Let the Sun Shine in:
Vitamin D and other Supplements in the ICU

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Disclosures

None to report
Why Consider Supplements?

- Perceived safe therapeutic window
- Ease of use
- Inexpensive
- Little “down side”
- Do we really need RCTs?
Skin and heat produce vitamin D₃

Vitamin D₃

Food source and supplemental vitamin D₃ added

Liver converts Vitamin D₃ to 25(OH)D (calcidiol).

Liver provides calcidiol to the kidney, brain, nerves, muscle, heart, lungs, bone and other tissue.

Numerous other tissues

Kidney (and other tissues) convert Calcidiol to 1,25(OH)₂D (Calcitriol) (the activated form of Vitamin D)

VDR (binding sites) in most body tissues
Vitamin D

- Synthesized from cholesterol upon exposure to UVB light
- Deficiency is more prevalent in certain groups
  - Age, skin color, geography, sun exposure
- Functions in the body as a steroid hormone
  - Calcium/phosphate homeostasis / bone
  - Immune, cardiovascular, muscle, brain, pancreas and cell cycle control
  - VDR is present in the nucleus of many tissues not involved in calcium and phosphate metabolism
- Epidemiologic evidence demonstrates an association between Vitamin D deficiency and diseases
Vitamin D

Potential Role of Vitamin D Supplementation

- General Health and Deficiency
- CV Disease
  - HTN, HF, ASD
  - Statin myopathy
- Diabetes
- Respiratory Diseases
  - Asthma/COPD
- Eye Disease
- Infectious Diseases
  - TB/ URIs
  - Immune function
- Neurologic Disease
  - MS, Depression, Dementia
  - Migraines
- Cancer
  - Colon and Breast

Haines ST et al. Pharmacotherapy 2012;32:354-182
Vitamin D in Critical Illness

- Vitamin D Deficiency (< 20 ng/ml) in 50%
  - 17% have undetectable levels
- Associated with adverse outcomes:
  - Infections
  - LOS
  - Kidney Injury
  - Mortality (although conflicting results)
- Unknown cause/effect relationship
- Reduction likely due to decrease in Vitamin D binding protein (VDBP)
- Guidelines do not recommend routine supplementation
  - Bariatric surgery patients in ASPEN/SCCM guidelines
Evaluation of Vitamin D Concentrations

- Plasma protein binding
  - VDBP 90%, Albumin ~ 10%, Free 1%
- Calcidiol (25(OH)D) best indicator of vitamin D status
  - Represents vitamin D produced by the skin and that consumed (diet + supplements)
  - Circulating half-life of 15 days
  - 25(OH)D functions as a biomarker of exposure, but not tissue stores
- Calcitriol (1,25(OH)\(_2\)D) poor indicator of vitamin D
  - Short half-life of 15 hours
  - Serum concentrations are closely regulated by parathyroid hormone, calcium, and phosphate
  - Levels do not decrease until deficiency is severe
Vitamin D in Critical Illness

Meta-analysis

Additional endpoints evaluated

- ICU and hospital LOS, infection rate, MV days

Antioxidants
## Components of the Oxidative Balance

<table>
<thead>
<tr>
<th>The Bad Guys</th>
<th>The Good Guys</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reactive Oxygen Species (ROS)</strong></td>
<td><strong>Antioxidant Enzymes</strong></td>
</tr>
<tr>
<td>- Superoxide Anion ($\text{O}_2^-$)</td>
<td>- Superoxide dismutase (SOD)</td>
</tr>
<tr>
<td>- Hydroxyl Radical (OH)</td>
<td>- Catalase (CAT)</td>
</tr>
<tr>
<td>- Hydrogen Peroxide ($\text{H}_2\text{O}_2$)</td>
<td>- Glutathione peroxidase (GPx)</td>
</tr>
<tr>
<td><strong>Reactive Nitrogen Species (RNS)</strong></td>
<td>- Thioredoxin system (TRX)</td>
</tr>
<tr>
<td>- Nitric Oxide (NO⁻)</td>
<td><strong>Antioxidant Compounds</strong></td>
</tr>
<tr>
<td>- Peroxynitrite (ONOO⁻)</td>
<td>- Vitamins A, C, E</td>
</tr>
<tr>
<td></td>
<td>- Selenium, Zinc</td>
</tr>
</tbody>
</table>
Consequences of Oxidative Stress

