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

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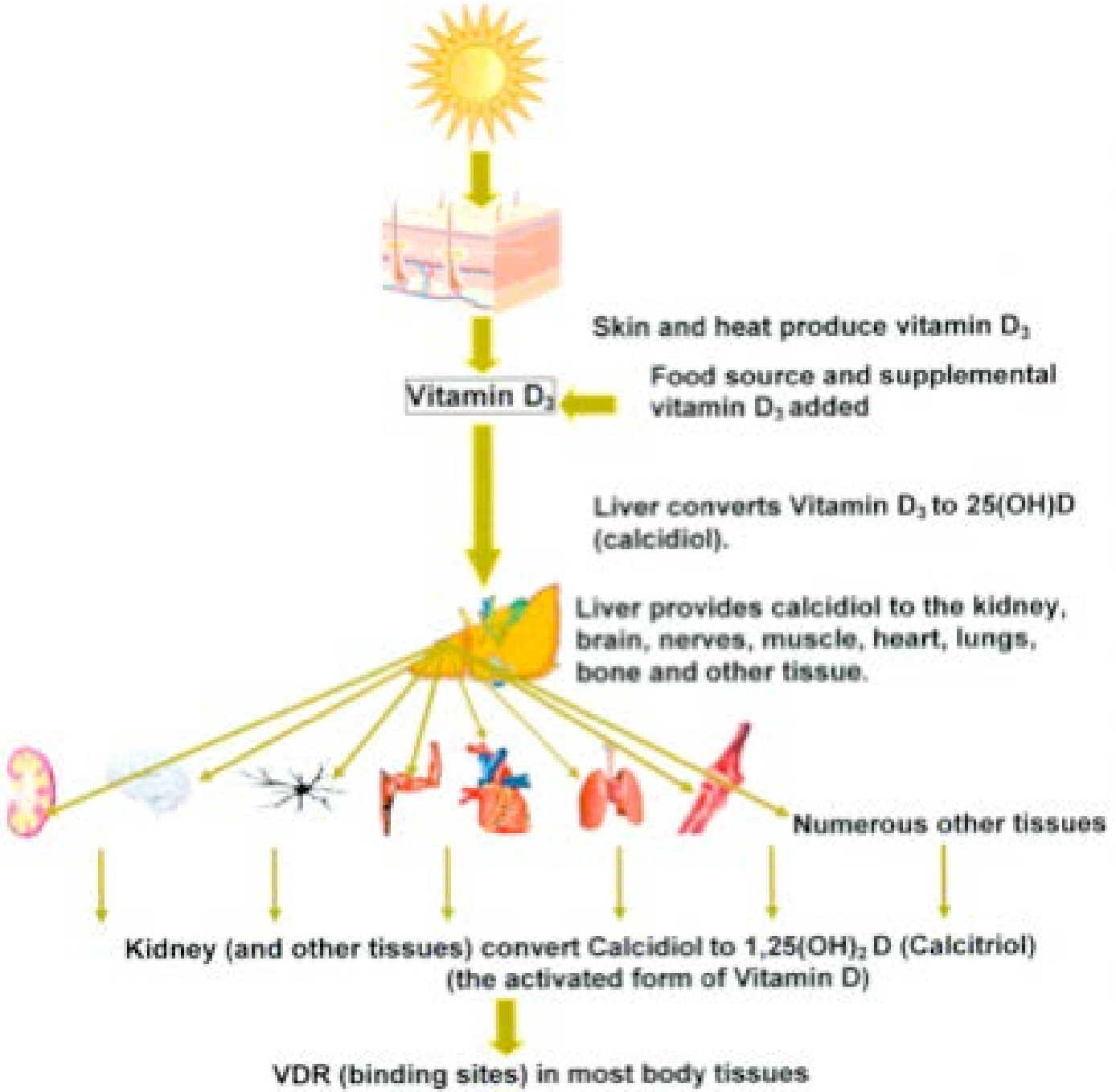
Disclosures

