital LOS with post-op Gln-TPN (p=0.02)
 - Reduced infections with post-op Gln-TPN (p=0.24)
- Gln-PN improves outcomes in surgery - meta-analysis (13)
 - Reduces hospital LOS (4 d for alanyl-glutamine, p<0.001)
 - Reduces infectious complications (p=0.02)

B. Severe burns/ trauma patients

- Severe burns (~50 % TBSA) (14)
 - Supplemental IV Gln (0.57g/kg/d) led to:
 - Improved prealbumin (p<0.04)
 - Reduced CRP (p<0.01)
 - Reduced Gram-negative bacteremia (p<0.04)
- Adult burn patients given EN glutamine (15)
 - Decreased mortality and infectious morbidity (per intention to treat: p<0.05; per protocol: p<0.01)
- Enteral glutamine in burns : other RCTs (0.35-0.5 g/kg bw /day)
 - Reduced wound infections and hospital LOS (p=0.003) (16)
 - Improved wound healing and shorter hospital stay (p<0.05) (17)
 - Improved wound healing, less infections, shorter LOS (p=0.041, p<0.05, p=0.026 respectively) (18)
 - Enteral Gln reduces infection in trauma (4)

C. ICU patients/ complicated surgery with IV Gln supplementation of TPN

- IV Gln reduces mortality up to 6 months in ICU patients (2,19)
- French multicenter study (3)
 - TPN supplemented with Ala-Gln dipeptide in ICU patients is associated with a reduced rate of infectious complications and better metabolic tolerance
 - *More than half of patients underwent major oncologic surgery
- Spanish multicenter study (20)
 - TPN supplemented with alanyl-glutamine in ICU patients is associated with a reduced rate of infectious complications and better glycemic control
- Scandinavian multicenter trial (21)
 - Multicenter RCT, 413 ICU patients – reduced ICU mortality
- 2009 Meta-analysis: GLN-supplementation of TPN reduces mortality – 29% reduction of mortality (22)

D. Global guidelines

- ESPEN (23)

“When PN is indicated in ICU patients the amino acid solution should contain 0.2–0.4 g/kg/day of L-glutamine (e.g. 0.3–0.6 g/kg/day alanyl-glutamine dipeptide). (Grade A)”
- ASPEN - SCCM (24)

“When PN is used in the critical care setting, consideration should be given to supplementation with parenteral glutamine. (Grade: C)
- CCPG 2009 – 2013 (25)

“When parenteral nutrition is prescribed to critically ill patients, parenteral supplementation with glutamine, where available, is strongly recommended.”
After publication of the REDOXs trial, the 2013 recommendation was revised to:
“When parenteral nutrition is prescribed to critically ill patients, parenteral supplementation with glutamine should be considered.”

Summarized above was the status of previously established glutamine utilization at the time that the REDOXs trial was published in NEJM in April 2013.

REDOXS trial (REducing Deaths from OXidative Stress) (26)

“A Randomized Trial of Glutamine and Antioxidants in Critically Ill Patients” (REDOXS trial)

- 1223 patients, 40 ICUs in Canada, US, Europe
- Multicenter RCT of glutamine* and antioxidants in critical illness (*only glutamine aspects to be discussed here)
- Very severely ill patients (APACHE II score about 26)
 - Respiratory failure
 - Renal failure (>30%)
 - Septic shock (98%)
 - Low platelet count
- Administration of study supplements parenterally & enterally
- Early administration, within 24 hr of admission
- Independently from clinical nutrition
- Glutamine dose and route of administration
0.35 g/kg glutamine (IV) plus 30 g/d glutamine (enterally)
= 0.5 g/kg Ala-Gln (Dipeptiven) IV plus 42 g/d glutamine-dipeptide (EN)
- Antioxidants: IV: selenium, plus enteral: selenium, Vit. C+E, zinc, β-carotene

Results

- Primary outcome parameter: 28-day mortality
 - Trend for increased 28 day mortality in glutamine groups (NOT statistically significant)
- Secondary outcome parameters:
 - Significantly higher hospital mortality & 6-months mortality in glutamine groups

REDOXS analysis

Several important factors made the REDOXS study entirely different from all other previous studies that had shown benefit with the use of glutamine:

1. Glutamine was administered to patients in renal failure (approx. 36%);
2. Glutamine was administered to patients in shock (approx. 98%);
3. Glutamine dose was the largest dose ever given- (up to double the recommended dose);
4. Glutamine was delivered through both IV and enteral routes; and
5. Glutamine administration was dissociated from complete clinical nutrition.

