Current Controversies in Critical Care Nutrition

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Kingston, ON Canada
Critical Care Nutrition

is dedicated to improving nutrition therapies in the critically ill through knowledge generation, synthesis, and translation. We engage in a broad range of research activities and promote a culture of best practices in critical care nutrition. Ultimately, this will result in improved clinical outcomes for critically ill patients and increased efficiencies to our health care systems.

www.criticalcarenutrition.com
Learning Objectives

• Describe the optimal amount of protein and calories to support positive outcomes in the ICU patient.

• Identify ICU patients that benefit most from nutrition intervention.

• Current role of pharmaconutrients and future research agenda
Creating Clarity Out of Confusion!

Large, Negative RCTs

- **EPaNIC** *NEJM* 2011
- **EDEN** *JAMA* 2012
- **PERMIT** *NEJM* 2015
- **NEPHROPROTECT** *ICM* 2015
- **EAT-ICU** *ICM* 2017
DKH: setting such conservative targets will result in significantly less in the first few days.

Worse outcomes

Koekkoek, Curr Opin Anesthesiol 2018, 31:136–143
Initial Feeding Strategy Determines Overall Success

Graph showing the received/prescribed calories (%) over ICU days.

- **Blue line**: Keep Nil Per Os (NPO)
- **Green line**: Initiate EN: start at hourly rate determined by 24-hour volume goal
- **Blue square**: Initiate EN: start at low rate and progress to hourly goal rate
- **Blue diamond**: Initiate EN: keep a low rate (trophic feeds: no progression)

Key:
- **IN**: Received/prescribed calories (%)
- **ICU day**: X-axis

Legend:
- **ICU**
ICU Patients Are Not All Created Equal... Should We Expect the Impact of Nutrition Therapy to be the Same Across All Patients?
The Prevalence of Iatrogenic Underfeeding in the Nutritionally ‘At-Risk’ Critically Ill Patient

% high risk patients who failed to meet minimal quality targets (80% overall energy adequacy)

Of all at-risk patients, 14% were ever prescribed volume-based feeds 15% ever received sPN

Heyland
Clinical Nutrition 2015
What do the Guidelines say?

- Canadian CPGs- use of supplemental PN and trophic feeds a function of nutrition risk

- ASPEN/SCCM CPGs- withhold nutrition therapy for patients with low nutrition risk and who cannot maintain volitional intake

- New ESPEN CPGs 2018- no risk stratification
4620 patients randomized to early vs. late parenteral nutrition (EPANIC)

• Right patient population?
  ● Majority (90%) surgical patients (mostly cardiac-60%)
  ● Short stay in ICU (3-4 days)
  ● Low mortality (8% ICU, 11% hospital)
  ● >70% normal to slightly overweight

• Applicability of the intervention
  ● No one gives too much IV glucose in first few days
  ● No one practices tight glycemic control

• Not an indictment of PN
  ● Clear separation of groups after 2-3 days
  ● Early group only received PN on day 3 for 1-2 days on average
  ● Late group –only ¼ received any PN

Casaer NEJM 2011
Implications for Practice

Results of 2014 INS (186 sites worldwide and approx. 4000 patients)

In all comers:

• At a patient level, 16% of patients averaged more than 80% protein adequacy
• At a site level, 6% (11 sites) averaged more than 80% in all patients

In High NUTRIC patients:

• 16% of high NUTRIC Score patients received more than 80% of prescribed amount
  • 7% (16 sites) managed to provide more than 80% of prescribed amounts to high-risk patients

Performance in ‘all’ patients same as High NUTRIC patients
A Conceptual Model for Nutrition Risk Assessment in the Critically Ill

Nutrition Status
- Micronutrient levels
- Immune markers
- Muscle mass

Starvation
- Acute
  - Reduced po intake
  - Pre ICU hospital stay
- Chronic
  - Recent weight loss
  - BMI?

Inflammation
- Acute
  - IL-6
  - CRP
  - PCT
- Chronic
  - Comorbid illness
The Development of the NUTrition Risk in the Critically Ill Score (NUTRIC Score)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Range</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt;50</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>50-&lt;75</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt;=75</td>
<td>2</td>
</tr>
<tr>
<td>APACHE II</td>
<td>&lt;15</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>15-&lt;20</td>
<td>1</td>
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<tr>
<td></td>
<td>20-28</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>&gt;=28</td>
<td>3</td>
</tr>
<tr>
<td>SOFA</td>
<td>&lt;6</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>6-&lt;10</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt;=10</td>
<td>2</td>
</tr>
<tr>
<td># Comorbidities</td>
<td>0-1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2+</td>
<td>1</td>
</tr>
<tr>
<td>Days from hospital to ICU admit</td>
<td>0-&lt;1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1+</td>
<td>1</td>
</tr>
<tr>
<td>IL6</td>
<td>0-&lt;400</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>400+</td>
<td>1</td>
</tr>
<tr>
<td>AUC</td>
<td></td>
<td>0.783</td>
</tr>
<tr>
<td>Gen R-Squared</td>
<td></td>
<td>0.169</td>
</tr>
<tr>
<td>Gen Max-rescaled R-Squared</td>
<td></td>
<td>0.256</td>
</tr>
</tbody>
</table>

BMI, CRP, PCT, weight loss, and oral intake were excluded because they were not significantly associated with mortality or their inclusion did not improve the fit of the final model.
The Validation of the NUTrition Risk in the Critically Ill Score (NUTRIC Score)

