Can a Vitamin or Antioxidant a Day Keep the Sepsis Away?

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Mayo Clinic Dept of Pharmacy
Disclosures

All planners, presenters, reviewers, and ASHP staff of this session report no financial relationships relevant to this activity.
Learning Objectives

• Describe the mechanisms of action, toxicities, and pharmacokinetic considerations of vitamin C, thiamine, selenium, zinc, and vitamin E in sepsis.
• Evaluate recent literature describing the effect of vitamin or antioxidant supplementation on outcomes in patients with sepsis.
• Recommend appropriate vitamin or antioxidant supplements in patients with sepsis.
Patient Case: CW

- CW is a 37 year-old male with no PMH who presents with a 2 day history of fever, chills, and productive cough. His CXR demonstrates multifocal pneumonia and VS include T 39.1°C, BP 84/53 mmHg, HR 118 bpm, RR 25 bpm, O2sat 91% (RA). Appropriate broad-spectrum antibiotics and fluid challenge are administered. CW quickly decompensates, is intubated and placed on mechanical ventilation and requires norepinephrine 30 mcg/min for hypotension. Additional IVF boluses are administered and CW is no longer fluid-responsive. The following labs are noted:

  Na 142 mEq/L, K 4.7 mEq/L, Cl 116 mmol/L, CO2 19 mEq/L, BUN 30 mg/dL, Scr 1.8 mg/dL (baseline 1.1 mg/dL), Glu 119 mg/dL
  WBC 17.1 cells/μL, platelets 109 cells/μL, lactate 8.7 mmol/L
Question:

Is Vitamin C/Thiamine/Hydrocortisone being used in these scenarios in your institution?

A Yes
B No
Sepsis

- Life-threatening organ dysfunction caused by dysregulated host response to infection
  - Organ dysfunction: SOFA score ≥2
- Septic shock
  - Sepsis with persistent hypotension requiring vasopressor support (MAP ≥65 mmHg) and lactate >2 mmol/L
- United States
  - 1.7 million cases per year
  - 265,000 deaths per year
  - Present in 35% of deaths in U.S. hospitals
- Worldwide
  - 30 million cases per year
  - 6 million deaths per year

Current Therapeutic Approaches Impacting Mortality

• **Resuscitation**
  – Early administration of fluid challenge (≥30 mL/kg)
  – Continuous re-assessment of fluid responsiveness
  – Maintain MAP ≥65 mmHg with vasopressors
  – Normalization of lactate

• **Antimicrobial Therapy**
  – Early administration (within 1 hour)
  – Adequate empiric coverage

• **Source Control**
  – Obtain within 6-12 hours

Graveyard of Septic Shock

https://twitter.com/bob_wachter/status/789896356831703040
Pathophysiology of Oxidative Stress in Sepsis

- Sepsis
  - Inflammation
  - ↑ Free radicals
  - ↓ Antioxidants
- ↑ NO
- Mitochondrial damage
  - ↑ vascular permeability
  - ↑ vasodilation
  - ↓ ATP
  - ↓ O2 utilization
- Endothelial dysfunction
  - Hypotension
- Cellular apoptosis
- Organ failure

Oxidants

• Accept electrons
• Involved in production of deoxyribonucleotides, prostaglandin, oxidation, others
• Reactive Oxygen Species (ROS)
  – Superoxide ($\text{O}_2^-$)
  – Hydroxyl radicals (HO)
  – Hydrogen peroxide ($\text{H}_2\text{O}_2$)
• Reactive Nitrogen Species (RNS)
  – Nitric oxide (NO)
  – Peroxynitrite (ONOO$^-$)
• Free radical production required for host defense

Antioxidants

• Enzymes
  – Glutathione peroxidase (GPx): $H_2O_2 \rightarrow H_2O$
  – Superoxide dismutase (SOD): $O_2^- \rightarrow O_2/H_2O_2$
  – Catalase (CAT): $H_2O_2 \rightarrow H_2O + O_2$
  – TRX peroxidase: $H_2O_2 \rightarrow H_2O$
• Enzyme cofactors
  – Copper (SOD)
  – Selenium (GPx, TRX)
  – Zinc (SOD)
• Antioxidant compounds
  – Ascorbic acid
  – $\alpha$-tocopherol (vitamin E)

