Parenteral Glutamine in ICU: Where Do We Go From Here?

Paul Wischmeyer M.D.
Associate Chair, Clinical and Translational Research Director, Nutrition Therapy Service Professor of Anesthesiology University of Colorado SOM
One Size
Does NOT Fit All...
Madelyn W. - 72 yr old with hx of CHF on lasix recovering from hip fx...

Feels like heart is racing intermittently...labs/EKG ordered...
Madelyn W. - 72 yr old with hx of CHF on lasix recovering from hip fx...

HR: 150 - 170 with BP: 78/50!
Atrial Fibrillation
Madelyn W. - 72 yr old with hx of CHF on lasix recovering from hip fx...

Beta-Blocker given...
Madelyn W. - 72 yr old with hx of CHF on lasix recovering from hip fx...

Heart Rate slows to 85...and BP to 120/60
Samuel R. - a 44 yr. old Male with Colon Cancer Post-Colectomy...
Samuel R. - a 44 yr. old Male with Colon Cancer Post-Colectomy...

Feels like heart is racing intermittently...labs/EKG ordered...
Samuel R. - a 44 yr. old Male with Colon Cancer Post-Colectomy...

HR: 150 - 170 with BP: 78/50!
Beta-Blocker?
No!
Wolff Parkinson White
One Size Does NOT Fit All...
We Don’t Give The Same Drug To Every Patient At All Times...
Why Would We Give The Same Nutrients At All Times?...
We Must Study Our Nutrients...

Like Other DRUG THERAPY!!
Glutamine Still Improves Outcome!
In the RIGHT Patients...
We Can Finally Tell You When To Use GLN...

And When Not To...
Phases of Metabolic/Inflammatory Response to Critical Illness and Surgery

- Acute phase (1st 48-72 h Post ICU-Admission)
- Chronic phase
- Recovery Phase

Pre-injury

Change from baseline

+ time

-
How Did We Get Here?...
Glutamine Science and Pharmacology
GLN: Conditionally Essential Amino Acid?

GLN levels drop:
- After major surgery
- During critical illness

Low GLN levels associated with:
- Increased Oxidant Stress
- Heat Shock Protein Impairment
- Immune/Gut Barrier Dysfunction

Higher mortality in critically ill patients!
Cellular and Organ Benefits of Glutamine

Enhanced insulin sensitivity

Critical Illness

Glutamine Therapy

Decreased Oxidant Stress

Glutathione Synthesis

Maintenance of Intestinal Mucosal Barrier

Reduced Translocation Enteric Bacteria or Endotoxin

Elimination of Translocating Bacteria

Enhanced Heat Shock Protein

Inflammatory Cytokine Attenuation

NF-KB

Glutamine Pool (GLN)

Fuel for Enterocytes

Maintenance of Lymphocyte Function

Fuel for Lymphocytes

Preserved Cellular Energetics - ATP content

Enhanced insulin sensitivity

Control of NO formation (Anti-inflammatory)

Reversal of Cytopathic Hypoxia

Hexosamine Synthesis

Nucleotide Synthesis

Glutamine Therapy

Clinical Data for GLN

Who Do We Know GLN Helps...
Who Does GLN Help?

- Cancer Pts undergoing Major Surgery
- Severe Burns/Trauma Pts
- Complicated Surgery, ICU Pts?
Who Does GLN Help?

- Cancer Pts undergoing Major Surgery
- Severe Burns/Trauma Pts
- Complicated Surgery, ICU Pts?
Post-operative TPN + IV-Gln Improves Outcome in Post-Operative Cancer Pts
(0.2-0.35 g/kg bw/day dipeptide)

Post-operative PN + GLN is beneficial vs std TPN after major surgery for GI cancer:

Mrlion 1998,
Powell-Tuck 1999
Jiang 1999,
Fürst 1999 + Mertes 2001
Jacobi 2001, Karwowska 2000,
Di Cosmo 2000...
Post-operative TPN + IV-Gln Improves Outcome in Post-Operative Cancer Pts
(0.2-0.35 g/kg bw/day dipeptide)

Novak et al (Crit Care Med 2002, meta-analysis)
Significant reduction in hospital stay and infectious complications!
Reduced LOS with Post-Op Gln-TPN