Interaction between NUTRIC Score and nutritional adequacy (n=211)
The Validation of the NUTrition Risk in the Critically Ill Score (NUTRIC Score)

- Validated in 3 separate databases including the INS Dataset involving over 200 ICU’s worldwide
  1,2,3
- Validated without IL-6 levels (modified NUTRIC) 2
- Independently validated in Dutch, Brazilian, Portuguese, and Asian populations 4,5,6,7
- Predictive validity superior than MUST (malnutrition assessment) 7
- Not validated in post hoc analysis of the PERMIT trial 8
  – RCT of different caloric intake (protein more important)
  – Underpowered, very wide confidence intervals
- Discriminates patients who benefit the most in post hoc analysis of TOP uP trial

1. Heyland Critical Care 2011, 15:R28
3. Compher, CCM, 2016
5. Mendes J Crit Care 2017
8. Arabi AmJRCCM 2016
9. Wischmeyer Crit Care 2017
Results of TOP UP Pilot Trial
A RCT of supplemental PN in low and high BMI ICU patients

Post-hoc subgroup analysis
Review

Determination of Nutrition Risk and Status in Critically Ill Patients: What Are Our Considerations?

Zheng-Yii Lee, MSc¹,² ID; and Daren K. Heyland, MD, MSc, FRCPC³

Abstract
The stress catabolism state predisposes critically ill patients to a high risk of malnutrition. This, coupled with inadequate or delayed nutrition provision, will lead to further deterioration of nutrition status. Preexisting malnutrition and iatrogenic underfeeding are associated with increased risk of adverse complications. Therefore, accurate detection of patients who are malnourished and/or with high nutrition risk is important for timely and optimal nutrition intervention. Various tools have been developed for nutrition screening and assessment for hospitalized patients, but not all are studied or validated in critically ill populations. In this review article, we consider the pathophysiology of malnutrition in critical illness and the currently available literature to develop recommendations for nutrition screening and assessment. We suggest the use of the (modified) Nutrition Risk in the Critically Ill (mNUTRIC) for nutrition risk screening and the subjective global assessment (SGA) together with other criteria relevant to the critically ill patients, such as gastrointestinal function, risk of aspiration, determination of sarcopenia and frailty, and risk of refeeding syndrome for nutrition assessment. Further research is needed to identify suitable nutrition monitoring indicators to determine the response to the provision of nutrition. (Nutr Clin Pract. 2019;34:96–111)
What is current nutrition practice look like today?
Results of 2014 INS

In 2014 INS, on average, patients were prescribed 1.3 grams/kg/day (interquartile range, 1.0-1.5 grams/kg/day, overall range, 0.5-3.8 grams/kg/day).

On average, patients receive 55% of prescription.
Is that sufficient?
Do they need more?
Hard to Argue that Meeting Caloric Goals is Important!

Large, Negative RCTs

- EPaNIC NEJM 2011
- EDEN JAMA 2012
- PERMIT NEJM 2015
- NEPHROPROTECT ICM 2015
- EAT-ICU ICM 2017
Systematic Review of RCTs of High vs. Low Dose Protein

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>High Dose</th>
<th></th>
<th>Low Dose</th>
<th></th>
<th>Risk Ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
<td>M-H, Random, 95% CI</td>
<td></td>
</tr>
<tr>
<td>Clifton 1985</td>
<td>1</td>
<td>10</td>
<td>1</td>
<td>10</td>
<td>1.00 [0.07, 13.87]</td>
<td>1985</td>
</tr>
<tr>
<td>Rugeles 2013</td>
<td>11</td>
<td>40</td>
<td>12</td>
<td>40</td>
<td>0.92 [0.46, 1.83]</td>
<td>2013</td>
</tr>
<tr>
<td>Doig 2015</td>
<td>42</td>
<td>236</td>
<td>47</td>
<td>235</td>
<td>0.89 [0.61, 1.29]</td>
<td>2015</td>
</tr>
<tr>
<td>Ferrie 2016</td>
<td>12</td>
<td>59</td>
<td>9</td>
<td>60</td>
<td>1.36 [0.62, 2.98]</td>
<td>2016</td>
</tr>
<tr>
<td>Allingstrup 2017</td>
<td>30</td>
<td>100</td>
<td>32</td>
<td>99</td>
<td>0.93 [0.61, 1.40]</td>
<td>2017</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>445</td>
<td>100%</td>
<td>444</td>
<td></td>
<td>0.94 [0.74, 1.21]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>96</td>
<td></td>
<td>101</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 4 (P = 0.92); I² = 0%
Test for overall effect: Z = 0.46 (P = 0.65)
What is the evidence that exogenously administered amino acids/protein favorably impacts clinical outcomes?

