Nutrition Support — A Few Hot Topics
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Disclosures
• None

Objectives
• Discuss the role of glutamine and antioxidant supplementation in the critically ill.
• Discuss the role of alternative intravenous lipid emulsions in critical illness

Glutamine and Antioxidants

Antioxidants
• In critical illness reactive oxygen species (ROS) can cause cellular and tissue damage
• The body protects itself from ROS with enzymes, glutathione, and vitamins
  - Enzyme cofactors: selenium, zinc, manganese, iron
  - Vitamins: Vitamin E, Vitamin C, beta-carotene (Vitamin A)
• Increased severity of illness leads to depletion of antioxidants
• Low endogenous stores of antioxidants increases free radicals, inflammatory response, morbidity and mortality

Antioxidants - Selenium
• Thought to be one of the key antioxidants for critically ill patients
• 2013 Meta-analysis showed:
  - Reduced mortality in septic patients
  - Doses ≥ 1000 mcg/day beneficial
  - Loading doses may be helpful
  - Longer duration of therapy better (>7 days)
  - No adverse effects noted
Antioxidants - Selenium

- Decreased mortality in patients with SIRS or sepsis

Antioxidants – 2009 SCCM/ASPEN Guidelines

F2. A combination of antioxidant vitamins and trace minerals (specifically including selenium) should be provided to all critically ill patients receiving specialized nutrition therapy. (Grade: B)

- Grade of recommendation
  - B
- Level of evidence
  - I
- Large, randomized trials with clear-cut results

Antioxidant Meta-Analysis - 2005

- Decreased mortality in critically ill patients

Hylant et al. Intensive Care Med 2005

Antioxidant Meta-Analysis - 2012

- Decreased mortality in critically ill patients

- Decreased number of ventilator days in critically ill patients

Antioxidant Meta-Analysis - 2012

- Trend toward decreased infections in critically ill patients

Manusans et al. Critical Care 2012
Antioxidant Meta-Analysis - 2012

- Other results
  - Patients with high severity of illness benefited more
  - Selenium alone was not found to have significant effect on mortality
  - Some studies excluded from prior meta-analysis

Antioxidants - 2013 Canadian Guidelines

- Supplemental antioxidants, including selenium: "Should be considered in critically ill patients"
  - Large heterogeneity in studies
  - Lack of defined doses
  - Large randomized trials did not show benefit

  - No concerns with regard to safety, feasibility, or cost

Dose Recommendations

<table>
<thead>
<tr>
<th>Antioxidant</th>
<th>Dose range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selenium</td>
<td>50-1000 μg/day</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>400-1000 IU/day</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>300-500-1500 mg/day</td>
</tr>
<tr>
<td>Zinc</td>
<td>12-20 mg/day</td>
</tr>
<tr>
<td>Copper</td>
<td>40-60 μmol/day</td>
</tr>
<tr>
<td>Beta carotene</td>
<td>10 mg</td>
</tr>
</tbody>
</table>

- Crimi et al dosing: Enteral Vitamin C 500 mg/day; Enteral Vitamin E 400 IU/day

Glutamine

- Preferred amino acid fuel for gut and immune system
- Critical illness associated with decreased serum levels
  - Low levels associated with increased mortality and immune dysfunction
- Supplementation in critical illness may help:
  - Maintain GI integrity and reduce permeability
  - Preserve skeletal muscle, improve nitrogen balance
  - Enhance immune function
  - Provide anti-oxidant effects as precursor to glutathione

Glutamine - 2009 SCCM/ASPEN Guidelines

F3. The addition of enteral glutamine to an EN regimen (not already containing supplemental glutamine) should be considered in burn, trauma, and mixed ICU patients. (Grade: B)

  - 0.3-0.5 g/kg/day

G5. When PN is used in the critical care setting, consideration should be given to supplementation with parenteral glutamine. (Grade: C)

  - 0.5 g/kg/day

Glutamine - Available formulations

- Enteral
  - Various formulations
  - Powder packets to mix with water, soda or juice

- Parenteral
  - US - Free L-glutamine
  - Non-sterile powder - USP 797 High risk compounding
    - Requires post compounding cold membrane sterilization
  - Parenteral glutamine Dipeptide
    - Heat sterilized, long shelflife

Hegland et al. NEM 2013
Crimi et al. Anesth Analg 2005
Miiclose et al. JPEN 2009
Glutamine and the REDOX Study

A Randomized Trial of Glutamine and Antioxidants in Critically Ill Patients

Dawne Hayland, M.D., John Morinoff, M.D., Paul E. Wischmeyer, M.D., Deborah Cook, M.D., Guyan Jones, M.D., Martin Albert, M.D., Gunnar Ellek, M.D., Miltie M. Berger, M.D., Ph.D., and Andrew G. Day, M.Sc., for the Canadian Critical Care Trials Group