Thus, REDOXS was an exploratory study, investigating a previously untested use of glutamine with new “off-label“ indications & doses:

- Extremely severe critical illness in ICU (shock, MOF, esp. renal failure)
- Huge doses (double) combining IV + enteral routes, separate from nutrition therapy

The REDOXS authors sought, neither to confirm nor disprove the previously reported results of glutamine therapy, but rather to investigate an entirely different use of glutamine. The negative results merely showed that the untested clinical use beyond accepted indications and dosage were not successful. In fact, the package insert (PI), specifically lists the indication for IV glutamine: “*as part of a clinical nutrition regimen in patients in hypercatabolic or hypermetabolic stress*” and the contraindications to the use of IV glutamine (Dipeptiven) to include the following: “*severe renal insufficiency, severe hepatic insufficiency, severe metabolic acidosis*” (as found in septic shock). It might therefore be said that the negative results of REDOXS actually succeeded in validating these contraindications.

Implications on clinical practice

1. Patients likely to benefit from glutamine therapy, at the recommended dose of 0.2–0.4 g/kg/day of L-glutamine or 0.3–0.6 g/kg/day alanyl-glutamine dipeptide (ESPEN) (23) or 0.3-0.5g/kg/day alanyl-glutamine dipeptide (PI), and together with clinical nutrition therapy:
 - ICU patients receiving PN
 - Major surgery patients (esp cancer) receiving PN (Cancer patients are more glutamine deficient)
 - These ICU/ surgical patients should be hemodynamically stable, not in renal failure, not in hepatic failure
 - These are in accordance with the previously established use of glutamine, as recommended by global guidelines, and in accordance with the product instructions (PI) or Summary of Product Characteristics (SmPC), also referred to as “on-label” use.

2. Patients at risk of harm from glutamine administration, esp. in excessive doses and dissociated from adequate clinical nutrition support:
 - Renal failure*, as manifested by any of the following parameters:
 - Creatinine >171 mmol/L
 - Rise in creatinine >80 mmol/L from baseline creatinine
 - Creatinine clearance <25ml/min (according to Dipeptiven contraindications)
 - Urine output < 500 ml/24 hr or < 80 ml/last 4 hr

**Glutamine mortality risk in REDOXS was primarily related to renal failure*
 - Hepatic failure, as manifested by:
 - Ammonia levels over 50µmol/L and rising; or
or steady at 100 and above
 - Based on REDOXS results, bilirubin and transaminases are not reliable indices in the context of glutamine administration
 - Unresuscitated shock or shock requiring significant or escalating vasopressor support
 - Increasing lactate (> 2-3mmol/L) despite adequate fluids
 - MvO² saturation < 70% (NOT caused by low Hct)
 - Low mean arterial BP (< 60mmHg) on high or increasing doses of vasopressors
 - A patient may be admitted in shock, but if these parameters stabilize during resuscitation and it is deemed appropriate for nutrition therapy to be started, then glutamine may be given
 - On the other hand, patients remaining in shock despite resuscitative measures should not be given nutrition, and consequently should not be given glutamine. (Note: Such patients rarely survive > 48 hrs)

Glutamine publications after REDOXS

1. An updated glutamine meta-analysis presented by P Wischmeyer at ASPEN 2013 raises the previous number of 17 RCTs in 2009 to 26 in 2013. The new RCTS include Grau 2011, Andrews 2011, Wernerman 2011, Eroglu 2009, Perez Barcena 2010, Ozgultekin 2008, Ziegler 2013, Cekman 2011 + 3 Chinese RCTs.

- 26 studies identified in > 2300 pts
- ICU pts with diagnoses ranging from pancreatitis, trauma, burns and sepsis
 - 22 studies gave GLN with PN; 4 studies gave GLN with only EN
- 33% decrease in mortality (compared to 29% in the 2009 meta-analysis)
- 2.6 days shorter hospital LOS

Conclusions of the new meta-analysis:

- Parenteral glutamine leads to significant improvement in:
 - Hospital mortality (33%)
 - Hospital LOS (2.6 days)
- Trend towards improvement with strong signals for benefit in:
 - Infections and ventilator-associated pneumonia
 - ICU LOS
- Parenteral glutamine supplementation of parenteral nutrition is safe and continues to reduce mortality and improve outcome in 26 trials of ~2300 patients (cite PW ASPEN)