Clinical Outcomes Related to Protein Delivery in a Critically Ill Population: A Multicenter, Multinational Observation Study

Michele Nicolo, MS, RD, CNSC¹; Daren K. Heyland, MD, MSc, FRCPC²; Jesse Chittams, MS³; Therese Sammarco, BA³; and Charlene Compher, PhD, RD, CNSC, LDN, FADA, FASPEN³
# Impact of Protein Intake on 60-day Mortality

Data from 2828 patients from 2013 International Nutrition Survey

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients in ICU ≥ 4 d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>60-Day Mortality, Odds Ratio (95% CI)</td>
</tr>
<tr>
<td></td>
<td>Adjusted¹</td>
</tr>
<tr>
<td>Protein Intake (Delivery ≥ 80% of prescribed vs. &lt; 80%)</td>
<td>0.61</td>
</tr>
<tr>
<td></td>
<td>(0.47, 0.818)</td>
</tr>
<tr>
<td>Energy Intake (Delivery ≥ 80% vs. &lt; 80% of Prescribed)</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td>(0.56, 0.89)</td>
</tr>
</tbody>
</table>

¹ Adjusted for BMI, Gender, Admission Type, Age, Evaluable Days, APACHE II Score, SOFA Score
² Adjusted for all in model 1 plus for calories and protein

Nicolo JPEN 2015
Rate of Mortality Relative to Adequacy of Protein and Energy Intake Delivered

Heyland JPEN 2015

TIACOS ICM 2011
INTACT JPEN 2014

Heyland JPEN 2015
Post-hoc analysis of EPANIC

Figure 3. Time to live discharge from the intensive care unit (ICU): Relation to glucose dose as compared with protein dose. Effect size per 10% increments of target per day in cumulative glucose intake (\(\sim \pm 28 \text{ g/d}\) (yellow) and cumulative protein intake (\(\sim \pm 7 \text{ g/d}\) (green)) in a time-to-ICU discharge analysis corrected for severity and type of disease. Normalized glucose target was 276.4 (\(\pm 70.8\) g/day and normalized protein target was 72.3 (\(\pm 18.5\) g/day. This target was derived from the amount of glucose and protein the patient would have received with the standard commercial parenteral (PN) preparation when receiving 100% of his calculated energy target.
Role of timing and dose of energy received in patients with acute lung injury on mortality in the Intensive Nutrition in Acute Lung Injury Trial (INTACT): a post hoc analysis

Carol L Braunschweig, Sally Freels, Patricia M Sheean, Sarah J Peterson, Sandra Gomez Perez, Liam McKeever, Omar Lateef, David Gurka, and Gianila Fantuzzi

• 78 patient with ALI randomized to Intensive Medical therapy (30 kcal/kg/day) or usual care (40-60% of target)
• Stopped early because of excess deaths in intensive group
• Post hoc analysis suggests increased death from early protein!

TABLE 3
Proportional hazards multiple regression models for hazard of death on or after 8 d for INTACT participants

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>β Hat</th>
<th>SE</th>
<th>P</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean kcal/kg received during days 1–7 $^2$</td>
<td>0.1575</td>
<td>0.0441</td>
<td>0.0004</td>
<td>1.17 (1.07, 1.28)</td>
</tr>
<tr>
<td>Time-dependent mean daily kcal/kg received during days 1–7 and after day $^2$</td>
<td>−0.0967</td>
<td>0.0471</td>
<td>0.04</td>
<td>0.91 (0.83, 1.0)</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean daily g protein/kg received during days 1–7 $^3$</td>
<td>2.18</td>
<td>0.69</td>
<td>0.002</td>
<td>8.87 (2.3, 34.3)</td>
</tr>
<tr>
<td>Time-dependent mean daily g protein/kg received during days 1–7 and after day $^3$</td>
<td>−1.89</td>
<td>1.00</td>
<td>0.06</td>
<td>0.15 (0.02, 1.07)</td>
</tr>
</tbody>
</table>

1 Models were adjusted for age, sex, and baseline SOFA score, n = 66 (15 deaths). INTACT, Intensive Nutrition in Acute Lung Injury Trial: SOFA, Sequential Organ Failure Assessment.
2 Mean increase of 1 kcal/kg.
3 Mean increase of 1 g/kg.
RCTs do not suggest any evidence of harm and observational studies suggest increased protein intake associated with...

- Reduced mortality\(^1\)
- Quicker Time-to-discharge-alive\(^1\)
- Greater preservation of muscle \(^2,3\)
- Reduced infection \(^4\)
- Increased mortality\(^5\)
- Slower time-to-discharge-alive from ICU\(^6\)
- Greater loss of muscle mass and increased weakness\(^7,8\)

1. Nicolo JPEN 2015
2. Ferrie JPEN 2016
3. Fetterplace JPEN 2018
4. Heyland JPEN 2010
5. Braunschweig Am J Clin Nutr 2017
6. Casaer Am J Respir Crit Care Med 2013
7. Puthucheary JAMA 2013
8. Hermans Lancet Respir 2013
The **Effect of Higher Protein Dosing in Critically Ill Patients:**

The EFFORT Trial

A multicentre, pragmatic, volunteer-driven, registry-based, randomized, clinical trial.
Participation Across the 5 Years of the INS: 708 Distinct ICUs

Canada: 95
USA: 225

Europe and Africa: 109

Asia: 145

Latin America: 53

Australia: 73
New Zealand: 8

- Colombia: 19
- Brazil: 10
- Argentina: 7
- Uruguay: 5
- Mexico: 3
- Chile: 3
- Venezuela: 2
- Peru: 1
- Paraguay: 1
- El Salvador: 1
- Puerto Rico: 1

- UK: 37
- Turkey: 11
- Ireland: 12
- Italy: 9
- Norway: 8
- South Africa: 13
- Switzerland: 4
- Spain: 4
- Slovenia: 1
- Sweden: 3
- Czech Republic: 3
- Austria: 2
- Portugal: 1
- France: 1

- China: 38
- Japan: 43
- India: 36
- Taiwan: 5
- Singapore: 11
- Saudi Arabia: 2
- Philippines: 2
- Iran: 2
- Thailand: 2
- UAE: 1
- Malaysia: 2
- Indonesia: 1
Recommendations: Based on 8 level 2 studies, we recommend early enteral nutrition (within 24-48 hrs following resuscitation) in critically ill patients.
# Study Population