<table>
<thead>
<tr>
<th>Study</th>
<th>Glutamine</th>
<th>Control</th>
<th>WMD</th>
<th>Weight %</th>
<th>WMD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>mean(sd)</td>
<td></td>
<td></td>
<td>(95%CI Random)</td>
</tr>
<tr>
<td>Exner</td>
<td>15</td>
<td>17.00(13.00)</td>
<td>-0.30</td>
<td>-11.54,10.94</td>
<td>1.9</td>
</tr>
<tr>
<td>Jiang ZM(Asia-CN)</td>
<td>30</td>
<td>12.50(5.10)</td>
<td>-3.90</td>
<td>-7.03,-0.77</td>
<td>11.5</td>
</tr>
<tr>
<td>Li HY(Asia-CN)</td>
<td>20</td>
<td>10.80(2.61)</td>
<td>-2.22</td>
<td>-4.90,-0.35</td>
<td>15.8</td>
</tr>
<tr>
<td>Liang CH(Asia-CN)</td>
<td>12</td>
<td>17.80(4.20)</td>
<td>-1.00</td>
<td>-4.87,2.87</td>
<td>9.4</td>
</tr>
<tr>
<td>Meritas</td>
<td>15</td>
<td>12.80(2.60)</td>
<td>-4.70</td>
<td>-3.15,-1.25</td>
<td>10.5</td>
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<tr>
<td>Morlion</td>
<td>15</td>
<td>16.50(0.72)</td>
<td>-6.20</td>
<td>-7.77,-6.83</td>
<td>16.9</td>
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<tr>
<td>Neri</td>
<td>16</td>
<td>11.50(2.50)</td>
<td>-3.50</td>
<td>-5.38,-1.62</td>
<td>15.8</td>
</tr>
<tr>
<td>Yao GX(Asia-CN)</td>
<td>14</td>
<td>10.70(1.50)</td>
<td>-1.40</td>
<td>-2.51,-0.29</td>
<td>15.8</td>
</tr>
<tr>
<td>Subtotal(95%CI)</td>
<td>137</td>
<td>136</td>
<td>100.0</td>
<td>-3.25</td>
<td>4.87,1.62</td>
</tr>
<tr>
<td>Total(95%CI)</td>
<td>137</td>
<td>136</td>
<td>100.0</td>
<td>-3.25</td>
<td>4.87,1.62</td>
</tr>
</tbody>
</table>

Test for heterogeneity chi-square=27.48, df=7, p=0.0003
Test for overall effect z=3.92, p=0.00009
Reduced Infections with Post-Op Gln-TPN