Critical illness
- Sepsis
- ARDS
- Ischemia Reperfusion-injury

Pro-oxidants↑

Antioxidants↓

Increased loss
- Redistribution
- Increased use

Oxidative Stress

- Lipid peroxidation
- Protein oxidation
- DNA damage

Cell damage

Tissue damage

Organ damage

Induction of pro-oxidant enzymes (NOX/NOS)
Increased production of ROS/RNS by leukocytes and anaerobic cell metabolism
Oxidative Stress in Critical Illness

- **Sepsis**
  - Large amounts of radical produced by phagocytes and up-regulated enzymes (i.e. NADPH, iNOS)
    - Increased production of ROS/RNS
  - Produces oxidative stress and stimulates inflammatory mediators
    - Mitochondrial damage results in organ dysfunction
    - Vascular hyporeactivity to catecholamines and increased permeability
    - Glutathione unable to impact vascular and endothelial dysfunction due to inactivation by peroxynitrite
  - Reduced antioxidant status
    - Redistribution, body fluid losses, dilution, inadequate intake
Oxidative Stress in Critical Illness

- Ischemia / reperfusion injury
  - Increased mitochondrial ROS production and xanthine oxidase activity
    - Hypoxanthine accumulated during hypoxia reacts with oxygen upon reperfusion to produce superoxide
  - Vascular NADPH oxidase and eNOS
    - Induce superoxide and NO production resulting in peroxynitrite

- ARDS
  - Activated neutrophil migration into alveoli produces inflammatory mediators including ROS/RNS
    - Peroxynitrate is produced which inactivates surfactant / DNA damage
    - $O_2$ and NO administration increase oxidant production
  - Glutathione usually abundant in lungs is reduced
Selenium

- Essential micronutrient that functions as a enzymatic cofactor of more than 30 selenoproteins
  - Biologic activity includes the antioxidant defense system, thyroid and immune function
  - 50% have antioxidant activity
  - 60% found in serum as selenoprotein P (SePP)
- Excellent absorption
- Renal excretion
- Homeostasis effected by SIRS
  - Redistributed to tissues involved in protein synthesis and immune
Selenium Status in Critically Ill Patients

- Levels lower vs normal
- Sepsis and shock show a greater decrease compared to other ICU populations
- Urinary excretion remains constant
- Lower levels correlated with adverse outcomes:
  - Negative correlation with sepsis severity scores
  - 3 x higher mortality and 3.5 x higher rate of organ failure with level below 0.70 µmol/L
  - SePP levels 70% lower on admission for septic patients and significantly lower in non-survivors
  - Levels below 60 µg/L (0.78 µmol/L) predict mortality with a 81.2% specificity
Does selenium supplementation improve outcomes?

<table>
<thead>
<tr>
<th>Meta-Analysis</th>
<th>Population (N)</th>
<th>Mortality RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang et al 2013</td>
<td>ICU septic patients 965</td>
<td>0.83 (0.70 – 0.99)</td>
</tr>
<tr>
<td>Alhazzani et al 2013</td>
<td>ICU septic patients 792</td>
<td>0.73 (0.54 – 0.98)</td>
</tr>
<tr>
<td>Kong et al 2013</td>
<td>ICU septic patients 530</td>
<td>0.89 (0.73 – 1.07)</td>
</tr>
<tr>
<td>Landucci et al 2014</td>
<td>Critically Ill patients 921</td>
<td>0.84 (0.71 – 0.99)</td>
</tr>
<tr>
<td>Canadian practice guidelines 2015</td>
<td>Critically Ill patients 3918</td>
<td>0.99 (0.90 – 1.08)</td>
</tr>
<tr>
<td>Cochrane Review 2015</td>
<td>Critically Ill patients 1391</td>
<td>0.82 (0.72 – 0.93)</td>
</tr>
<tr>
<td>ASPEN/SCCM 2016</td>
<td>Critically Ill patients 1888</td>
<td>0.94 (0.84 – 1.06)</td>
</tr>
</tbody>
</table>
Zinc

- Essential trace element required for normal immune function, glucose control, neurocognitive function, wound healing and oxidative stress response
  - Cofactor in > 300 enzymes
  - Role in DNA and protein synthesis, cell proliferation and cell membrane integrity
- No specific storage system
  - Body stores determined by intake and renal/intestinal excretion
- Low plasma levels common in critically ill / SIRS
  - Redistribution, increased utilization, enhanced urinary excretion and poor nutrition all contributory
Zinc’ role in the antioxidant activity