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Rationale for Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. &gt;18 years old</td>
<td>1. &gt;96 continuous hours of mechanical ventilation before screening</td>
<td>Intervention is likely most effective when delivered early</td>
</tr>
<tr>
<td></td>
<td>2. Expected death or withdrawal of life-sustaining treatments within 7 days from screening</td>
<td>Patients unlikely to receive benefit</td>
</tr>
<tr>
<td>2. Nutritionally “high-risk” (meeting one of the below criteria)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Low (&lt;25) or High BMI (&gt;35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Moderate to severe malnutrition (as defined by local assessments)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. Frailty (Clinical Frailty Scale, 5 or more from proxy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d. Sarcopenia – (SARC-F score of 4 or more from proxy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>e. From point of screening, projected duration of mechanical ventilation &gt;4 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Requiring mechanical ventilation with actual or expected total duration of mechanical ventilation &gt;48 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. The responsible clinician feels that the patient either needs low or high protein</td>
<td>Uncertainty doesn't exist; patient safety issues</td>
<td></td>
</tr>
<tr>
<td>5. Patient requires parenteral nutrition only and site does not have products to reach the high protein dose group.</td>
<td>Site will be unable to reach high protein dose prescription.</td>
<td></td>
</tr>
</tbody>
</table>
How do I achieve the high protein intake?

- High protein containing EN solutions
- EN protein supplements
- PN
- Parenteral amino acids
- Or combinations of the above!
The PEP uP Protocol!
The Efficacy of Enhanced Protein-Energy Provision via the Enteral Route in Critically Ill Patients:

• Different feeding options based on hemodynamic stability and suitability for high volume intragastric feeds.

• In select patients, we start the EN immediately at goal rate, not at 25 mL/hr.

• We target a 24 hour volume of EN rather than an hourly rate and provide the nurse with the latitude to increase the hourly rate to make up the 24 hour volume.

• Start with a very high protein solution; semi elemental solution then progress to polymeric

• Motility agents and protein supplements are started immediately, rather than started when there is a problem

• Tolerate higher GRV threshold (300 mL or more)

Heyland Crit Care 2010
see www.criticalcarenutrition.com for more information on PEP uP tools
• Resulted in a significant improvement in nutrition delivery (12-14% increase with no overfeeding)
• No change in clinical outcomes (not powered to do so)
• Observed a 4% reduction in mortality from baseline in PEP uP group

**TABLE 4. Clinical Outcomes Between Groups and Across Time (All Patients – n = 1,059)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intervention</th>
<th>Baseline</th>
<th>Follow-Up</th>
<th>Control</th>
<th>Baseline</th>
<th>Follow-Up</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>270</td>
<td>252</td>
<td>270</td>
<td>267</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU mortality (%)</td>
<td>47 (17.4)</td>
<td>35 (13.9)</td>
<td>49 (18.1)</td>
<td>42 (15.7)</td>
<td>0.57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Died within 60 d of ICU admission (%)</td>
<td>70 (25.9)</td>
<td>68 (27.0)</td>
<td>65 (24.1)</td>
<td>63 (23.6)</td>
<td>0.53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of stay among 60d-survivors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days on mechanical ventilation</td>
<td>3.7 (1.6, 9.1)</td>
<td>4.3 (1.3, 9.9)</td>
<td>3.1 (1.4, 8.4)</td>
<td>3.0 (1.4, 7.3)</td>
<td>0.57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days in ICU</td>
<td>6.1 (3.4, 11.4)</td>
<td>7.2 (3.4, 11.1)</td>
<td>6.4 (3.3, 12.6)</td>
<td>5.7 (2.8, 11.8)</td>
<td>0.35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days in hospital</td>
<td>14.2 (6.1, 29.8)</td>
<td>13.5 (6.1, 28.4)</td>
<td>10.7 (7.5, 27.7)</td>
<td>13.8 (7.1, 26.6)</td>
<td>0.73</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p values test against the null hypothesis that the mean within ICU change is the same in both arms.
Results of the Canadian PEP uP Collaborative

Results of 2013 International Nutrition Survey (INS)

Heyland JPEN 2014
Start PEP uP Protocol in all patients within 24-48 hrs of admission

**EN**
- End of day 3: ≥80% of goal?
  - **YES**: Carry on!
  - **NO**: High risk?*
    - **YES**: Maximize EN with
      - motility agents
      - small bowel feeding
      - protein supplements
    - **NO**: Consider supplemental PN

**High risk?***
- **YES**: Good job! Continue monitoring nutritional adequacy!
- **NO**: End of day 4: Tolerating EN ≥80%?
  - **YES**: Good job! Continue monitoring nutritional adequacy!
  - **NO**: Consider supplemental PN

* Nutric Score > 5 or
  - mod-severe malnourished
  - Frail and/or sarcopenia?
  - ICU LOS > 96 hrs

Heyland, Right here, Right now!
For more information on the EFFORT Trial (or EFFORT-X)

See www.criticalcarenutrition.com

Or contact:

Daren Heyland
Dkh2@queensu.ca
Or
Zheng Yil Lee
zheng_yii@hotmail.com
Pharmaconutrition

Nutrition therapy that modulates the underlying disease process and impacts outcome

Adjunctive Supportive Care

Proactive Primary Therapy
Pharmaconutrition: End of an Era?
“We do not recommend…”

- Arginine-containing diets
- IV/EN glutamine supplementation
- IV/PN selenium, alone or in combination with other antioxidants
- IV/PN combined vitamins and trace elements
- Fish oils
**Large-scale Trials Have Failed to Demonstrate Any Positive Treatment Effect**

<table>
<thead>
<tr>
<th>REDOXS, Metaplus, SIGNET</th>
<th>Glutamine and Antioxidants</th>
</tr>
</thead>
<tbody>
<tr>
<td>SISPCT</td>
<td>IV Selenium</td>
</tr>
<tr>
<td>Omega</td>
<td>Fish Oils</td>
</tr>
<tr>
<td>Meta-analysis of large scale RCTs</td>
<td>Arginine</td>
</tr>
</tbody>
</table>
Where do we go from here?
Glutamine:
A conditionally essential amino acid?