Comparison: Infection
Outcome: Glutamine vs. control

<table>
<thead>
<tr>
<th>Study</th>
<th>Glutamine (n/N)</th>
<th>Control (n/N)</th>
<th>RR (95% CI Fixed)</th>
<th>Weight %</th>
<th>RR (95% CI Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chen SL (Asia-CN)</td>
<td>1 / 15</td>
<td>2 / 15</td>
<td>0.50 [0.05, 4.94]</td>
<td>5.4</td>
<td>0.50 [0.05, 4.94]</td>
</tr>
<tr>
<td>Cheng AQ (Asia-CN)</td>
<td>3 / 20</td>
<td>3 / 20</td>
<td>1.00 [0.23, 4.37]</td>
<td>6.0</td>
<td>1.00 [0.23, 4.37]</td>
</tr>
<tr>
<td>Huang MS (Asia-CN)</td>
<td>0 / 11</td>
<td>2 / 11</td>
<td>0.20 [0.01, 3.74]</td>
<td>6.7</td>
<td>0.20 [0.01, 3.74]</td>
</tr>
<tr>
<td>Jiang ZH (Asia-CN)</td>
<td>0 / 30</td>
<td>3 / 30</td>
<td>0.14 [0.01, 2.65]</td>
<td>9.4</td>
<td>0.14 [0.01, 2.65]</td>
</tr>
<tr>
<td>Li HY (Asia-CN)</td>
<td>2 / 20</td>
<td>4 / 20</td>
<td>0.50 [0.10, 2.43]</td>
<td>10.7</td>
<td>0.50 [0.10, 2.43]</td>
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<tr>
<td>Liang CH (Asia-CN)</td>
<td>1 / 12</td>
<td>3 / 12</td>
<td>0.33 [0.04, 2.77]</td>
<td>6.0</td>
<td>0.33 [0.04, 2.77]</td>
</tr>
<tr>
<td>Neri</td>
<td>1 / 16</td>
<td>4 / 17</td>
<td>0.27 [0.03, 2.13]</td>
<td>10.4</td>
<td>0.27 [0.03, 2.13]</td>
</tr>
<tr>
<td>Yao QX (Asia-CN)</td>
<td>0 / 14</td>
<td>2 / 14</td>
<td>0.20 [0.01, 3.82]</td>
<td>6.7</td>
<td>0.20 [0.01, 3.82]</td>
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<tr>
<td>Zhu J (Asia-CN)</td>
<td>5 / 24</td>
<td>10 / 24</td>
<td>0.50 [0.20, 1.25]</td>
<td>26.8</td>
<td>0.50 [0.20, 1.25]</td>
</tr>
<tr>
<td>Zhu MA (Asia-CN)</td>
<td>1 / 15</td>
<td>3 / 15</td>
<td>0.33 [0.04, 2.85]</td>
<td>8.0</td>
<td>0.33 [0.04, 2.85]</td>
</tr>
<tr>
<td>Subtotal</td>
<td>14 / 177</td>
<td>38 / 178</td>
<td></td>
<td>100.0</td>
<td>0.42 [0.24, 0.72]</td>
</tr>
</tbody>
</table>

Test for heterogeneity chi-square = 2.65 df = 9 p = 0.97
Test for overall effect z = -3.15 p = 0.002

Clin Nutr Suppl: 17–23, 2004
2010 meta-analysis of 14 RCTs

Gln-PN Improves Outcome In Surgery

Reduces of Hospital LOS
(4 d for Alanyl-GLN, p<0.001)

> 30% Reduced Infectious Complications
(p=0.02)

JPEN, 34:521-9, 2010
Who Does GLN Help?

- Cancer Pts undergoing Major Surgery
- Severe Burns/Trauma Pts
- Complicated Surgery, ICU Pts?
Glutamine administration reduces Gram-negative bacteremia in severely burned patients: A prospective, randomized, double-blind trial versus isonitrogenous control

31 patients with severe burns (~50 % TBSA)

Randomized To Enteral Feeds w/:
-IV Glutamine (0.5 g/kg/d)
-Control Amino Acid
Glutamine administration reduces Gram-negative bacteremia in severely burned patients: A prospective, randomized, double-blind trial versus isonitrogenous control

Supplemental GLN Led To:

- Improved Prealbumin
- Reduced CRP
- Reduced Gram Negative Bacteremia!
  \[p=0.04\]
Decreased mortality and infectious morbidity in adult burn patients given enteral glutamine supplements: A prospective, controlled, randomized clinical trial*

<table>
<thead>
<tr>
<th></th>
<th>No. of deaths (intention to treat)</th>
<th>No. of deaths (per protocol analysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Glutamine</td>
<td>2*</td>
<td>0*</td>
</tr>
</tbody>
</table>

* = P < 0.05

Decreased mortality and infectious morbidity!
Enteral GLN Reduces Infection in Trauma

Houdijk et al. Lancet 1998
Who Does GLN Help?

- Cancer Pts undergoing Major Surgery
- Severe Burns/Trauma Pts
- Complicated Surgery, ICU Pts?
IV GLN Supplementation of TPN

What Do We Know...
IV Gln Reduces Mortality in ICU patients

*Improved survival,
\[ p = 0.049 \]

- Glutamine 57% *
  - 24/42
- Pre-study 38%
  - 10/26
- Control 33%
  - 14/42

Days from admission to 6 months

Griffiths, Nutrition 1997
L-alanyl-L-glutamine dipeptide–supplemented total parenteral nutrition reduces infectious complications and glucose intolerance in critically ill patients: The French controlled, randomized, double-blind, multicenter study*