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 D_3
Vitamin D_3
Food source and supplemental vitamin D_3 added
Liver converts Vitamin D_3 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$(OH)_2$ D (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 supplemention
  - Bariatric surgery patients in ASPEN/SCCM guidelines

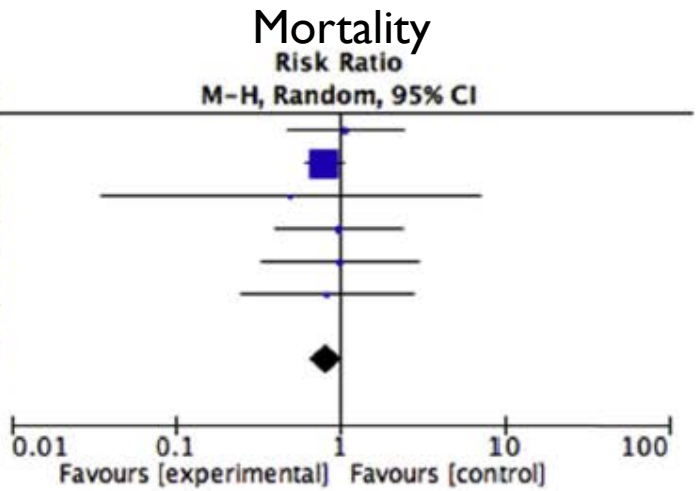
Evaluation of Vitamin D Concentrations

- 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 ($1,25(OH)_2D$) 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

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Amrein 2011	6	12	6	13	8.1%	1.08 [0.48, 2.45]
Amrein 2014	67	237	84	238	76.3%	0.80 [0.61, 1.04]
Han 2016	1	20	1	10	0.8%	0.50 [0.03, 7.19]
Leaf 2014	8	36	7	31	6.8%	0.98 [0.40, 2.40]
Nair 2015	5	25	5	25	4.4%	1.00 [0.33, 3.03]
Quraishi 2015	5	20	3	10	3.7%	0.83 [0.25, 2.80]
Total (95% CI)		**350**		**327**	**100.0%**	**0.84 [0.66, 1.06]**
Total events	92		106			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.86$, df = 5 (P = 0.97); $I^2 = 0\%$
Test for overall effect: Z = 1.48 (P = 0.14)



- Additional endpoints evaluated
  - ICU and hospital LOS, infection rate, MV days

Langlois PL et al Clin Nutr May 11 2017. http://dx.doi.org/10.1016/j.clnu.2017.05.006. pii: S0261-5614(17)30167-X