Vitamin C

- Water-soluble antioxidant used clinically since 1949
- Involved in immune function, Fe/FA metabolism; collagen, cortisol, catecholamine production
- Humans completely dependent on exogenous sources of Vit C
  - Cannot perform synthesis in liver
- Vitamin C metabolism altered in critical illness
  - Increased cellular expression of Vit C transporter w/oxidative stress

## Vitamin C Levels in Critically Ill

<table>
<thead>
<tr>
<th>Day</th>
<th>Multi-organ Failure</th>
<th>Non-Multi-organ Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.8 ± 1</td>
<td>12 ± 3.2</td>
</tr>
<tr>
<td>Last Day in ICU</td>
<td>4.1 ± 1.3</td>
<td>11.9 ± 3.6</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Group</th>
<th>Average Age</th>
<th>Vitamin C Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU (n=62)</td>
<td>60 years</td>
<td>11 μmol/L (8-22 μmol/L)</td>
</tr>
<tr>
<td>Healthy (n=29)</td>
<td>29 years</td>
<td>61.8 μmol/L (55-72 μmol/L)</td>
</tr>
</tbody>
</table>

Vitamin C Antioxidant Mechanisms

- Inhibits NOX and iNOS: reduce ROS/RNS production
- Scavenger of ROS/RNS
- Regenerates α-tocopherol (strongest antioxidant responsible inhibiting lipid peroxidation)
- Repairs GSH
- Substrate for ascorbate peroxidase (H₂O₂ -> H₂O)
- Prevents endothelial damage from ROS

Marik PE, et al. CHEST 2017;151(6):1229-1238
Effects of Vitamin C Administration

- Increases endogenous NE and vasopressin production
  - Cofactor of dopamine β-hydroxylase and tyrosine hydroxylase
- May improve vascular function in sepsis
  - Increased capillary blood flow in animal models
  - Reduced endothelial barrier permeability
    - Synergistic effect with hydrocortisone: reverse LPS-induced endothelial barrier dysfunction
    - Increased arterial responsiveness to vasopressors
- May reduce immunosuppression in setting of sepsis
- Bacteriostatic

Barabutis N, et al. CHEST 2017;152(5):954-962
Pharmacokinetic Considerations

- Concentrations > 1000 μmol/L required for free radical scavenging
- Oral administration
  - Limited by SVCT-1: intestinal transporter, saturable
  - 12 g/day = 220 μmol/L
- IV administration
  - 3 g/day = 1760 μmol/L
  - 5 g/day = 2870 μmol/L
  - 10 g/day = 5580 μmol/L

Vitamin C Toxicity

- Calcium oxalate nephropathy
  - Oxalate increases with high-dose IV vitamin C
  - May accumulate in renal dysfunction, crystallize in kidney
  - May result in worsened renal failure
- Thiamine deficiency increases conversion of glyoxylate to oxalate
  - Thiamine supplementation may lead to replenishment of thiamine pyrophosphate
  - Co-enzyme for conversion of glyoxylate to CO₂
  - Possible renoprotective effect?

“Fictitious hyperglycemia”

- Amperometric interference with electrochemical assays with high dose Vit C
- Additional negative charge created by Vitamin C oxidation
- Increases electron production, falsely elevate bedside glucose measurements

Selenium

• Enzymatic cofactor of many selenoproteins
  – Antioxidant system
  – Thyroid hormone metabolism
  – Humoral/cell-mediated immune response
• Many formulations exist
  – Selenium yeast
  – Selenomethionine (F=0.9)
  – Selenite (F=0.5)
  – Selenate
• Stored mostly in kidney, liver, muscle
  – Selenoprotein P (SePP): 60% of plasma selenium
  – GPx: 30%
  – Albumin: 6-10%

Selenium Pharmacokinetics

- Oral administration
  - Free selenium/selenocysteine
  - Incorporated into selenoproteins
- IV administration
  - Most effective w/inorganic (ie: sodium selenite)
  - Selenite -> selenodiglutathione -> hydrogen selenide -> dimethyl selenide + trimethyl selenide
  - Antioxidant properties; excreted via lungs and kidneys