Glutamine levels drop:
- following extreme physical exercise
- after major surgery
- during critical illness

Low glutamine levels are associated with:
- immune dysfunction
- higher mortality in critically ill patients

Novak F, Heyland DK, Avenell et al., Crit Care Med 2002
Oudemans-van Straaten HM, Bosman RJ, Treskes Met al., Intensive Car Med 2001
Putative Mechanisms of Glutamine Supplementation

- Maintenance of immune cell function
  - Maintenance of lymphocyte/NK cell function
  - Reduced lymphocyte apoptosis

- Attenuation of inflammation from gut immune cells
  - Attenuation of cytokine release
  - Attenuated iNOS expression

- Maintenance of gut barrier function
  - Enhanced gut IgA levels
  - Prevents lymphocyte depletion in Peyer's patches

- Protection against cell injury
  - Enhanced HSP expression
  - Preservation of GSH
  - Gut energy source

- Attenuation of lung injury
  - Enhanced pulmonary HSP expression
  - Preservation of cell metabolism (ATP)
  - Reduce ARDS/long term lung injury from burn/smoke inhalation

- Preserved muscle metabolism
  - Improved insulin sensitivity
  - Improved protein synthesis
  - Improved functional recovery?

- Cardiac protection
  - Prevents burn-related myocardial injury
- Randomized >1200 critically ill patients with multi-organ failure
- High dose of combined EN/IV doses
- Demonstrated increased mortality overall
- Subgroup analysis suggested this was in renal failure patients
Plasma Levels of Glutamine in Subset of Patients from REDOXS Study

Glutamine and glutathione at ICU admission in relation to outcome

Figure 2: All-cause 6-month mortality (open bars) and ICU mortality (filled bars) of consecutive patients admitted to the general ICU (n=174) at Karolinska Huddinge.

(b) Stepwise multiple logistic regression analysis

<table>
<thead>
<tr>
<th>OR (CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.092 (0.0002–0.016)</td>
</tr>
<tr>
<td>APACHE (per patient)</td>
<td>1.14 (1.07–1.22)</td>
</tr>
<tr>
<td>Gln &lt;900 or &gt;930</td>
<td>2.95 (1.38–6.32)</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>1.04 (1.01–1.07)</td>
</tr>
<tr>
<td>eGSH/GSH &gt; 0.65</td>
<td>2.35 (1.02–5.41)</td>
</tr>
</tbody>
</table>
Future Trials Require Bedside Testing?

GM7 Micro-Stat
Rapid Multi-Assay Analyser

Major Application Areas:
- Diabetes Research Studies
- Clinical Research
- Metabolic studies
- Biochemical Research
- Sports Medicine

Main Features:
- Extended range of analytes for diabetes research studies
- Small Sample size typically 3-25μl
- One low-cost electrode membrane for all analytes
- Printed results in 20-25 Seconds
- Data output facility

A Research Analyser with a Unique Assay Menu Including:
- Acetoacetate
- Alcohol
- Ammonia
- Cholesterol
- Creatinine
- Glucose
- Glutamine
- Glycerol
- Lactate
- 3-Hydroxybutyrate
- Pyruvate
- Triglycerides
- Urate
- Urea
Plasma Glutamine Levels in Burn-injured Patients

Parry-Billings Lancet 1990
The existing data in burn-injured patients is positive...

Effect on Mortality (n=4)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Glutamine Supplementation</th>
<th>Control</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>Wischmeyer 2001</td>
<td>1</td>
<td>12</td>
<td>4</td>
<td>14</td>
<td>0.29 [0.04, 2.27]</td>
</tr>
<tr>
<td>Zhou 2003</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Garrel 2003</td>
<td>2</td>
<td>21</td>
<td>12</td>
<td>24</td>
<td>0.19 [0.05, 0.78]</td>
</tr>
<tr>
<td>Patterson 2009</td>
<td>0</td>
<td>15</td>
<td>2</td>
<td>15</td>
<td>0.20 [0.01, 3.89]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>3</td>
<td>68</td>
<td>73</td>
<td>100.0%</td>
<td>0.22 [0.07, 0.62]</td>
</tr>
</tbody>
</table>

Risk Ratio

Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 2 (P = 0.94); I² = 0%
Test for overall effect: Z = 2.81 (P = 0.005)

RR, 0.22, 95% CI 0.07, 0.62, p = 0.005

...But the existing data set is small and from single centered studies (unreliable estimate). Therefore, we need a larger, multicenter trial!
A Randomized Trial of ENTERal Glutamine to Minimize Thermal Injury:

Double blind treatment

1200

2700 patients with TBSA

≥ 20% if 18-39 yrs age

≥ 15% if 18-39 yrs age with inhalation injury

≥ 15% if 40-59 yrs age

≥ 10% if ≥ 60 yrs age

EN glutamine

Concealed Stratified by site

Maltodextran placebo

6 month mortality

729 enrolled to date!
Total: 66 Sites Worldwide

Active Sites: 45  Closed: 2  Sites in Start-up: 21

Sites in Start-up will have a deadline of 31 March 2019 for activation
Updated Meta-analysis of IV Glutamine

Influence of the number of study sites involved in the trial

### Hospital Mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Chutamine Events Total</th>
<th>Control Events Total</th>
<th>Weight</th>
<th>Risk Ratio M-H Fixed 95% CI Year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.1 Multi-center studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wuschmeyer 2004</td>
<td>18</td>
<td>256</td>
<td>0.78</td>
<td>0.97 [0.94, 1.0] 2006</td>
</tr>
<tr>
<td>Greer 2011</td>
<td>9</td>
<td>59</td>
<td>13</td>
<td>4.5</td>
</tr>
<tr>
<td>Airdrake 2011</td>
<td>8</td>
<td>850</td>
<td>40</td>
<td>212</td>
</tr>
<tr>
<td>Wernerman 2001</td>
<td>11</td>
<td>209</td>
<td>12</td>
<td>180</td>
</tr>
<tr>
<td>Perez-Roman 2014</td>
<td>11</td>
<td>71</td>
<td>5</td>
<td>73</td>
</tr>
<tr>
<td>Zinger 2016</td>
<td>17</td>
<td>73</td>
<td>13</td>
<td>75</td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>718</td>
<td>730</td>
<td>41.1%</td>
<td>1.00 [0.81, 1.24]</td>
</tr>
<tr>
<td>Total events</td>
<td>122</td>
<td>124</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 17.9, df = 5 (p = 0.081), I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.49 (p = 0.000)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Chutamine Events Total</th>
<th>Control Events Total</th>
<th>Weight</th>
<th>Risk Ratio M-H Fixed 95% CI Year</th>
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</thead>
<tbody>
<tr>
<td><strong>1.2 Single-center studies</strong></td>
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<tr>
<td>Wuschmeyer 2004</td>
<td>18</td>
<td>83</td>
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<td>85</td>
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<td>Greer 2011</td>
<td>11</td>
<td>17</td>
<td>4</td>
<td>14</td>
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<tr>
<td>Geerts 1997 &amp; 2002</td>
<td>18</td>
<td>42</td>
<td>25</td>
<td>42</td>
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<td>Geerts 2002</td>
<td>7</td>
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<td>7</td>
<td>35</td>
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<tr>
<td>Fontes-Gonzalez 2004</td>
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<td>17</td>
<td>3</td>
<td>10</td>
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<td>Carosi 2004</td>
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<tr>
<td>Xian-Li 2004</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>20</td>
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<tr>
<td>Zhou 2004</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>Parner 2006</td>
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<td>Torn 2006</td>
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<td>Zhang 2007</td>
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<td>Yang 2007</td>
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<td>Saha 2008</td>
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<td>20</td>
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<tr>
<td>Yang 2008</td>
<td>1</td>
<td>25</td>
<td>3</td>
<td>25</td>
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<tr>
<td>Liu 2008</td>
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<td>11</td>
<td>0</td>
<td>9</td>
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<tr>
<td>Perez-Roman 2006</td>
<td>12</td>
<td>15</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>Fontes-Gonzalez 2008</td>
<td>2</td>
<td>22</td>
<td>5</td>
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<tr>
<td>Orgadslund 2008</td>
<td>12</td>
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<td>12</td>
<td>20</td>
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<td>Duska 2008</td>
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<td>6</td>
<td>10</td>
</tr>
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<td>Elhady 2008</td>
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<td>55</td>
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<tr>
<td>Efron 2008</td>
<td>1</td>
<td>20</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>Perez-Roman 2010</td>
<td>4</td>
<td>23</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>Cukman 2011</td>
<td>3</td>
<td>15</td>
<td>6</td>
<td>15</td>
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<tr>
<td>Cincotta 2014</td>
<td>4</td>
<td>48</td>
<td>4</td>
<td>49</td>
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<tr>
<td>Koolak 2014</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>615</td>
<td>615</td>
<td>54.9%</td>
<td>0.72 [0.53, 0.94]</td>
</tr>
<tr>
<td>Total events</td>
<td>197</td>
<td>149</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 13.70, df = 5 (p = 0.089), I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.49 (p = 0.000)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Total events | 249 | 273 | | |
| Heterogeneity: Chi² = 19.75, df = 5 (p = 0.000), I² = 0% |
| Test for overall effect: Z = 2.15 (p = 0.03) |
| Test for subgroup differences: Chi² = 4.56, df = 1 (p = 0.03), I² = 78.1% |

www.criticalcarenutrition.com
Rationale for Antioxidants

OFR production > OFR consumption = 

Depletion of Antioxidant Enzymes
OFR Scavengers
Vitamins/Cofactors

Impaired
- organ function
- immune function
- mucosal barrier function

Complications and Death
Selenium in Critical Illness

Circulating serum levels

Glutathionperoxidase (GPx) activity

HV=healthy volunteers

Correlation of selenium levels and GPx activity

Low plasma selenium levels result in suboptimal AOX-enzyme activities!
The SISPCT study

1180 ICU patients
Evidence of severe sepsis

PCT guidance

Factorial 2x2 design

No PCT guidance

Selenium
N= 273

Placebo
N= 267

Selenium
N= 279

Placebo
N= 270

Survival Curves: Placebo versus Selenium

Is sepsis too heterogeneous of a disease to manifest a positive treatment effect?
Why Cardiac Surgery as a Model for a Trial of Pharmaconutrition?