Antioxidants

Components of the Oxidative Balance

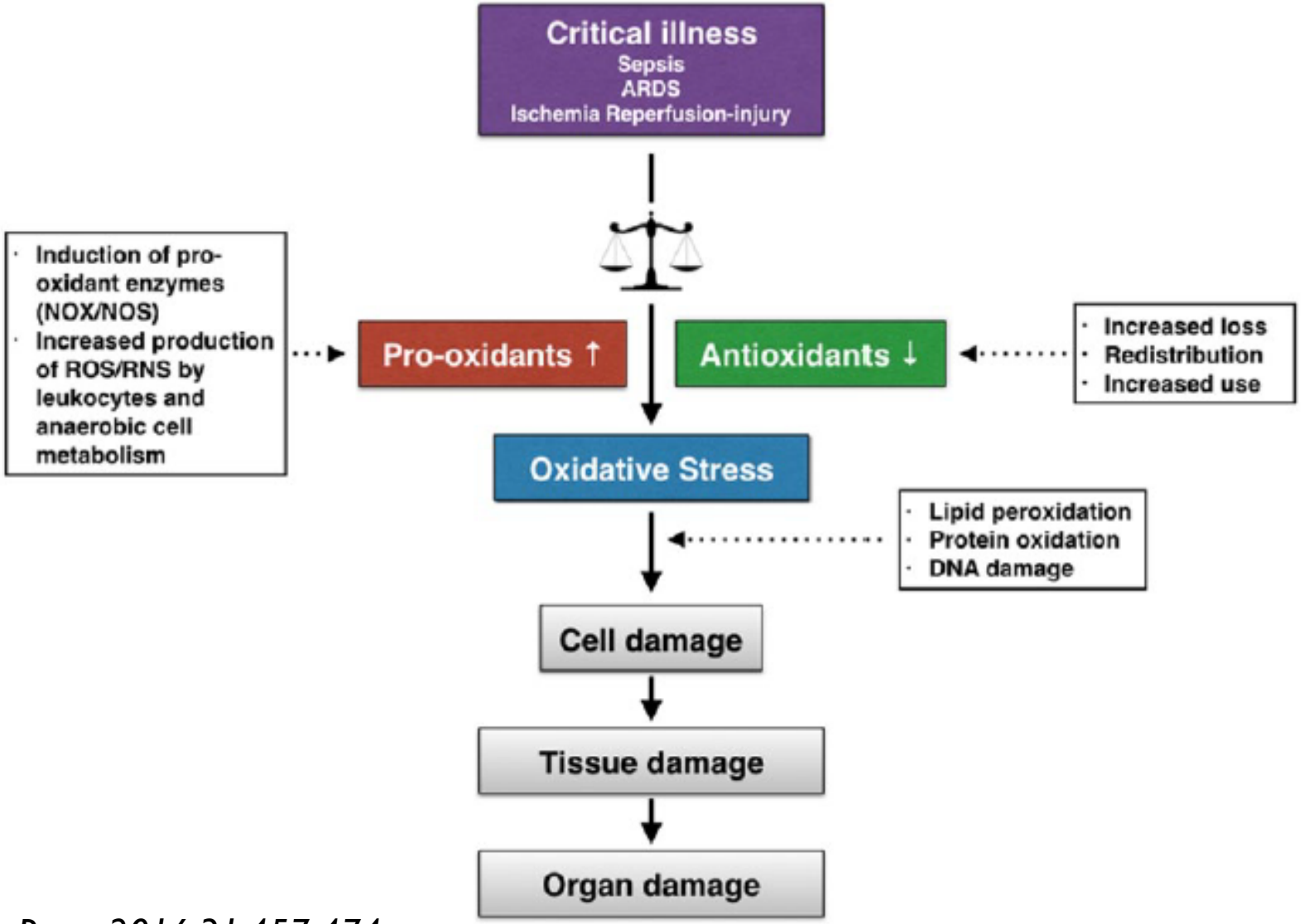
The Bad Guys

- Reactive Oxygen Species (ROS)
  - Superoxide Anion (O_2^-)
  - Hydroxyl Radical (OH)
  - Hydrogen Peroxide (H_2O_2)
- Reactive Nitrogen Species (RNS)
  - Nitric Oxide (NO^-)
  - Peroxynitrite ($ONOO^-$)

The Good Guys

- Antioxidant Enzymes
  - Superoxide dismutase (SOD)
  - Catalase (CAT)
  - Glutathione peroxidase (GPx)
  - Thioredoxin system (TRX)
- Antioxidant Compounds
  - Vitamins A, C, E
  - Selenium, Zinc