Selenium

• **Antioxidant Mechanisms**
  – Cofactor for GPx
    • Reduces $H_2O_2$ and protects endothelium
  – Inhibits NF-κB activation thru redox signaling
    • Decrease ROS/RNS production
  – In presence of inflammation has initial pro-oxidant effect
    • Followed by antioxidant activity once SePP incorporated into selenoenzymes
    • Inhibits IL and TNF-α activity

• **Toxicities**
  – Selenosis: occurs mainly from environmental exposure, high concentrations in drink water/food
  – N/V/D, fatigue
  – Neurotoxicity, anemia, liver injury rare

Selenium Deficiency

- Loss occurs with shift to interstitium with capillary leak
- Exacerbated by blood draws, malnutrition, dialysis
- Decreased GPx activity
  - Low GSH levels in critical illness
  - Enhanced ROS production
- Selenium levels significantly lower in ICU patients
  - Levels < 0.7 μmol/L: mortality increased 3.5x
- Septic shock
  - SePP levels 70% lower compared to pts w/o
  - SePP levels lower in non-survivors

Vitamin E

• Maintains membrane stability and immune response to infection
• Group of lipid-soluble tocopherols/tocotrienoles
  – α-tocopherol most active
  – Mostly present in cell membranes
• α-tocopherol antioxidant mechanism
  – Reduces lipid peroxidation
  – Direct scavenger of $O_2^-$ and HO
• ? altered metabolism or deficiency in critically ill: difficult to assess status
  – Typically measured in plasma
  – Vitamin E mostly present in cell membranes
  – Good correlation between RBC and tissue concentrations

Other Important Cofactors

• Zinc
  – DNA repair, protein synthesis, glycemic control, wound healing
  – Inhibits NOX and NOS; increases SOD, GPx, CAT; cofactor of SOD; inhibits Fenton reaction (H2O2 -> OH-)
  – Redistributed in sepsis due to catabolism

• Copper
  – Prevents anemia, connective tissue formation, bone regulation
  – Cu/Zn superoxide dismutase (free radical scavenger)
  – Unknown how develops in sepsis (loss of dermal barrier in burns)

Walravens PA. West J Med 1979;130:133-142
Primary Literature for Antioxidants in Sepsis
Rationale for Primary Literature Inclusion

• Studies of antioxidants in humans with sepsis
  – Antioxidants
    • Vitamins C, E
    • Trace minerals selenium, zinc, and copper
    • Antioxidant combinations or ‘cocktails’
  – Excluded
    • Animal studies
    • Studies in ‘critically ill’ patients without sepsis

• Evaluated clinical outcomes
Phase I Vitamin C Study

Inclusion
MICU patients with severe sepsis

Lo-Vit C
n=8
50mg/kg/24hr IV divided Q6hr x 96h

Hi-Vit C
n=8
200mg/kg/24hr IV divided Q6hr x 96h

Placebo (D5W)
n=8

Results

Plasma Ascorbate Level

- 3000 μM
- 300 μM
- Normal (50 μM)
- 15 μM

Delta SOFA Score

No adverse safety events observed

High Dose Vitamin C and Vasopressor Requirement

**Inclusion**
Abd surgery pts with septic shock

<table>
<thead>
<tr>
<th>Vitamin C</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=14</td>
<td>n=14</td>
</tr>
</tbody>
</table>

- 25mg/kg IV Q6hr x72h

**Baseline Variable**

<table>
<thead>
<tr>
<th>Baseline Variable</th>
<th>Vit C</th>
<th>Placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>64 ± 16</td>
<td>64 ± 14</td>
<td>0.94</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>19.1 ± 5</td>
<td>23 ± 6</td>
<td>0.06</td>
</tr>
<tr>
<td>SOFA score</td>
<td>11.8 ± 2</td>
<td>12.4 ± 3</td>
<td>0.53</td>
</tr>
<tr>
<td>Baseline SCr</td>
<td>1.5 ± 1.2</td>
<td>2.3 ± 1.7</td>
<td>0.11</td>
</tr>
<tr>
<td>Infection Source</td>
<td>Abdominal</td>
<td>Pulmonary</td>
<td>Urinary Tract</td>
</tr>
<tr>
<td></td>
<td>43%</td>
<td>29%</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td>14%</td>
<td>29%</td>
<td>21%</td>
</tr>
</tbody>
</table>

## Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Vit C (n=14)</th>
<th>Placebo (n=14)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>NE dose during 72hr study mean ± SD, mcg/min</td>
<td>7.4 ± 3.7</td>
<td>13.8 ± 3.7</td>
<td>0.004</td>
</tr>
<tr>
<td>NE duration mean ± SD, h</td>
<td>49.6 ± 25.7</td>
<td>71.6 ± 1.6</td>
<td>0.003</td>
</tr>
<tr>
<td>ICU Length of Stay mean ± SD, d</td>
<td>21.5 ± 10.2</td>
<td>20.1 ± 13.0</td>
<td>0.85</td>
</tr>
<tr>
<td>28-day mortality</td>
<td>14%</td>
<td>64%</td>
<td>0.009</td>
</tr>
</tbody>
</table>

1° Outcomes

Inclusion
Severe sepsis or septic shock
Procalcitonin ≥ 2 ng/mL

Before
June – Dec 2015
n=47

Hydrocortisone allowed per attending discretion
(60% received)
No Vitamin C, thiamine

After
Jan – July 2016
n=47

Vitamin C 1.5g IV Q6hrs x 4d
Hydrocortisone 50mg IV Q6hrs x 7d*
Thiamine 200mg IV Q12hrs x 4d†

*or until ICU discharge, followed by 3d taper
† or until ICU discharge

## Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before (n=47)</th>
<th>After (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean ± SD, yrs</strong></td>
<td>62.2 ± 14.3</td>
<td>58.3 ± 14.1</td>
</tr>
<tr>
<td>Primary Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>40%</td>
<td>38%</td>
</tr>
<tr>
<td>Urosepsis</td>
<td>21%</td>
<td>23%</td>
</tr>
<tr>
<td>Primary bacteremia</td>
<td>15%</td>
<td>15%</td>
</tr>
<tr>
<td>GI/Biliary</td>
<td>13%</td>
<td>13%</td>
</tr>
<tr>
<td>Other</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>28%</td>
<td>28%</td>
</tr>
<tr>
<td>Lactate, mean ± SD, mM</td>
<td>3.1 ± 2.8</td>
<td>2.7 ± 1.5</td>
</tr>
<tr>
<td>PCT, median (IQR)</td>
<td>15.2 (5.9-39.0)</td>
<td>25.8 (5.8-93.4)</td>
</tr>
</tbody>
</table>

### Illness Severity

<table>
<thead>
<tr>
<th>Illness Severity</th>
<th>Before (n=47)</th>
<th>After (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mech Vent</td>
<td>55%</td>
<td>47%</td>
</tr>
<tr>
<td>Vasopressors</td>
<td>46%</td>
<td>46%</td>
</tr>
<tr>
<td>AKI</td>
<td>64%</td>
<td>66%</td>
</tr>
<tr>
<td>Day 1 SOFA mean ± SD</td>
<td>8.7 ± 3.7</td>
<td>8.3 ± 2.8</td>
</tr>
<tr>
<td>APACHE II mean ± SD</td>
<td>22.6± 6.3</td>
<td>22.1± 6.3</td>
</tr>
</tbody>
</table>
### Results

#### Hospital Mortality %

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Predicted</th>
<th>Observed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>ICU Length of Stay</td>
<td>42</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>P&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Pressor duration*</td>
<td>40</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>9</td>
</tr>
<tr>
<td>Δ SOFA, 72 hrs*</td>
<td>40</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>33%</td>
<td>10%</td>
</tr>
</tbody>
</table>

*denotes statistical significance

**Propensity Adjusted Odds of Mortality = 0.13 (95% CI 0.04-0.48, p=0.002)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU Length of Stay</td>
<td>4 (4-10)</td>
<td>4 (3-5)</td>
</tr>
<tr>
<td>Pressor duration*</td>
<td>54.9 ± 28.4</td>
<td>18.3 ± 9.8</td>
</tr>
<tr>
<td>Δ SOFA, 72 hrs*</td>
<td>0.9 ± 2.7</td>
<td>4.8 ± 2.4</td>
</tr>
<tr>
<td>RRT for AKI*</td>
<td>33%</td>
<td>10%</td>
</tr>
</tbody>
</table>

*denotes statistical significance
Vitamin C (cocktail) in the Headlines

“Doctor Says Improvised ‘Cure’ for Sepsis Has Had Remarkable Results”

“Did An IV Cocktail of Vitamins and Drugs Save This Lumberjack From Sepsis?”