• Scheduled insult
• Mortality & Morbidity relatively common
• Morbidity often involves multiple organs = systemic process
• Large body of evidence implicating excessive systemic inflammation
The Systemic Inflammatory Response In Cardiac Surgery

**Stimulus**
- Hypoxia/Ischemia/Reperfusion/Endotoxin
- Contact Activation with Components of the CPB Circuit
- Surgical Tissue Trauma

**Treatment Approaches**

**Block or reduce stimulus**
- E.g., Coated Circuits, SDD, Pulsatile Perfusion, Leukofiltration, Cardioplegia, Oxygenator Off-pump Surgery, Cardiotomy Suction, Limitations to transfusion, Cell Washing

**Block Cellular Activation**
- E.g., Agents directed at blocking Adhesion Molecules or Integrins, Open Lung Mechanical Ventilation

**Block Signaling Mechanisms**
- E.g., Insulin, Pentoxyfylline, Glucocorticoids, Serine Protease Inhibitors, Statins, Phosphodiesterase Inhibitors, Eritoran

**Antimediator Therapies**
- E.g., Anti-Complement Strategies, Monoclonal Antibodies, Receptor Blocking Agents

**Block or reduce Free Radical Production**
- E.g., NAC, Methylene Blue

**Use of Life-Sustaining Treatments**

**Persistent Organ Dysfunction and Death**

- Microcirculatory Coagulopathy
- Generation of Free Radicals
- Apoptosis
- Organ Dysfunctions & Acute Multiorgan Failure
Selenium blood concentrations in patients undergoing elective cardiac surgery and receiving perioperative sodium selenite

Christian Stoppe M.D. a,b,*, Jan Spillner M.D. c, Rolf Rossaint M.D. a, Mark Coburn M.D. a, Gereon Schälte M.D. a, Anika Wildenhues M.D. a, Gernot Marx M.D. d, Steffen Rex M.D. a,e

- Open label, observational
- 104 CPB patients
- ICU LOS 3.3 ± 4.5 d
- 2000 µg Na₂SeO₃ IV bolus, then 1000 µg Na₂SeO₃ per ICU day
- 42 patients matched (EuroSCORE / Surgical Procedure) to historical control

Nutrition 29 (2013) : 158-165
Selenium blood concentrations in patients undergoing elective cardiac surgery and receiving perioperative sodium selenite

Christian Stoppe M.D.\textsuperscript{a,b,*}, Jan Spillner M.D.\textsuperscript{c}, Rolf Rossaint M.D.\textsuperscript{a}, Mark Coburn M.D.\textsuperscript{a}, Gereon Schälte M.D.\textsuperscript{a}, Anika Wildenhues M.D.\textsuperscript{a}, Gernot Marx M.D.\textsuperscript{d}, Steffen Rex M.D.\textsuperscript{a,e}
SodiUm SeleniTe Administration IN Cardiac Surgery
(SUSTAIN CSX®-trial)

1400 high-risk patients undergoing cardiac surgery

Double blind treatment

IV Selenium

Concealed Stratified by site

placebo

910 enrolled to date!

Alive and free of POD
Or Time to freedom from life-sustain treatments
High Dose Vitamin C Supplementation?

- Vitamin C
  - potent antioxidant
  - support endothelium reducing permeability and microvascular dysfunction
  - multiple effects on immunity
  - Co-factor in synthesis of catecholamines
  - Promotes wound healing
Hydrocortisone, Vitamin C and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Single Center Study

- Cocktail of Hydrocortisone 50 mg q 6h x 7 days, IV Ascorbic Acid 1.5 grams q 6h, and Thiamine 200 mg q 12h x 4 days

### TABLE 2 ] Outcome and Treatment Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treated (n = 47)</th>
<th>Control (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital mortality, No. (%)</td>
<td>4 (8.5)</td>
<td>19 (40.4)</td>
</tr>
<tr>
<td>ICU LOS, median and IQR, d</td>
<td>4 (3-5)</td>
<td>4 (4-10)</td>
</tr>
<tr>
<td>Duration of vasopressors, mean ± SD, h</td>
<td>18.3 ± 9.8</td>
<td>54.9 ± 28.4</td>
</tr>
<tr>
<td>RRT for AKI, No. (%)</td>
<td>3 of 31 (10%)</td>
<td>11 of 30 (33%)</td>
</tr>
<tr>
<td>ΔSOFA, 72 h</td>
<td>4.8 ± 2.4</td>
<td>0.9 ± 2.7</td>
</tr>
<tr>
<td>Procalcitonin clearance, median % and IQR, 72 h</td>
<td>86.4 (80.1-90.8)</td>
<td>33.9 (-62.4 to 64.3)</td>
</tr>
</tbody>
</table>

AKI = acute kidney injury; LOS = length of stay; RRT = renal replacement therapy; ΔSOFA = change in Sepsis-Related Organ Failure Assessment score. See Table 1 legend for expansion of other abbreviations.

\( ^a P < .001 \)

\( ^b P = .02 \)
• Single-center RCT of 28 patients
• Treated patients received 25 mg/kg intravenous ascorbic acid every 6 h for 72 h.