Dechlotte et al

<table>
<thead>
<tr>
<th></th>
<th>Ala-GLN</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complicated outcome</td>
<td>24</td>
<td>34</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>(41.4%)</td>
<td>(60.7%)</td>
<td></td>
</tr>
<tr>
<td>Infections (per pt)</td>
<td>0.45</td>
<td>0.71</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Total adverse events</td>
<td>116</td>
<td>159</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

More Then Half Pts Major Oncologic Surgery!
The effect of L-alanyl-L-glutamine dipeptide supplemented total parenteral nutrition on infectious morbidity and insulin sensitivity in critically ill patients

- **Double Blind, 12 Center PRCT**
- **127 ICU Pts (PN for 5-9 days)**
- **0.5 g/kg Ala-GLN vs Iso-N Cont**
- **Most common enrollment Dx- GI Oncology Surgery**
The effect of L-alanyl-L-glutamine dipeptide supplemented total parenteral nutrition on infectious morbidity and insulin sensitivity in critically ill patients

**GLN Therapy:**

- Reduced Nosocomial Pneumonia
- Reduced UTI
- Better Glycemic Control
Scandinavian GLN Trial


Multicenter RCT, 413 ICU Pts

Reduced ICU Mortality!
GLN-supplementation of TPN Reduces Mortality

29% MORTALITY
So...Where Did We Go Next?
“Goliath” Trial
Hard Lessons from “Goliath” Trials?
Now for the rest of story....
Slingers... A Formidable Force...
Why Didn’t Goliath See This Coming?
David, Goliath, and Smiley's People

Acromegaly...

Before Surgery

From Pituitary Tumor
**David and Goliath**

From:
Stanley Sprecher, MD
Department of Radiology, Peninsula Hospital Center
51-15 Beach Channel Drive, Far Rockaway, NY 11691

Editor:
I am confident that I am in the company of many radiologists when I thank Drs Shapiro and Mintz for their interesting “Interlude” (1), which appeared in the January 1990 issue of Radiology. However, I was surprised that they dismissed the second case of head injury described in the Bible (1 Samuel 17:49–50) without any discussion, suggesting their belief that the cause was relatively straightforward. In fact, David’s use of a stone to slay Goliath is a far more complex and problematic situation than Sisera’s death, and it certainly merits discussion. As already pointed out by Drs Rabin and Rabin (2), there is a clear-cut pathophysiologic explanation for how a callow youth like David could have slain the great giant Goliath with a stone.

Undoubtedly Goliath’s great size was due to acromegaly secondary to a pituitary macroadenoma. This pituitary adenoma was apparently large enough to induce visual field deficits by its pressure on the optic chiasm, which made Goliath unable to follow the young David as he circled him. The stone entered Goliath’s cranial vault through a markedly thinned frontal bone, which resulted from enlargement of the frontal paranasal sinus, a frequent feature of acromegaly. The stone lodged in Goliath’s enlarged pituitary and caused a pituitary hemorrhage, resulting in transtentorial herniation and death.

---

Rabin and Rabin (2) postulate that Goliath’s acromegaly was part of a syndrome, type 1 multiple endocrine neoplasia (Wermer syndrome), which is characterized by hyperparathyroidism and pancreatic islet-cell tumors in addition to pituitary adenomas. According to their hypothesis, David’s stone entered Goliath’s brain via a parathyroid brown tumor in the frontal bone. However, I shall defer to Occam’s razor on this point. One disease is sufficient to explain Goliath’s timely demise.

**References**

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What Can We Learn About Glutamine And Critical Care Trials?
Critical Care/Sepsis Clinical Trial History

~ 79 “goliath” clinical trials in sepsis therapies have been conducted in last 20 years

~72 have been negative

~6 have shown “harm”

1 was “positive”
Critical Care/Sepsis Clinical Trial History

1 positive trial of “high-risk” drug

Proven Negative in 2 further trials!
Are we making “Goliath” Mistakes in Our ICU Trials?