“Doctor Turns Up Possible Treatment for Deadly Sepsis”
Lessons From the Sepsis Graveyard

**Intervention**
- Activated Protein C
- G-CSF
- Intensive Insulin

**Early Trials**
- Multicenter, DB, RCT with 1690 pts showing 6% ARR
- Multicenter, DB, RCT with 18 pts showing 50% ARR
- Single-center, DB, RCT with 1200 pts showing 10% ARR for this in ICU ≥3 days
Study Discussion

Defined sepsis population
Early initiation of therapies
Some measures to control for confounding variables

Retrospective
Single center and small sample
No a priori sample size determination
~50% required mechanical ventilation, vasopressors
Balance of baseline characteristics
Important processes of care not reported (in detail)
Different time periods of treatment
# Selenium in Sepsis Meta-Analyses

<table>
<thead>
<tr>
<th>Year</th>
<th># Studies</th>
<th># Patients</th>
<th>RR of Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang, et al.</td>
<td>2013</td>
<td>9</td>
<td>965</td>
</tr>
<tr>
<td>Alhazzani, et al.</td>
<td>2013</td>
<td>9</td>
<td>792</td>
</tr>
<tr>
<td>Kong, et al.</td>
<td>2013</td>
<td>5</td>
<td>530</td>
</tr>
<tr>
<td>ASPEN / SCCM</td>
<td>2016</td>
<td>9</td>
<td>1888</td>
</tr>
</tbody>
</table>
Selenium Meta-Analyses: What do they agree on?

- Sepsis population (mostly)
- IV Selenium administered
- Risk of bias present in many studies
- Overall low quality of evidence
- Mostly European countries

Inclusion/Exclusion
- SIRS vs. sepsis
- Severity of illness

Dosing
- Daily dose 155-10,000 mcg
- Duration 5-28d
- Use of LD and cont infusion
**SISPCT Trial**

33 ICUs in Germany
Nov 2009 – Jun 2013

**Inclusion**
Severe sepsis or septic shock
beginning ≤ 24° before randomization

**Exclusion**
Longer abx duration recommended,
Immunocompromised,
Not committed to full therapy

**Selenium (n=543)**
- Selenium-PCT n=273
- Selenium-CVT n=270

Sodium selenite 1,000mcg LD x1, then
1,000mcg/day cont infusion until ICU d/c

**Placebo (n=546)**
- Placebo-PCT n=279
- Placebo-CVT n=267

PCT = Procalcitonin
CVT = Conventional (No PCT guidance)

## Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Se-PCT</th>
<th>Se-CVT</th>
<th>Plac-PCT</th>
<th>Plac-CVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, yrs</td>
<td>63.9 ± 14.9</td>
<td>65.8 ± 14.3</td>
<td>67.3 ± 12.4</td>
<td>65.6 ± 12.7</td>
</tr>
<tr>
<td>Septic Shock</td>
<td>88%</td>
<td>88%</td>
<td>86%</td>
<td>87%</td>
</tr>
<tr>
<td>Infection Source</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>50%</td>
<td>44%</td>
<td>45%</td>
<td>43%</td>
</tr>
<tr>
<td>Abdomen</td>
<td>37%</td>
<td>42%</td>
<td>35%</td>
<td>40%</td>
</tr>
<tr>
<td>Urogenital</td>
<td>7%</td>
<td>11%</td>
<td>10%</td>
<td>9%</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>23.6 ± 7.9</td>
<td>24.7 ± 7.6</td>
<td>24.2 ± 7.2</td>
<td>24.4 ± 7.7</td>
</tr>
<tr>
<td>Mechanical Ventilation</td>
<td>73%</td>
<td>74%</td>
<td>76%</td>
<td>68%</td>
</tr>
<tr>
<td>Lactate, mean ± SD, mM</td>
<td>2.6 (1.6-4.7)</td>
<td>2.8 (1.7-5.4)</td>
<td>2.8 (1.7-4.7)</td>
<td>2.7 (1.7-4.7)</td>
</tr>
<tr>
<td>Recent surgery</td>
<td>59%</td>
<td>56%</td>
<td>59%</td>
<td>52%</td>
</tr>
</tbody>
</table>