2. New meta-analysis in abdominal surgery (27)

- RCTs = 16; n = 773
- Perioperative PN-Glutamine:
 - Shortened LOS (CI[-5.51, -0.82], p=0.008)
 - Reduced postoperative infectious complications (CI[0.32, 0.72], p=0.0004)
 - Improved nitrogen balance (CI[3.16, 11.63], p=0.0006)

3. One of the most recent meta-analysis of PN glutamine (28)

- 40 RCTs, 3107 patients: surgery, critical illness, (mixed)
- Reduced mortality in the critically ill (p=0.024)
- Mortality reduction is usually not seen in surgery, as mortality is usually quite low
- Reduced infection risk in all patients (p=0.009)
- Reduced hospital LOS in all patients (p=0.001)
- High end of recommended dose was used (> 0.3 g/kg bw/day of glutamine dipeptide)
- Conclusion: Significant reduction of short term mortality, infections and length of stay

Pharmacoeconomic benefits of glutamine supplementation (29)

- Effectiveness and cost-effectiveness of supplemental glutamine dipeptide in TPN in critically ill patients
 - Reduced mortality rate (24.6% ± 1.6% vs. 34.5% ± 2.1%)
 - Reduced infection rate (13.8% ± 2.9% vs. 18.8% ± 3.9%)
 - Reduced hospital LOS (24.9 ± 0.3 vs. 26.0 ± 0.3 days)
 - Lower total cost/pt (23,409 ± 3,345 vs. 24,161 ± 3,523 Euro)
 - Achieves cost containment of -5,844 ± 1,162 € per patient discharged alive from ICU compared to standard PN
 - The initial figures were based on a 2008 meta-analysis, but a new pharmacoeconomic analysis was updated using data from the 2013 Bollhalder meta-analysis, and the total savings per patient actually increases. (*Presented at ESPEN 2013 in Leipzig*)

Over-all Conclusions

In considering the currently existing evidence of benefit for glutamine administration in critical illness and surgery, it is important to identify the realistic implications of the REDOXS trial on clinical practice:

- Glutamine administration at the doses studied, in unresuscitated shock, dissociated from adequate clinical nutrition support does not improve clinical outcomes in severe critical illness with multi-organ failure.
- When considering multi-organ failure, glutamine mortality risk was primarily related to renal failure and unresuscitated shock, and of course the excessive dose.
- In this connection, there are no specific objections to the combination of EN glutamine and IV glutamine, as long as the recommended dose is not exceeded. Typically, however, the administration of IV glutamine together with PN is most commonly used and the dose should be 0.2–0.4 g/kg/day of L-glutamine (e.g. 0.3–0.6 g/kg/day alanyl-glutamine dipeptide.*

*Intravenous glutamine has to be administered in accordance with the local product information: The registration of IV glutamine comprises a daily dosage range of up to 0.4g L-alanyl-L-glutamine/kg/BW/d (corresponding up to 2.0 ml Dipeptiven/kg BW/d = 0.28 g L-glutamine) or up to 0.5g L-alanyl-L-glutamine/kg/BW/d (corresponding up to 2.5 ml Dipeptiven/kg BW/d = 0.35 g L-glutamine).

- Glutamine still saves lives and improves outcomes, but should not be given in patients with:
 - Renal or hepatic failure
(*See Implications on clinical practice, Sec. 2 above*)
 - Unresuscitated shock requiring vasopressor support
(*See Implications on clinical practice, Sec. 2 above*)
 - Dissociated from clinical nutrition
- The clinical benefits of glutamine supplementation are also associated with considerable pharmacoeconomic benefits.

Expert Panel Members

Australia:

Frank van Haren, Canberra Hospital, A/Professor in Intensive Care and Gastroenterology

China:

Yuan Xu, Beijing Tongren Hospital, China, Professor of ICU, specializes in Emergency & Nutrition Therapy Services; representative of CSPEN/ CSCCM

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Bin Ouyang, The First Affiliated Hospital of Sun Yat-sen University, Associate professor of ICU, specializes in overall management of ICU & ICU nutrition support

India:

Pravin Amin, Bombay Hospital, Mumbai, Intensivist, past Chairman, ISCCM

Deepak Govil, Medanta Hospital, New Delhi, Intensive Care specialist

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Indonesia:

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Malaysia:

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Philippines:

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Thailand:

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