Consequences of Oxidative Stress



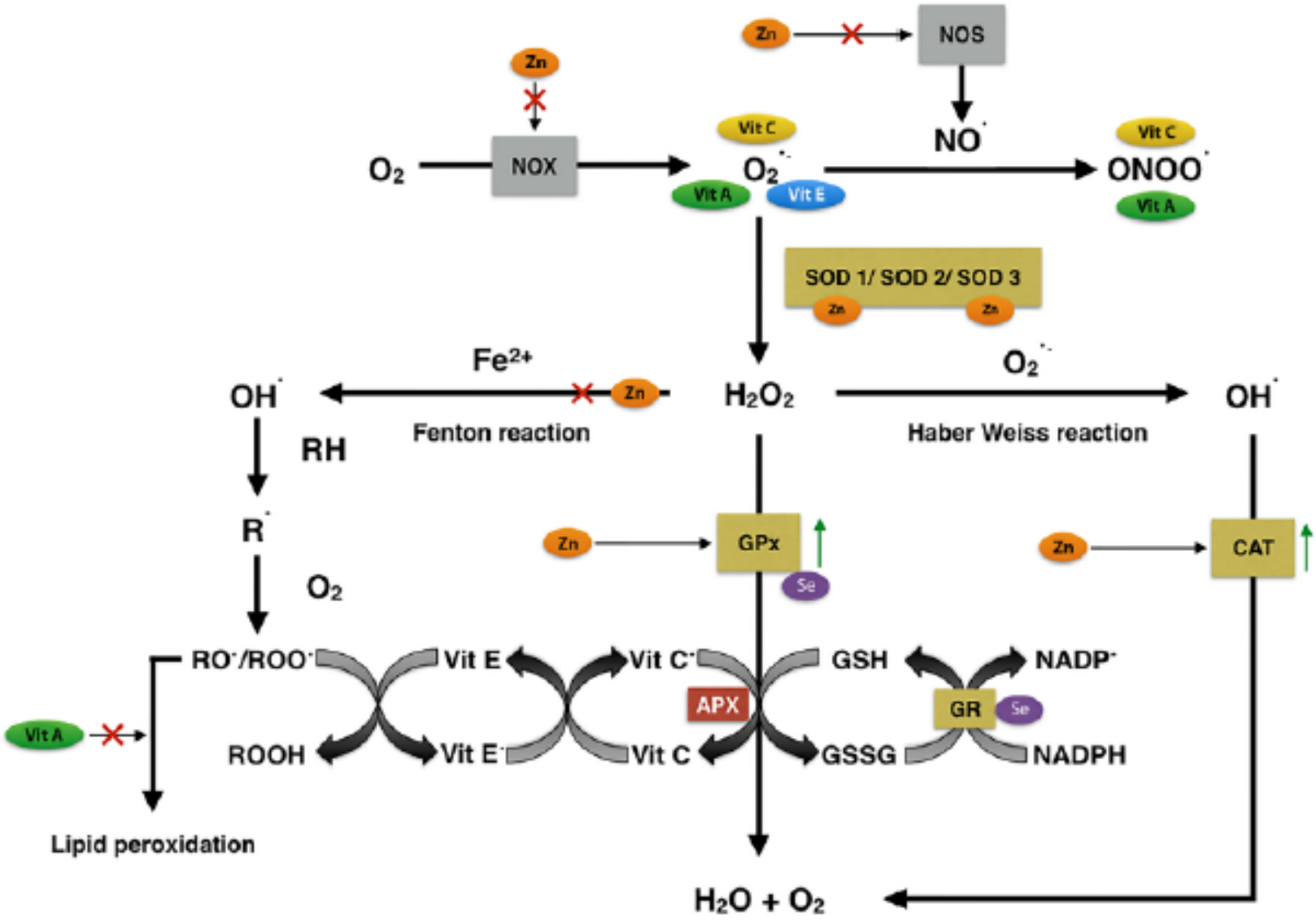
Nutr Clin Pract. 2016;31:457-474

Oxidative Stress in Critical Illness

- Sepsis
  - Large amounts of radical produced by phagocytes and up-regulated enzymes (ie 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 upong 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



Nutr Clin Pract. 2016;31:457-474

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?