PCT = Procalcitonin  CVT = Conventional (No PCT guidance)
Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Selenium</th>
<th>Placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU LOS median (IQR), d</td>
<td>11 (5-22)</td>
<td>12 (6-24)</td>
<td>.08</td>
</tr>
<tr>
<td>Hospital LOS median (IQR), d</td>
<td>26 (16-42)</td>
<td>29 (17-50)</td>
<td>.02</td>
</tr>
<tr>
<td>Vent-free days</td>
<td>2 (0-5)</td>
<td>2 (0-5)</td>
<td>.22</td>
</tr>
<tr>
<td>RRT-free days</td>
<td>7 (2-15)</td>
<td>8 (3-18)</td>
<td>.05</td>
</tr>
</tbody>
</table>

Interaction between 2 interventions found; Among CVT group, worse outcome with selenium

CVT = Conventional (No PCT guidance)
Primary Literature: Antioxidants in Sepsis

<table>
<thead>
<tr>
<th>No prospective trials in septic patients</th>
<th>Combination Therapy or “Cocktail”</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Vitamin E monotherapy</td>
<td>• Rationale</td>
</tr>
<tr>
<td>• Zinc</td>
<td>– Multiple mechanisms and</td>
</tr>
<tr>
<td>– Small studies in burn and trauma</td>
<td>greater antioxidant effect</td>
</tr>
<tr>
<td>patients</td>
<td>– Regeneration of other</td>
</tr>
<tr>
<td>– Often in combination with</td>
<td>antioxidants</td>
</tr>
<tr>
<td>other antioxidants</td>
<td>• Very limited prospective trials</td>
</tr>
<tr>
<td>• Copper monotherapy</td>
<td>focused on sepsis</td>
</tr>
<tr>
<td></td>
<td>– REDOXS Trial</td>
</tr>
<tr>
<td></td>
<td>• “Critically ill”</td>
</tr>
<tr>
<td></td>
<td>– SIGNET Trial</td>
</tr>
<tr>
<td></td>
<td>– MetaPlus Trial</td>
</tr>
</tbody>
</table>

REDOXS Trial

Inclusion
Randomization within 24h ICU admit, Required mechanical ventilation and with ≥ 2 organ failures

Exclusion:
- Moribund
- Not committed to full therapy
- CI to enteral nutrients
- Advanced cancer
- Cirrhosis
- Seizure d/o

Glutamine
n=301
0.35g/kg IV and 30g enterally

Antiox
n=307

Glut + Antiox
n=310

Placebo
n=300

Selenium 500 mcg IV + 300 mcg enteral
Vitamin C 1500mg enteral
Vitamin E 500mg enteral
Zinc 20 mg enteral
β-carotene 10 mg enteral

