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

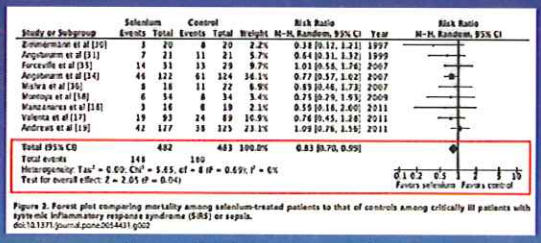
Heyland et al. Intensive Care Med 2005

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

Huang et al. PLoS One 2013

Antioxidants - Selenium



- Decreased mortality in patients with SIRS or sepsis

Huang et al. PLoS One 2013

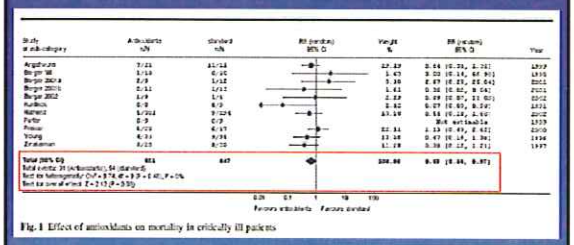
Antioxidants – 2009 SCCM/ASPEN Guidelines

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	Supported by one level I investigation
Level of evidence	
I	Large, randomized trials with clear-cut results

McClave et al. JPEN 2009

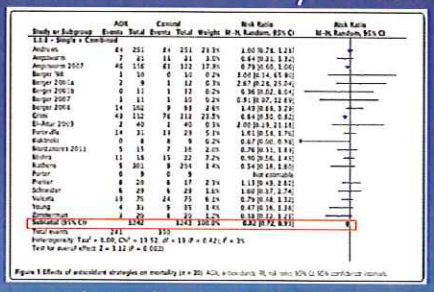
Antioxidant Meta-Analysis - 2005



- Decreased mortality in critically ill patients

Heyland et al. Intensive Care Med 2005

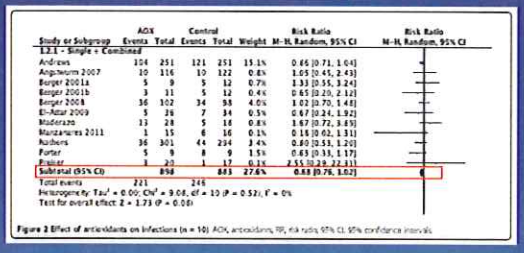
Antioxidant Meta-Analysis - 2012



- Decreased mortality in critically ill patients

Manzanares et al. Critical Care 2012

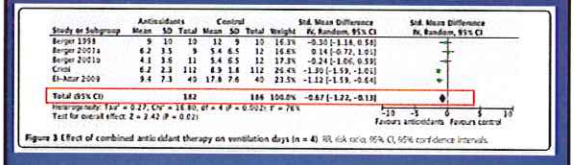
Antioxidant Meta-Analysis - 2012



- Trend toward decreased infections in critically ill patients

Manzanares et al. Critical Care 2012

Antioxidant Meta-Analysis - 2012



- Decreased number of ventilator days in critically ill patients

Manzanares 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

Manzanares et al. Critical Care 2012

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**

Dhaliwal et al. Nutr Clin Pract 2014

Dose Recommendations

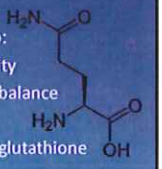
Antioxidant	Dose range
Selenium	50-**1000** µg/day
Vitamin E	**400**-1000 IU/day
Vitamin C	300-**500**-**1500** mg/day
Zinc	**12**-20 mg/day
Copper	**40**-60 µmol/day
Beta carotene	10 mg

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

Crimi et al. Anesth Analg 2004

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



Heyland et al. NEJM 2013

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 <u>High risk compounding</u>**
      - **Requires post compounding cold membrane sterilization**
    - Poor aqueous stability
  - International – glutamine dipeptide
    - Heat sterilized, long shelf-life

Vanek et al. Nutr Clin Pract 2011

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**

McClave et al. JPEN 2009

Glutamine and the REDOX study

ORIGINAL ARTICLE

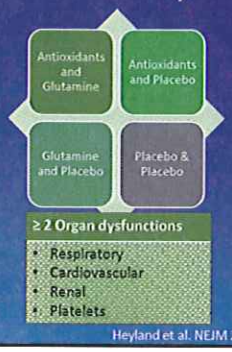
A Randomized Trial of Glutamine and Antioxidants in Critically Ill Patients

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

Heyland et al. NEJM 2013

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



≥ 2 Organ dysfunctions
- Respiratory
- Cardiovascular
- Renal
- Platelets

Heyland et al. NEJM 2013

Glutamine and the REDOX Study

Table 3. Clinical Outcomes in All 1218 Study Patients.