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

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[1]
  - 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[2]
  - Trend toward reduced mortality and ICU LOS but 3 of the 4 studies included additional antioxidants

[1] J Neurotrauma 1996;13:25 – 34 [2] JPEN 2008;32:509-19

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 (α, β, γ)
  - β 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)

- Nutr Hosp. 2012;27:1981-1986

Vitamin E

- Family of lipid-soluble tocopherols and tocotrienoles
  - α-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!

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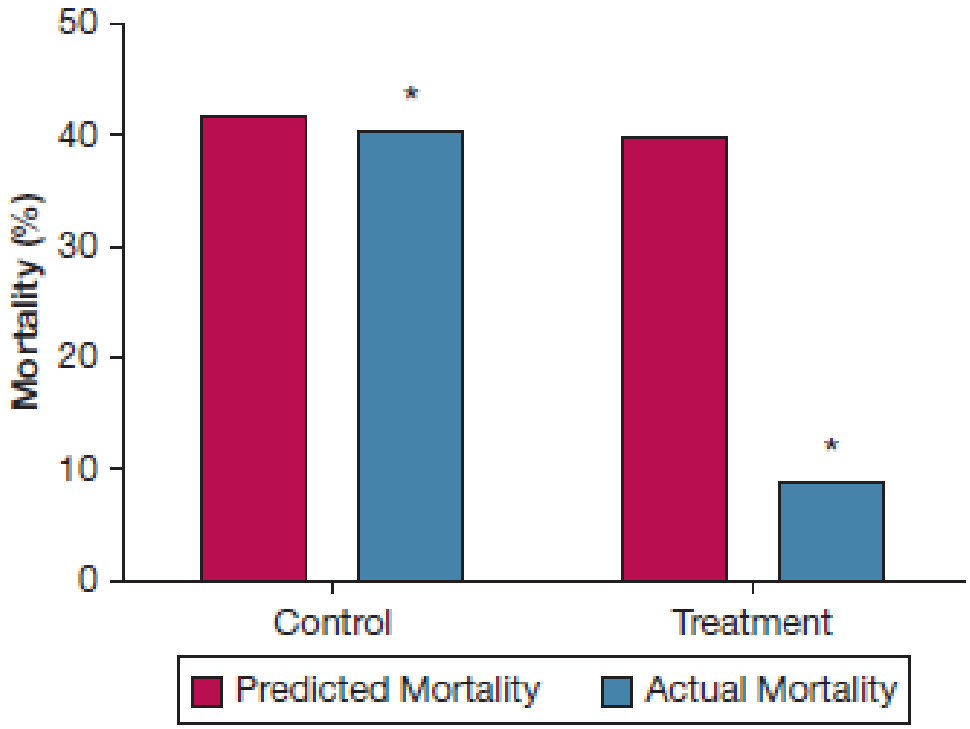
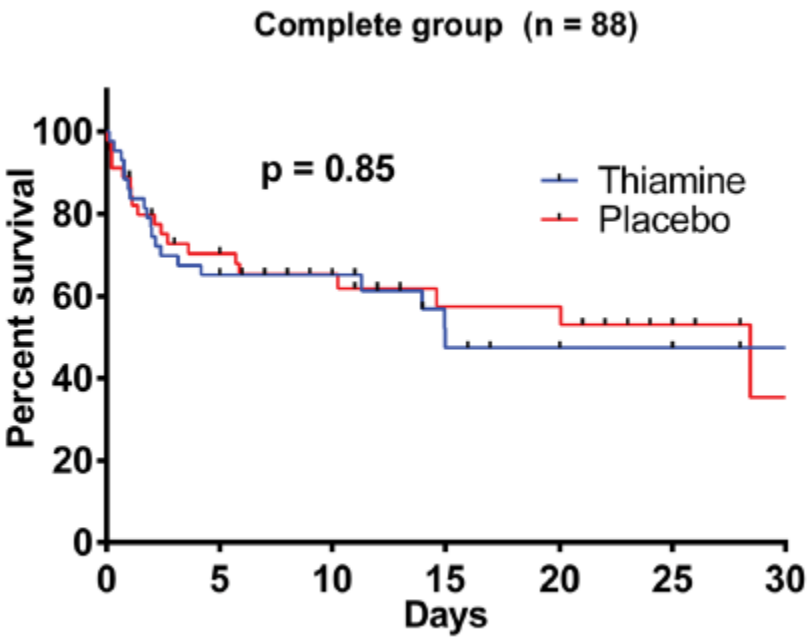