# REDOXS Trial

<table>
<thead>
<tr>
<th>Variable</th>
<th>Glutamine</th>
<th>Antioxidant</th>
<th>Glut/Antiox</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, yrs</td>
<td>62.8 ± 15.0</td>
<td>63.6 ± 14.3</td>
<td>64.3 ± 14.0</td>
<td>62.8 ± 13.7</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>26.6 ± 7.9</td>
<td>25.9 ± 7.1</td>
<td>26.8 ± 7.4</td>
<td>26.0 ± 7.4</td>
</tr>
<tr>
<td>Primary ICU diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>34%</td>
<td>31%</td>
<td>27%</td>
<td>32%</td>
</tr>
<tr>
<td>Sepsis</td>
<td>29%</td>
<td>32%</td>
<td>34%</td>
<td>29%</td>
</tr>
<tr>
<td>CV/Vascular</td>
<td>7%</td>
<td>11%</td>
<td>10%</td>
<td>9%</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>23.6 ± 7.9</td>
<td>24.7 ± 7.6</td>
<td>24.2 ± 7.2</td>
<td>24.4 ± 7.7</td>
</tr>
<tr>
<td>Shock Presence</td>
<td>97%</td>
<td>98.7%</td>
<td>98.4%</td>
<td>97%</td>
</tr>
<tr>
<td># of Organ Failures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>68%</td>
<td>77%</td>
<td>70%</td>
<td>74%</td>
</tr>
<tr>
<td>3</td>
<td>28%</td>
<td>23%</td>
<td>29%</td>
<td>25%</td>
</tr>
</tbody>
</table>
## REDOXS Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Antiox (n=617)</th>
<th>Glut/Placebo (n=601)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU LOS median (IQR), d</td>
<td>8.4 (4.6-150.3)</td>
<td>8.9 (5.1-15.8)</td>
<td>.87</td>
</tr>
<tr>
<td>Hospital LOS median (IQR), d</td>
<td>16.9 (8.0-36.2)</td>
<td>16.6 (8.1-33.0)</td>
<td>.97</td>
</tr>
<tr>
<td>MV* duration median (IQR), d</td>
<td>6.0 (2.8-11.8)</td>
<td>6.1 (2.9-12.7)</td>
<td>.69</td>
</tr>
</tbody>
</table>

*MV = Mechanical ventilation

No interaction between 2 interventions found
No different findings in subgroups, including sepsis
What do the Guidelines Say?

**ASPEN / SCCM Nutrition**

“We cannot make a recommendation regarding selenium, zinc and antioxidant supplementation in sepsis at this time due to conflicting studies.”

[Quality of Evidence: Moderate]

**SSC Sepsis**

“We recommend against the use of IV selenium to treat sepsis and septic shock”

[Strong recommendation, moderate quality of evidence]

Primary Literature Summary

• No proven benefit with selenium supplementation in sepsis
• No proven benefit with antioxidant combination therapy in sepsis
• Recent vitamin C (with corticosteroids and thiamine) findings intriguing, but strength and quantity of evidence remains extremely limited
  – Clinical equipoise exists

Routine utilization of antioxidants in sepsis *cannot* be recommended currently and guideline statements are in agreement with this
## Ongoing Clinical Trials

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>1° Outcome</th>
</tr>
</thead>
</table>
| **VICTAS** | 2000 Sepsis
United States | Vit C + HC + T | Vasopressor and MV-free days |
| **CORVICTES** | 400 Septic Shock
Greece | Vit C + HC | Hospital Mortality |
| **ACTS** | 200 Septic Shock
United States | Vit C + HC + T | SOFA change, 72h |

- 12 additional, ongoing clinical trials with <200 patients, mostly focusing on organ function and vasopressor requirements as outcomes of interest

Information from: clinicaltrials.gov
Based on the available data, **would you recommend** the use of the Vitamin C / Thiamine / Hydrocortisone protocol in this patient with septic shock?

A. Yes
B. No
Patient Case CW Revisited

• The ICU team decides to initiate the Marik protocol, and CW becomes hemodynamically stable within the next 24 hours, allowing for discontinuation of vasopressor therapy. Vit C/thiamine/HCT are continued as well as broad-spectrum antibiotics, pending cultures and sensitivities. Based on your ICU’s hyperglycemia protocol, CW is started on an insulin drip (now running 6 units/hr) after POCT glucoses range between 249-333 mg/dL.
Question: Which of the following additional measures should be taken in regards to CW’s care at this point?

A. Nothing, everything looks great!
B. Taper the hydrocortisone off
C. D/C Vit C/Thiamine/HCT protocol, it harms patients
D. Check laboratory glucose to prevent hypoglycemia
KEY TAKEAWAYS

1) **KEY TAKEAWAY**
Oxidative stress plays an important role in sepsis-related pathophysiology and various antioxidant compounds may play a role in reversing its deleterious effects.

2) **KEY TAKEAWAY**
No proven benefits have been demonstrated with selenium or combination antioxidant supplementation therapy in patients with sepsis and they cannot be routinely recommended in this setting.

3) **KEY TAKEAWAY**
Recent evidence investigating Vitamin C, thiamine and hydrocortisone in combination demonstrate an association with improved outcomes that require validation in prospective, randomized trials.