Variable	Glutamine	No Glutamine	P Value	Antioxidants	No Antioxidants	P Value
Death — no. of patients/total no. (%)						
At day 28	198/611 (32.4)	165/607 (27.2)	0.05*	190/617 (30.8)	173/601 (28.8)	0.48
At day 14	157/611 (25.7)	129/607 (21.3)	0.07	154/617 (25.0)	132/601 (22.0)	0.23
In hospital	227/611 (37.2)	189/607 (31.0)	0.02	216/617 (35.0)	199/601 (33.1)	0.51
At 6 mo†	259 (43.7)	218 (37.2)	0.02	242 (40.4)	235 (40.6)	0.87

*Level of significance set at p ≤ 0.044

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

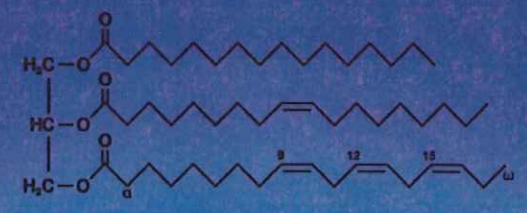
Heyland et al. NEJM 2013

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**

Dhaliwal et al. Nutr Clin Pract 2014

Alternative Lipid Emulsions



Lipid Emulsions

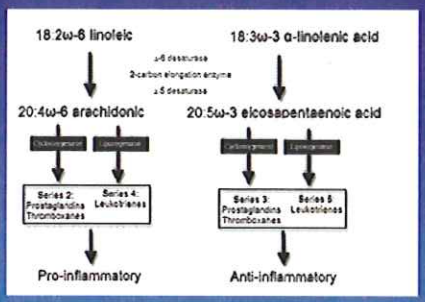
Key characteristics of widely available parenteral lipid emulsions

	Intralipid	Omegaven	ClinOleic
Manufacturer	Fresenius Kabi, Germany	Fresenius-Kabi, Germany	Baxter, France
Oil source (% by weight)	Soybean	Fish (100%)	Olive (80%), soybean (20%)
Typical FA composition (% of total FA)			
Caprioc			
Caprylic			
Capric			
Laurie			
Myristic		5	Trace
Palmitic	11	12	12
Stearic	4	4.5	2
Palmitoleic		9	1.5
Oleic	24	15	62
Linoleic	53	4.5	19
α-Linolenic	8	1.8	2.5
Arachidonic		2	
Eicosapentaenoic		20	
Docosapentaenoic		2	
Docosahexaenoic		12	
α-Tocopherol (μmol/L)	87	505	75

FA fatty acids

Calder et al. Intensive Care Med 2010

Fatty Acids and Inflammation



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)

McClave et al. JPEN 2009

Lipid Emulsions – 2009 SCCM/ASPEN Guidelines

Randomized Studies Evaluating Parenteral Nutrition (PN) With vs Without Lipids in Critically Ill Patients

Study	Population	Study Groups	ICU Mortality	Infections[a]	LOS Days, Mean ± SD	Ventilator Days, Mean ± SD
Battistella et al, 1997 Level II	Trauma (n = 57)	Without	2/27 (7%)	Pneumonia 13/27 (48%)[b]	27 ± 16 Hosp[b]	15 ± 12[b]
		With	0/30 (0%)	22/30 (74%)	39 ± 24 Hosp	27 ± 21
				Line sepsis 5/27 (19%)[b]	18 ± 12 ICU[b]	
				14/30 (48%)	29 ± 22 ICU	

SD, standard deviation; NR, not reported; ICU, intensive care unit; LOS, length of stay.
[a] All infections represent number of patients per group with infection unless otherwise stated.
[b] $P \leq .05$.

- **Significant decreases in infections, LOS, and ventilator days**

McClave 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

Edmunds et al. Crit Care Med 2014

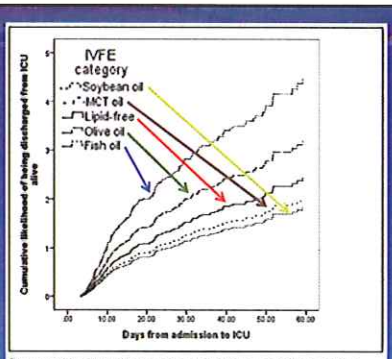


Figure 2. Cumulative hazard curve of the likelihood of patients being discharged from ICU alive for comparison of lipid free versus each IV fat emulsion (IVFE) category ($p < 0.001$). MCT = medium-chain triglyceride.

Edmunds et al. Crit Care Med 2014

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."*

Dhaliwal et al. Nutr Clin Pract 2014

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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