- Increases antioxidant enzymes
  - Increases activation of OC, GPx and CAT
  - Stimulates glutathione synthesis
- Reduces pro-oxidant enzyme activity
  - Inhibits NADPH, iNOS, NMDA
- Competes with redox active transition metals
  - Iron and copper are prohibited from catalyzing the formation of free radicals
- Protects proteins from oxidation through binding of sulfhydryl groups
- Enhances glucose transport into cells
- Binds to thionein proteins to form free radical scavenger metallothionein
Zinc supplementation in the critically ill

- Majority of clinical trials evaluating zinc supplements included it as part of an antioxidant cocktail

- One trial evaluated its use alone
  - Small (n=68), limited population (closed head injury), RCT who received zinc for 15 days in PN followed by oral for 3 months
  - One month mortality was lower in the zinc supplement group 12% vs 26%, p=0.09 with improved neurologic recovery
  - Control group had more subjects undergo craniotomies and receive barbiturates

- Systematic Review
  - Trend toward reduced mortality and ICU LOS but 3 of the 4 studies included additional antioxidants

Vitamin A

- Fat soluble vitamin essential for multiple physiologic functions including vision, cellular proliferation and differentiation, immune function, reproduction and antioxidant activity

- Consists of a group of retinoids (retinol, retinoic acid, retinal) and carotenoids ($\alpha$, $\beta$, $\gamma$)
  - $\beta$ carotene is the most potent antioxidant

- Retinol is absorbed in the small intestine, stored in the liver and excreted in the bile
  - Acute infection increases retinol and RBP urinary excretion

- Zinc deficiency may produce vitamin A deficiency
  - Inhibits RBP production as well as the enzyme that converts retinol to retinal (form used by the eye)

- Low plasma levels observed in > 50% critically ill / SIRS
Vitamin A Supplementation in critical illness

- β-carotene vs retinol
  - Carotenoids generally safer due to the highly regulated metabolic conversion
  - Evaluation of low carotenoid concentrations did not demonstrate correlation with

- Primarily studied as part of an antioxidant cocktail
- One study in 90 CABG patients randomized 2:1 placebo/vitamin A 5000 units daily x 21 days demonstrated vitamin A:
  - Reduced mortality (3.3% vs 8.3%)
  - Reduced ICU LOS (4.6 vs 8.5 days)
  - No difference in time on mechanical ventilation (2.1 vs 2.7 days)

Vitamin E

- Family of lipid-soluble tocopherols and tocotrienoles
  - $\alpha$-tocopherol is the most potent
  - Antioxidant, membrane stability and immune support in response to infection
  - Primarily found in the cell membrane
  - Protects the cell membrane from peroxidation by breaking the lipid radical chain reaction
- Lipid status influences measurement in plasma
  - Reduced concentrations noted in critically ill patients may be related to reduced lipid concentrations
  - No relationship observed between serum concentrations and patient outcomes
- Studies evaluating Vitamin E supplementation as a single intervention have not demonstrated impact on outcome
Vitamin C

- Ascorbic Acid
- Water soluble antioxidant that is a cofactor for several enzymes
  - Iron and Folic Acid Metabolism
  - Collagen, cortisol, cathecholamine and carnitine synthesis
  - Augments immune function via various pathways
- Absorbed in the small intestines
  - Saturable process
- Renally excreted
- Intracellular concentrations 25 – 80 x higher than plasma
  - Oxidative stress increases intracellular transport
Vitamin C as an antioxidant

- Limits generation of ROS
- Directly scavenges ROS/RNS
  - Superoxide, hydroxyl, peroxyl and nitroxyl
- Repairs other oxidized scavengers
  - Glutathione and Urate
- Regenerates Vitamin E
- Indirect activity results in conversion of H2O2 to water
- Low plasma concentrations in critical illness
  - Associated with inflammation, organ failure severity and mortality
  - Causes included inadequate intake, increase utilization and increased losses
Vitamin C supplementation in critical illness

- High frequency of deficiency in critical illness supports exploration of supplementation in critical illness
- Large doses appear to be necessary to normalize plasma concentrations (3 grams/day)
- Two cardiac surgery trial assessed efficacy on LOS
  - One study found a short hospital LOS (10 vs 12) but neither saw a reduction in ICU LOS.
- Sepsis
  - Phase 1 trial evaluated 2 dosing strategies vs placebo  N = 28
    - 50 mg/kg/day and 200 mg/kg/day
    - Reduction in biomarkers and SOFA scores
    - Mortality also reduced but not a powered
Vitamin C Cures Sepsis!