Are all critically ill patients the same?
One Size Does Not Fit All...
Can We Still Learn From “Goliath Trials” And the “David” Size Trials Too...
The Question?
In early critical illness with clinical evidence of Multi-Organ Failure:

- What is effect of High Dose GLN
- What is effect of AOXs

...on 28 d mortality?
REducing Deaths from OXidative Stress:
The REDOXS study

1223 Patients, 40 Centers Worldwide

Multicenter RCT of glutamine and antioxidants in critical illness

PI: Heyland/U.S. PI-Wischmeyer

Optimizing the Dose of Glutamine Dipeptides and Antioxidants In Critically Ill Patients: A Phase I dose finding study: (REDOXs)

Heyland, Wischmeyer et al, JPEN, 2007

<table>
<thead>
<tr>
<th></th>
<th>Parenterally</th>
<th>Enterally</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutamine/day</td>
<td>0.35 gms/kg</td>
<td>30 gms</td>
</tr>
<tr>
<td>Antioxidants per day</td>
<td>500 mcg Selenium</td>
<td>Vit C 1500 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vit E 500 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B carotene 10 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zinc 20 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Se 300 ug</td>
</tr>
</tbody>
</table>

- High dose appears safe?
- High dose associated with
  - no worsening of SOFA Scores
  - greater resolution of oxidative stress
  - greater preservation of glutathione
  - Improved mitochondrial function
In REDOXS... GLN group gets

> 50 g/d GLN

or...

~ 0.6–0.8 g/kg/d GLN
What Is Unique About REDOXs Versus Any Other GLN Trial?
What Is Unique About REDOXs Versus Any Other GLN Trials?

A. GLN in Renal Fx
B. EN + PN GLN
C. Largest GLN Dose Ever Given
D. GLN Given W/out Complete Nutrition
E. All of the Above
REDOXS: A New Paradigm!

“Nutrients Dissociated from Nutrition”
Results
Primary outcome of **28 day mortality** using all **1218** evaluable patients (ITT)

<table>
<thead>
<tr>
<th>Glutamine (glut)</th>
<th>Antioxidants (AOX)</th>
<th>Overall adjusted OR of AOX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>101/310 (32.6%) 97/301 (32.2%) 1.02 (0.72, 1.43)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>89/307 (29.0%) 76/309 (25.3%) 1.20 (0.84, 1.72)</td>
</tr>
<tr>
<td>Glut OR conditioned on AOX</td>
<td>Yes</td>
<td>1.18 (0.83-1.66) 1.40 (0.98-2.00)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1.09 (0.86-1.40; p=0.48*)</td>
</tr>
</tbody>
</table>

Overall adjusted OR for glut **1.28 (1.00-1.64; p=0.049*)**

*All odds ratios adjust for presence of shock at baseline. Overall ORs also adjust for other treatment factor.

*To account for two interim analyses, we pre-specified statistical significance of final analysis at two-sided p<0.044 in protocol.

**Thus, our primary outcome did not reach statistical significance for either intervention.**
Primary outcome of **28 day mortality** using 1025 patients who received ≥5 days of supplements

<table>
<thead>
<tr>
<th>Glutamine (glut)</th>
<th>Antioxidants (AOX)</th>
<th>AOX OR conditioned on Glut</th>
<th>Overall adjusted OR of AOX</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>55/255 (21.6%)</td>
<td>60/246 (24.4%)</td>
<td>0.85 (0.56-1.30)</td>
</tr>
<tr>
<td>No</td>
<td>55/263 (20.9%)</td>
<td>49/261 (18.8%)</td>
<td>1.14 (0.74-1.76)</td>
</tr>
</tbody>
</table>

Glut OR conditioned on AOX

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall adjusted OR for glut</td>
<td>1.20 (0.89-1.62; p=0.23)</td>
<td>AOX by glut interaction p=0.33</td>
</tr>
</tbody>
</table>

OR=odds ratio. ORs are presented with 95% confidence intervals in parentheses. An OR>1 indicates increased mortality with treatment.

All odds ratios adjust for presence of shock at baseline. Overall ORs also adjust for other treatment factor.
REDOXs...

Did we make a classic “Goliath Trial Error”?

...Moving away from all previous positive GLN trials inclusion/exclusion criteria
Historical Positive Trials of GLN

Treated PN-requiring pts only

Many Cancer Pts - More GLN Deficient?!!