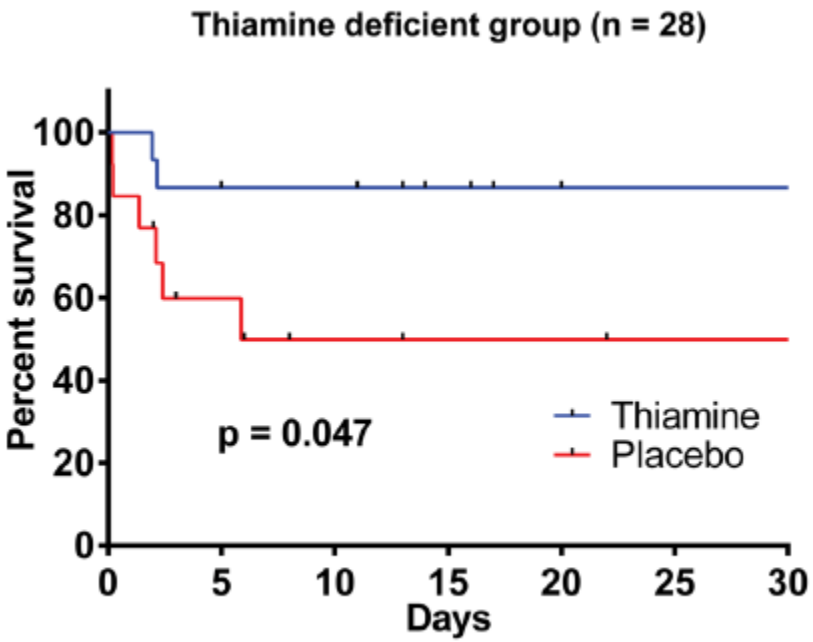
CHEST 2017; 151(6):1229-1238

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 7days or until d/c
- Individuals with a potential for thiamine deficiency (ie alcoholics) were excluded

Crit Care Med. 2016 February ; 44(2): 360–367.