Hydrocortisone for the Septic: A Retrospective Study

Paul E. Marik, MD, and John Catlin, MD

*CHEST 2017; 151(6):1229-1238*
Thiamine

- Essential for normal functioning of the Kreb’s cycle
  - Deficiency results in anaerobic metabolism
- Critically Ill patients deficient 10 – 70%
- Elevated lactate, acidosis and hypotension occur in both septic shock and thiamine deficiency
  - Increased lactate results from failure of oxygen utilization secondary to thiamine’s essential role in mitochondrial metabolism
Thiamine to resuscitate septic shock

- Thiamine dose 200 mg IV BID x 7 days or until d/c
- Individuals with a potential for thiamine deficiency (ie alcoholics) were excluded

Thiamine

- Retrospective cohort study of septic shock patients with a concurrent alcohol use disorder admitted to the ICU
- Patient characteristics were similar between groups except for a significant difference in platelets (p = 0.04)

<table>
<thead>
<tr>
<th></th>
<th>Thiamine N = 34</th>
<th>No Thiamine N = 19</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality (%)</td>
<td>15 (44)</td>
<td>15 (79)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hospital-free days</td>
<td>12</td>
<td>18</td>
<td>0.36</td>
</tr>
<tr>
<td>ICU-free days</td>
<td>21</td>
<td>21</td>
<td>0.71</td>
</tr>
</tbody>
</table>

Should we combine antioxidants?
## ASPEN / ACCM Guidelines

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Total</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrews, 2011</td>
<td>84</td>
<td>251</td>
<td>84</td>
<td>251</td>
<td>24.5%</td>
<td>1.00 [0.78, 1.28]</td>
<td></td>
</tr>
<tr>
<td>Kuklinski, 1991</td>
<td>0</td>
<td>8</td>
<td>8</td>
<td>9</td>
<td>0.2%</td>
<td>0.07 [0.00, 0.98]</td>
<td></td>
</tr>
<tr>
<td>Mishra, 2007</td>
<td>11</td>
<td>18</td>
<td>15</td>
<td>22</td>
<td>7.7%</td>
<td>0.90 [0.56, 1.43]</td>
<td></td>
</tr>
<tr>
<td>Crimi, 2004</td>
<td>49</td>
<td>112</td>
<td>76</td>
<td>112</td>
<td>24.7%</td>
<td>0.64 [0.50, 0.82]</td>
<td></td>
</tr>
<tr>
<td>Angstwurm, 1999</td>
<td>7</td>
<td>21</td>
<td>11</td>
<td>21</td>
<td>3.2%</td>
<td>0.64 [0.31, 1.32]</td>
<td></td>
</tr>
<tr>
<td>Angstwurm, 2007</td>
<td>46</td>
<td>116</td>
<td>61</td>
<td>122</td>
<td>18.9%</td>
<td>0.79 [0.60, 1.06]</td>
<td></td>
</tr>
<tr>
<td>Forceville, 2007</td>
<td>14</td>
<td>31</td>
<td>13</td>
<td>29</td>
<td>5.4%</td>
<td>1.01 [0.58, 1.76]</td>
<td></td>
</tr>
<tr>
<td>Zimmerman, 1997</td>
<td>3</td>
<td>20</td>
<td>8</td>
<td>20</td>
<td>1.3%</td>
<td>0.38 [0.12, 1.21]</td>
<td></td>
</tr>
<tr>
<td>Preiser, 2000</td>
<td>8</td>
<td>20</td>
<td>6</td>
<td>17</td>
<td>2.5%</td>
<td>1.13 [0.49, 2.62]</td>
<td></td>
</tr>
<tr>
<td>Valenta, 2011</td>
<td>19</td>
<td>75</td>
<td>24</td>
<td>75</td>
<td>6.5%</td>
<td>0.79 [0.48, 1.32]</td>
<td></td>
</tr>
<tr>
<td>Manzanares, 2011</td>
<td>3</td>
<td>15</td>
<td>5</td>
<td>16</td>
<td>1.1%</td>
<td>0.64 [0.18, 2.22]</td>
<td></td>
</tr>
<tr>
<td>Young, 1996</td>
<td>4</td>
<td>33</td>
<td>9</td>
<td>35</td>
<td>1.5%</td>
<td>0.47 [0.16, 1.38]</td>
<td></td>
</tr>
<tr>
<td>Berger, 2007</td>
<td>1</td>
<td>11</td>
<td>1</td>
<td>10</td>
<td>0.3%</td>
<td>0.91 [0.07, 12.69]</td>
<td></td>
</tr>
<tr>
<td>Berger 2001a</td>
<td>2</td>
<td>9</td>
<td>1</td>
<td>12</td>
<td>0.3%</td>
<td>2.67 [0.28, 25.04]</td>
<td></td>
</tr>
<tr>
<td>Berger 2001b</td>
<td>0</td>
<td>11</td>
<td>1</td>
<td>12</td>
<td>0.2%</td>
<td>0.36 [0.02, 8.04]</td>
<td></td>
</tr>
<tr>
<td>Schneider, 2011</td>
<td>6</td>
<td>29</td>
<td>6</td>
<td>29</td>
<td>1.7%</td>
<td>1.00 [0.37, 2.74]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 780 792 100.0% 0.80 [0.70, 0.92]