Late Administration of GLN

EXCLUDED: Renal/Liver Fx

No Shock/MOF

Lower Dose (0.3-0.5 g/kg/d)

Never Combined EN/PN
Unfortunately...

We made “goliath errors”...

Thinking...

“It’s just nutrients...
They must be good for ALL Pts”
Can we identify where we made the “Goliath Errors”?
Post hoc Sub-group Analysis
Glutamine vs. No Glutamine

28 day mortality, OR with 95% CI

Favours GLN                            Favours No GLN

Vasopressors >=15 mcg/min
Vasopressors <15 mcg/min

Renal dysfunction
No renal dysfunction

Baseline SOFA <7
Baseline SOFA between 7 and 8
Baseline SOFA between 8 and 10
Baseline SOFA >10

Apache I <21
Apache I between 21 and 26
Apache I between 26 and 31
Apache I >31

Medical
Surgical

Non-diabetic
Diabetic

BMI <25
BMI 25-34.9
BMI >35

Cardiovascular / Vascular
Respiratory
Gastrointestinal
Sepsis
Other

Non-cancer patients
Cancer patients

Critical Care Nutrition

p=0.35
p=0.75
p=0.85
p=0.85
p=0.02
p=0.21
p=0.34
p=0.13
p=0.98
p=0.075
p=0.54
p=0.06
p=0.87
p=0.22
p=0.38
p=0.079
p=0.56
p=0.58
p=0.16
p=0.27
p=0.31
p=0.37
p=0.077
p=0.63
p=0.026
p=0.59
p=0.051

p=0.077
p=0.56
p=0.58
p=0.16
p=0.27
p=0.31
p=0.37
p=0.077
p=0.63
p=0.026
p=0.59
p=0.051

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p=0.58
p=0.16
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p=0.31
p=0.37
p=0.077
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p=0.026
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p=0.051

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p=0.58
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p=0.27
p=0.31
p=0.37
p=0.077
p=0.63
p=0.026
p=0.59
p=0.051

28 day mortality, OR with 95% CI
Post hoc Sub-group Analysis
Glutamine vs. No Glutamine
On treatment Variables

GLN w/o Nutrition

28 day mortality,
OR with 95% CI
High-Dose GLN in Renal Failure Is A Mortality Risk!

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Deaths (%)</th>
<th>OR (95% CI) vs. Placebo</th>
<th>P Value</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>GLN Alone</td>
<td>AOX Alone</td>
</tr>
<tr>
<td>Renal Dysfunction</td>
<td></td>
<td>0.93 (0.6-1.46)</td>
<td>0.90 (0.58-1.4)</td>
</tr>
<tr>
<td>No</td>
<td>276/776 (28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>147/442 (33)</td>
<td>2.75 (1.5-5.0)</td>
<td>2.16 (1.15-4.0)</td>
</tr>
</tbody>
</table>

Heyland, Elke, Wischmeyer et al. JPEN, 2014
### REDOXS Trial - Post hoc analysis

**Treatment effect on 28-d mortality by baseline renal dysfunction and post-baseline dialysis**

<table>
<thead>
<tr>
<th>Multivariable Subgroup</th>
<th>OR (95% CI) compared to Placebo Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Glutamine</td>
</tr>
<tr>
<td>Admit Renal Dysfunction</td>
<td>Ever on Dialysis</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Heyland, Elke, Wischmeyer et al. JPEN, 2014
In Renal Failure...

GLN appears to lead to risk...

Improved by dialysis...
Who to stop GLN

In...

Creatinine >171 mmol/L or

Urine < 500 ml/24 h
(< 80 ml/last 4 h)

(...Or rise in Creat >80 mmol/L from baseline Cr)
Who to stop GLN
In...

Cr Clearance

< 25 ml/min

(What the Dipeptide package insert has always stated...)
Conclusions

GLN Dipeptide Should Not Be Given In:

- High Dose (> 0.5 g/kg/day)
- Renal failure (esp. w/o dialysis)
- Unresuscitated Shock Requiring Significant Vasopressor Support
What is Unresuscitated Shock?