Table 4: Primary and secondary outcomes of the study in ascorbic and placebo groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Ascorbic acid group (n=14)</th>
<th>Control group (n=14)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean dose of norepinephrine (mcg/min) during the study period (72 h)</td>
<td>7.44±3.65</td>
<td>13.79±6.48</td>
<td>0.004</td>
</tr>
<tr>
<td>Mean dose of norepinephrine (mcg/min) during first 24 h (mcg/min)</td>
<td>6.51±3.53</td>
<td>12.58±5.99</td>
<td>0.003</td>
</tr>
<tr>
<td>Total dose of norepinephrine during the first 24 h (mcg)</td>
<td>156.42±84.81</td>
<td>302.14±143.85</td>
<td>0.003</td>
</tr>
<tr>
<td>Duration of norepinephrine administration (h)</td>
<td>49.64±25.67</td>
<td>71.57±1.60</td>
<td>0.007</td>
</tr>
<tr>
<td>Length of ICU stay (days)</td>
<td>21.45±10.23</td>
<td>20.57±13.04</td>
<td>0.85</td>
</tr>
<tr>
<td>28-day mortality</td>
<td>2 (14.28)</td>
<td>9 (64.28)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Data presented as mean±SD or n (%). SD=Standard deviation, ICU=Intensive Care Unit
31 septic patients

Phase I Vit C dosing study in Sepsis

Placebo

Low dose (50 mcg/kg/day)

High dose (200mcg/kg/day)

Plasma levels
SOFA
Other biomarkers

Plasma Vitamin C Levels

EFFECT on Organ Failure and other Mechanistic Endpoints

+ Reduced CRP and PCT (markers of inflammation)
+ Reduced Thrombomodulin (marker of vascular injury)

Await results of Phase II trial!

Test Monotherapy, Not Combination therapy?
Systematic review of Vit C supplementation

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Total Weight</th>
<th>Odds Ratio M–H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
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<td></td>
</tr>
<tr>
<td>3.1.1 Combined therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beale 2008</td>
<td>7</td>
<td>27</td>
<td>7</td>
<td>26</td>
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<tr>
<td>Berger 2008</td>
<td>14</td>
<td>102</td>
<td>9</td>
<td>98</td>
</tr>
<tr>
<td>Crimi 2004</td>
<td>49</td>
<td>112</td>
<td>76</td>
<td>112</td>
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<tr>
<td>Nathens 2002</td>
<td>5</td>
<td>301</td>
<td>9</td>
<td>294</td>
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<tr>
<td>Preiser 2000</td>
<td>8</td>
<td>20</td>
<td>6</td>
<td>17</td>
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<tr>
<td>Schneider 2011</td>
<td>6</td>
<td>29</td>
<td>6</td>
<td>29</td>
</tr>
<tr>
<td>van Zanten 2014</td>
<td>38</td>
<td>152</td>
<td>33</td>
<td>149</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>743</td>
<td>725</td>
<td>88.2%</td>
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<tr>
<td>Total events</td>
<td>127</td>
<td>146</td>
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<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.22; Chi² = 13.05, df = 6 (P = 0.04); I² = 54%
Test for overall effect: Z = 0.68 (P = 0.49)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Total Weight</th>
<th>Odds Ratio M–H, Random, 95% CI</th>
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<tr>
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<td>Events</td>
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<td>3.1.2 Monotherapy</td>
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<tr>
<td>Fowler 2014</td>
<td>7</td>
<td>16</td>
<td>5</td>
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<tr>
<td>Zabet 2016</td>
<td>2</td>
<td>14</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>30</td>
<td>22</td>
<td>11.8%</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>9</td>
<td>14</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.47; Chi² = 1.56, df = 1 (P = 0.21); I² = 36%
Test for overall effect: Z = 1.90 (P = 0.06)

Total (95% CI)           | 773                 | 747            | 100.0%       | 0.72 [0.43, 1.20] |

Total events            | 136                 | 160            |              |                                |

Heterogeneity: Tau² = 0.30; Chi² = 18.27, df = 8 (P = 0.02); I² = 56%
Test for overall effect: Z = 1.26 (P = 0.21)
Test for subgroup differences: Chi² = 2.60, df = 1 (P = 0.11), I² = 61.5%
The Lessening Organ Injury/Dysfunction with VITamin C (LOVIT) Trial

Double blind treatment

IV Vit C (200mcg/kg/day in divided doses)

800 ICU patients with sepsis and vasopressors

Concealed Stratified by site

Saline placebo

28-day Persistent Organ Dysfunction (POD)+death*

*Heyland Crit Care 2011
Biggest Controversy of Them ALL

Do you see yourself as a Doctor that looks after patients ONLY

Or

As someone that examines and contributes to improving the system that we have created to care for these vulnerable patients?
Critical Care Nutrition at the Clinical Evaluation Research Unit (CERU)
is dedicated to improving nutrition therapies in the critically ill through knowledge generation, synthesis, and translation. We engage in a broad range of research activities and promote a culture of best practices in critical care nutrition. Ultimately, this will result in improved clinical outcomes for critically ill patients and increased efficiencies to our health care systems.

www.criticalcarenutrition.com
Summary

• Evidence base informing clinical nutrition practices is weak with conflicting signals

• Probably nutritionally high-risk patients will benefit the most from macronutrients;

• Protein more important than calories

• Pharmaconutrition still alive as a concept

• More research needed to define optimal dose of protein/calories and value of various micronutrients

• We need your help! See yourself as part of the solution!
QUESTIONS?