Total events 257 329

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 15.56$, df = 15 ($P = 0.41$); $\Gamma^2 = 4$

Test for overall effect: $Z = 3.27$ ($P = 0.001$)

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*Journal of Parenteral and Enteral Nutrition* 2016:40;159 - 211
## Antioxidant “cocktail” RCTs

<table>
<thead>
<tr>
<th>Trial / population</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SIGNET</strong> N= 502 BMJ 2011</td>
<td>ICU PN patients Selenium / glutamine / both vs. placebo up to 7 days</td>
<td>All endpoints negative except new infection for those treated &gt; 5 days</td>
</tr>
<tr>
<td><strong>REDOXS</strong> N=1223 NEJM 2013</td>
<td>ICU patients w/multiorgan failure w/in 24 hrs Antioxidants / glutamine / both vs. placebo up to 7 days Antioxidants 500 mcg IV Se + Enteral Se, Zn, β-carotene, Vit E, Vit C</td>
<td>Primary Endpoint: 28 Day Mortality Glutamine OR 1.28 (1.00-1.64) Antioxidants OR 1.09 (0.86 – 1.40) Suggested harm in patients with renal failure</td>
</tr>
<tr>
<td><strong>MetaPlus</strong> N=301 JAMA 2014</td>
<td>ICU patients on MV &gt; 72 hrs Immune modulating high protein (IMHP) EN vs HP EN IMHP included glutamine, Ω3 FA, Se, Zn, Vit C, Vit E</td>
<td>Primary Endpoint: Incidence of new infections – no difference 6 Month Mortality (medical subgroup): 54 % (40-67) IMHP vs 35 % (22-49) HP</td>
</tr>
</tbody>
</table>
Evaluating the effect of nutritional supplementation in critically ill patients

- Rigorous data on “normal” and association with risk of poor outcomes is not available
- Data demonstrating an association do not substantiate causation
  - Proper stress response?
  - RDAs are unknown in critical illness
- Dose response relationship unknown
  - Likely a u-shaped curve
- Bioavailability and interaction between antioxidants
  - Both therapeutic and antagonistic
- Should the inflammatory response be mitigated?
- Population heterogeneity and confounding
Conclusions

- Although preclinical and small trials indicate benefit with vitamin and anti-oxidant supplementation much controversy exists
  - Conflicting study results
  - Uncertainty regarding proper dosing
  - Potential for harm
- Current guidelines do not consider more recent studies
- Supplementation beyond physiologic (RDAs) is not supported with current evidence
  - Renally impaired patients seem most likely to be harmed
  - Consideration for populations with demonstrated needs (alcoholics, burns)
References

- **Selenium Meta-analysis**
Anti-oxidants cocktails


Self-Assessment Questions
Q1: Which of the following is correct regarding vitamin D status in ICU patients?

a) Observed in 25 % of patients
b) Deficiency causes an increased risk of infection
c) Supplementation of 5000 units/day has been shown to decrease ICU LOS
d) Values less than 20 ng/ml are considered deficient

Answer: d
Q2: Which of the following are vitamins and trace minerals involved in the antioxidant network (select all that apply)?

a) Selenium  
b) Thiamine  
c) Vitamin A  
d) Zinc

Answer: a, c, d
Q3: Antioxidant “cocktails” in critically ill patients may possibly be harmful to patients with:

a) Mechanical ventilation  
b) Renal failure  
c) Obesity  
d) Respiratory failure

Answer: b