Glutamine and the REDOX Study

- 1223 patients randomized
- Population
  - Mixed medical-surgical
  - More medical
  - Average age ~65
  - Mainly septic shock
  - APACHE II average ~29
  - Predicted >50% mortality

Glutamine and the REDOX Study

- Oxygen and glutamine
- Glutamine and Phloris
- Placebo & Phloris

Glutamine – 2013 Canadian Guidelines

- Enteral
  - Glutamine should be considered in burn and trauma patients
- Parenteral
  - When parenteral nutrition is prescribed to critically ill patients, parenteral supplementation with glutamine should be considered
  - Strongly recommend that any type of glutamine NOT be used in critically ill patients with shock and multi-organ failure

Glutamine – 2013 Canadian Guidelines

- Respiratory
- Cardiovascular
- Renal
- Pancreatic

Glutamine – 2013 Canadian Guidelines

- Increased hospital mortality in glutamine group
- No difference in antioxidant group

Alternative Lipid Emulsions

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\text{H}_2\text{C} & - \text{O} - \text{O} - \\
\text{H}_2\text{C} & - \text{O} - \text{O} - \\
\end{align*}
\]
Lipid Emulsions

Key characteristics of widely available parenteral lipid emulsions

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Intralipid 20%</th>
<th>Intralipid 10%</th>
<th>Lipid Emulsion 20%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source of EE</td>
<td>Triglycerides</td>
<td>Triglycerides</td>
<td>Triglycerides</td>
</tr>
<tr>
<td>Source of CE</td>
<td>Soybeans</td>
<td>Soybeans</td>
<td>Soybeans</td>
</tr>
<tr>
<td>Source of FFA</td>
<td>Soybeans</td>
<td>Soybeans</td>
<td>Soybeans</td>
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<tr>
<td>Typical FA composition% of total FA</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>16:0</td>
<td>31</td>
<td>31</td>
<td>27</td>
</tr>
<tr>
<td>18:0</td>
<td>47</td>
<td>47</td>
<td>47</td>
</tr>
<tr>
<td>20:4</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>22:6</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Other fatty acids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Phospholipids</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Calder et al. Intensive Care Med 2010

Fatty Acids and Inflammation

18:3ω-6 linoleic | 18:2ω-6 arachidonic

20:4ω-6 eicosapentaenoic

Pro-inflammatory

Calder et al. Intensive Care Med 2010

Lipid Emulsions – 2009

SCCM/ASPEN Guidelines

G3. In the first week of hospitalization in the ICU, when PN is required and EN is not feasible, patients should be given a parenteral formulation without soy-based lipids. (Grade: D)

McClure et al. JPEN 2009

Lipid Emulsions – 2009

SCCM/ASPEN Guidelines

Emulsified Fat and Parenteral Nutrition (PN) With and Without Lipids in Critically Ill Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>16:0%</th>
<th>18:0%</th>
<th>EFA 18:2n6</th>
<th>EFA 20:4n6</th>
<th>EFA 20:5n3</th>
<th>EFA 22:6n3</th>
<th>20:4n6 (mean)</th>
<th>20:5n3 (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>study 1</td>
<td>9%</td>
<td>27%</td>
<td>27%</td>
<td>15%</td>
<td>27%</td>
<td>15%</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>study 2</td>
<td>9%</td>
<td>27%</td>
<td>27%</td>
<td>15%</td>
<td>27%</td>
<td>15%</td>
<td>4%</td>
<td>4%</td>
</tr>
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All standard deviations are expressed as SD. EFA, essential fatty acids. Significance level of 0.05.


Significant decreases in infections, LOS, and ventilator days

McClure et al. JPEN 2009

International Nutrition Survey

- Study looking at data from the INS database with regard to lipid formulations
- 451 critically ill patients receiving only PN
- PN must have been given for at least 5 days


Figure 5. Cumulative incidence of survival patients with infection and complication of fat emulsion (FVE) category. ANOVA: RCT = randomized controlled trials.

Lipid Emulsions – 2013 Canadian Guidelines

"When parenteral nutrition with intravenous lipids is indicated, IV lipids that reduce the load of omega-6 fatty acids/soybean oil emulsions should be considered. However, there are insufficient data to make a recommendation on the type of lipids to be used that reduce the omega-6 fatty acid/soybean oil load in critically ill patients receiving parenteral nutrition."


Conclusions

• Consider anti-oxidant supplementation for critically ill patients
  • Optimal content, dosing and timing unknown
  • Selenium, Vitamin C + E, and Zinc appear to be safe with few minor side effects
• Consider enteral glutamine in burn and trauma patients
• Glutamine (enteral or IV) for patients in shock and MODS is NOT recommended
• Consider omega-6 minimization strategy when lipids are indicated in critically ill patients

As demonstrated in the recent REDOXS trial, glutamine use in critically ill patients with multi-organ failure resulted in which of the following?
  a) Increased hospital mortality
  b) Increased incidence of organ failure
  c) Increased duration of mechanical ventilation
  d) Increased incidence of infectious complications

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