Thiamine

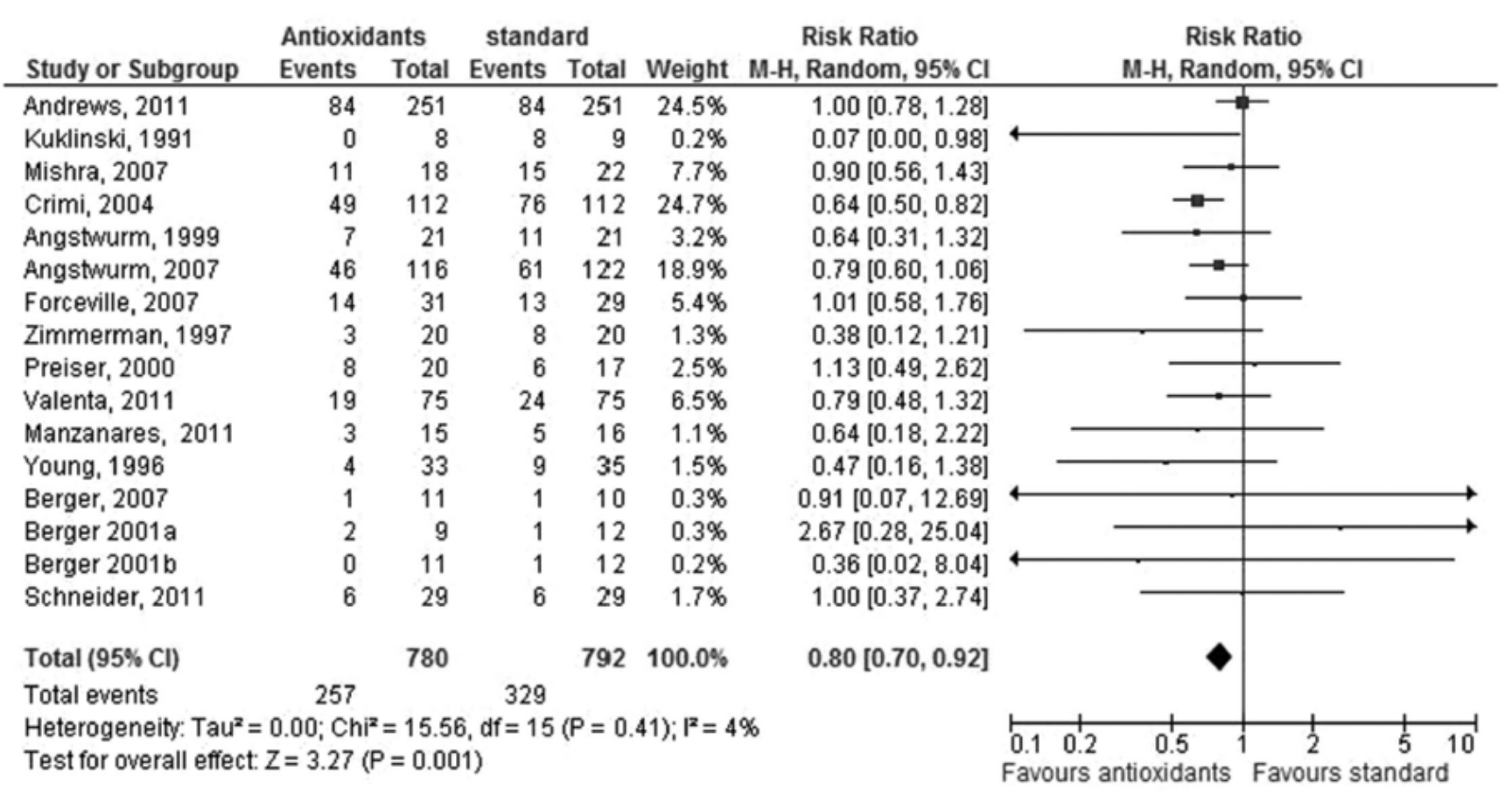
- Retrospective cohort study of septic shock patients with a concurrent alcohol use disorder admitted to the ICU
- Patient characteristics were similar between groups except for a significant difference in platelets (p = 0.04)

	Thiamine N = 34	No Thiamine N = 19	P-value
Mortality (%)	15 (44)	15 (79)	0.02
Hospital-free days	12	18	0.36
ICU-free days	21	21	0.71

Holmberg J Crit Care. Epub ahead of print doi: 10.1016/j.jcrc.2017.08.022.

Should we combine antioxidants?

ASPEN / ACCM Guidelines



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

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

- *Journal of Parenteral and Enteral Nutrition* 2016:40, ;159 - 211

Antioxidant "cocktail" RCTs

Trial / population	Intervention	Results
SIGNET N= 502 BMJ 2011	ICU PN patients Selenium / glutamine / both vs. placebo up to 7 days	All endpoints negative except new infection for those treated > 5 days
REDOXS N=1223 NEJM 2013	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	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
MetaPlus N=301 JAMA 2014	ICU patients on MV > 72 hrs Immune modulating high protein (IMHP) EN vs HP EN IMHP included glutamine, Ω3 FA, Se, Zn, Vit C, Vit E	Primary Endpoint: Incidence of new infections – no difference 6 Month Mortality (medical subgroup): 54 % (40-67) IMHP vs 35 % (22-49) HP

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)

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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