Patients in Unresuscitated Shock > 48 h Rarely Survive!
What is Unresuscitated Shock?

Defined As...

- Increasing Lactate (> 2-3) (Despite adequate fluids)
- MvO2 Saturation < 70%
- Low Mean Arterial BP (< 60) on high or increasing doses of vasopressors
Glutamine

Improved Survival in PN Pts w/o MOF!

Increased Risk of Death in Early MOF?
Nutrition must be the complete package?
Pharmaconutrients need to be given with adequate nutrition delivery for clinical effect....

TRUE!..in all other positive Fish Oil ARG and GLN trials!
PN Glutamine

2009 Recommendation

Based on 17 RCTS...When PN prescribed to critically ill pts, parenteral supplementation with GLN is strongly recommended.

Grau 2011
Andrews 2011
Wernerman 2011
Eroglu 2009
Perez Barcena 2010
Ozgultekin, 2008
Ziegler, 2013
Cekman, 2011
+ 3 Chinese RCTs

New RCTs = 11
New PN GLN Meta-Analysis

26 studies in 2317 pts:

Examined only parenteral GLN in ICU pts

26 studies: GLN with PN

3 studies: GLN with EN

Wischmeyer et al. Critical Care 18:76-81, 2014
# Hospital Mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PN GLN Events</th>
<th>Control Events</th>
<th>M-H, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Griffiths</td>
<td>25</td>
<td>20</td>
<td>0.15 [0.01, 0.32]</td>
<td>2001</td>
</tr>
<tr>
<td>Powell-Tuck</td>
<td>3</td>
<td>2</td>
<td>0.97 [0.44, 1.42]</td>
<td>2004</td>
</tr>
<tr>
<td>Wischmeyer</td>
<td>3</td>
<td>3</td>
<td>0.33 [0.12, 0.67]</td>
<td>2004</td>
</tr>
<tr>
<td>Fuentes-Orozco 2004</td>
<td>2</td>
<td>2</td>
<td>0.33 [0.12, 0.67]</td>
<td>2004</td>
</tr>
<tr>
<td>Xian-Li</td>
<td>3</td>
<td>2</td>
<td>0.33 [0.12, 0.67]</td>
<td>2004</td>
</tr>
<tr>
<td>Dechelotte</td>
<td>2</td>
<td>2</td>
<td>0.33 [0.12, 0.67]</td>
<td>2004</td>
</tr>
<tr>
<td>Bahin</td>
<td>2</td>
<td>2</td>
<td>0.33 [0.12, 0.67]</td>
<td>2004</td>
</tr>
<tr>
<td>Perez-Barcena 2008</td>
<td>0</td>
<td>11</td>
<td>Not estimable</td>
<td>2008</td>
</tr>
<tr>
<td>Luo</td>
<td>0</td>
<td>9</td>
<td></td>
<td>2008</td>
</tr>
<tr>
<td>Estivariz</td>
<td>1</td>
<td>3</td>
<td>0.16 [0.02, 1.26]</td>
<td>2008</td>
</tr>
<tr>
<td>Yang 2008</td>
<td>1</td>
<td>25</td>
<td>0.33 [0.04, 2.99]</td>
<td>2008</td>
</tr>
<tr>
<td>Perez-Barcena 2010</td>
<td>0</td>
<td>23</td>
<td>0.29 [0.01, 6.78]</td>
<td>2010</td>
</tr>
<tr>
<td>Ziegler</td>
<td>0</td>
<td>7</td>
<td></td>
<td>2008</td>
</tr>
</tbody>
</table>

**Total (95% CI):**
- PN GLN: 43 (95% CI: 0.00 - 1.00)
- Control: 86 (95% CI: 0.00 - 1.00)

**Heterogeneity:**
- Tau² = 0.00, Chi² = 8.31, df = 11 (P = 0.69), I² = 0%

**Test for overall effect:**
- Z = 2.67 (P = 0.008)

Wischmeyer et al. *Critical Care* 18:R76, 2014
Hospital Length Of Stay

Wischmeyer et al. Accepted Critical Care, March, 2014

Shorter LOS
Conclusions

Parenteral GLN Leads to:

Significant Benefit:
- HOSPITAL mortality
- Hospital LOS

Trend to Benefit:
- Infections and VAP
- ICU LOS

Wischmeyer et al. Critical Care 18:R76, 2014
Conclusions

Parenteral GLN Supplementation of Parenteral Nutrition is:

Safe and Continues to Reduce Mortality and Improve Outcome in 26 trials of ~2300 pts

Wischmeyer et al. Critical Care 18:R76, 2014
Recent Meta-Analysis of PN Gln

40 RCTs, 3107 pts
Surgery, Critical Illness, (mixed):

Reduced Mortality in Critically Ill
(p=0.024)

Reduced Infection Risk In All Pts
(p=0.009)

Bollhalder et al Clin Nutr 2013
Recent Meta-Analysis of PN Gln

40 RCTs, 3107 pts
Surgery, Critical Illness, (mixed):

Reduced Hospital LOS in All Pts
(p=0.001)

Higher Supplementation Dose Studies
(> 0.3 g/kg/d Dipeptide)
Significant Reduction of Short Term Mortality, Infections and LOS

Bollhalder et al Clin Nutr 2013
Based on 9 level 1 and 19 level 2 studies, when PN is prescribed to ICU pts...

2013 CPG Recommendation

Composition of PN: GLN Supplementation

-Parenteral Supplementation With GLN Should Be Considered
However, we recommend GLN NOT be used in critically ill patients with MOF/Renal Fx.
Glutamine Should Be Considered For ICU Pts on TPN!

(Canadian Critical Care Guidelines 2013)
The Future of Glutamine Research?
Could GLN Improve Physical Function?
Mortality Related to Severe Sepsis and Septic Shock Among Critically Ill Patients in Australia and New Zealand, 2000-2012

Kirsi-Maija Kaukonen, MD, PhD, EDIC; Michael Bailey, PhD; Satoshi Suzuki, MD; David Pilcher, FCICM; Rinaldo Bellomo, MD, PhD

“Given low ICU mortality...

Quality of Life

...will become focus of future trials”
“Are we creating survivors... or Victims?”
Could GLN Improve Physical Function?

REDOXs

Quality of Life Data?
GLN Improves SF-36 Quality of Life at 6 Months
Glutamine Still Improves Outcome! In the RIGHT Patients...
Low Cost!
One Size
Does NOT Fit All...
Who Are The Correct Patients?
PN Patients
Glutamine Should Be Considered For ICU Pts on TPN!

(Canadian Critical Care Guidelines 2013)
Dose is Important!

**GLN Dose**

- 0.35 g/kg/d (IV)
- 0.5 g/kg/d (Enteral)

A.S.P.E.N. Position Paper: Parenteral Nutrition Glutamine Supplementation
Nutr Clin Pract 2011 26: 479
Samuel M. - 58 y.o 3 d s/p Peritonitis...

Weight: 80 kg  
Protein Goal: 1.5-1.8 g/kg/d

Pt stabilized now off of vasopressors...Starting TPN

MVO2- 78%
Lactate 1.5

Not in Renal Failure
Samuel M. - 58 y.o 3 d s/p Peritonitis...

Weight: 80 kg  
Protein Goal: 1.5-1.8 g/kg/d

Alanyl-Glutamine Dose = 0.5 g/kg/d  
(0.35 g/kg/d GLN alone)
Metabolic Therapy in ICU and Surgery...

PN if EN not started at 1-2 d
- B-Blocker?
- No GLN in Shock/Renal Fx

(1st 24-48 h Post ICU-Admission)

Protein (1.2-2.0 g/kg)
- Oxandrolone?
- B-Blockers?
- Exercise

GLN in PN

Calories/Protein
- B-Blockers?
- Exercise

GLN in PN

"Survival for Critical Hours"

Change from baseline

Acute phase  Chronic phase  Recovery

"Survival of the Fittest"
Learn From Goliath Trials...
GLN Still Saves Lives...
We Have Thousands of Pts Studied Over Many Years...
Listen Closely To Master Yoda...

As He Asks Us...
You Must Unlearn What You Have Learned... Alright... I'll Give It a Try... NO! TRY NOT! DO or Do Not... There is no try!
Just Do It...