ashp MIDYEAR 2018
Clinical Meeting & Exhibition

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

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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

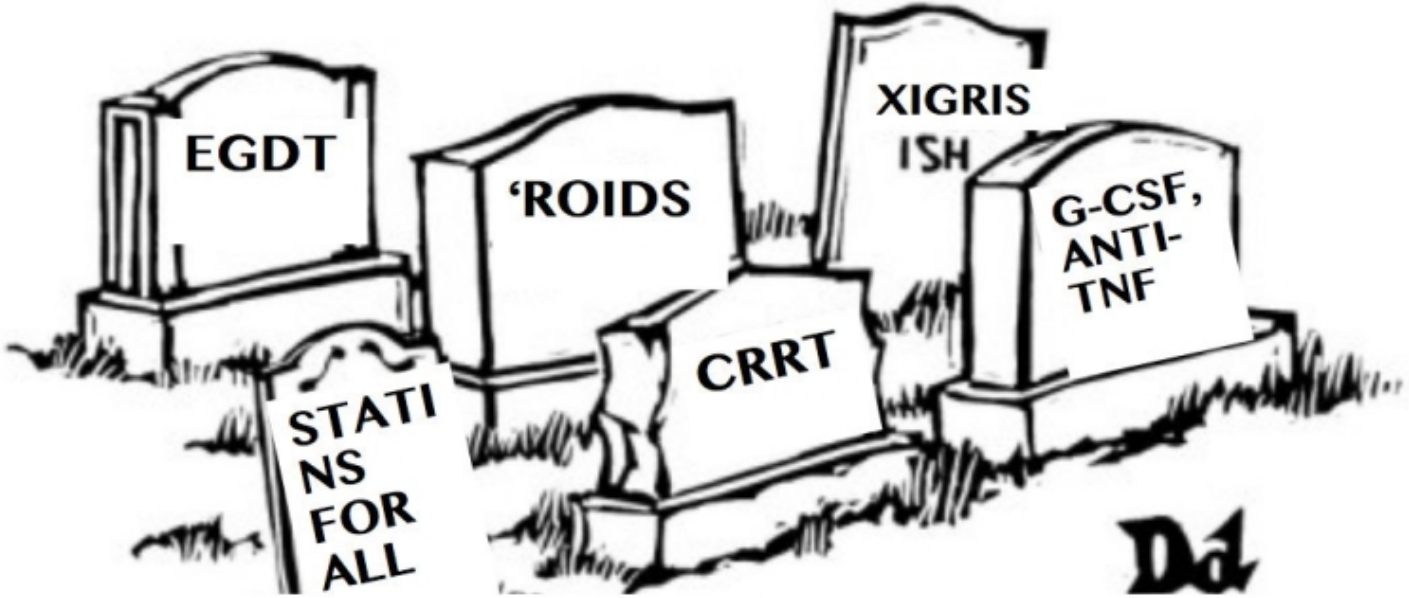
Singer M, et al. JAMA 2016;315(8):801-810
Rhee C, et al. JAMA 2017;318(13):1241-1249
Fleischmann C, et al. Am J Respir Crit Care Med 2016;193:259-272

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

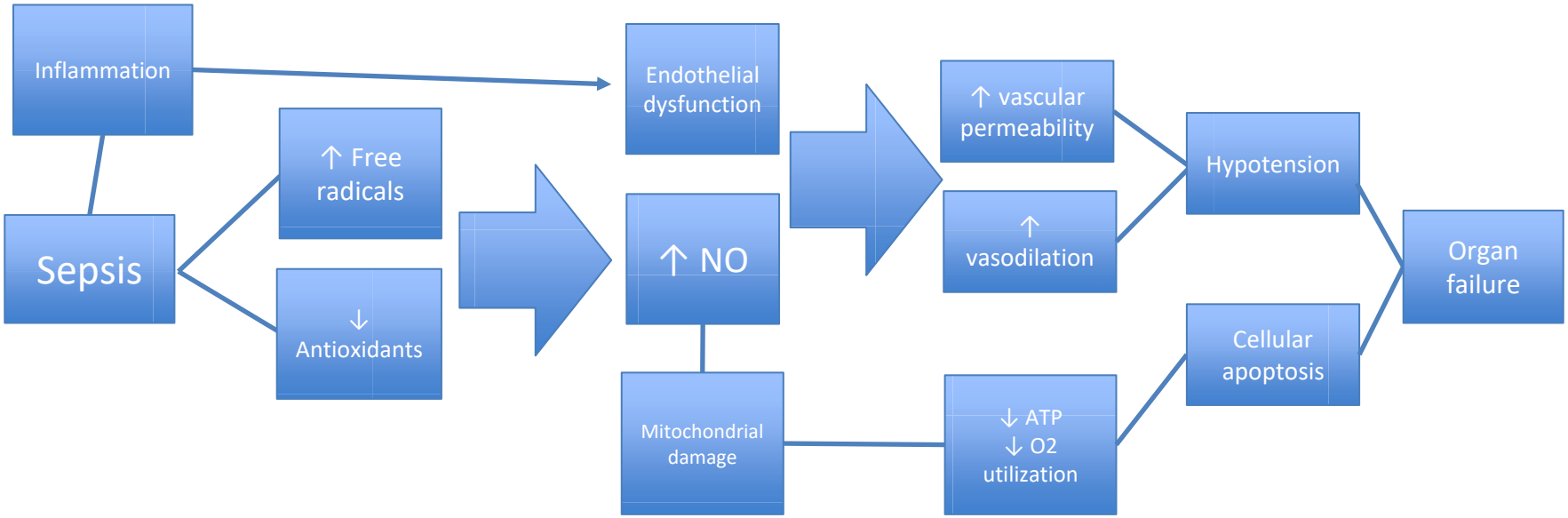
Rhodes A, et al. Crit Care Med 2017;45:486–552
Cecconi M, et al. Lancet 2018; 392: 75–87

Graveyard of Septic Shock



https://twitter.com/bob_wachter/status/789896356831703040

Pathophysiology of Oxidative Stress in Sepsis



Mantzarlis K, et al. Oxid Med Cell Longev 2017; 2017:5985209
Koekkoek WA, et al. Nutr Clin Pract 2016;31(4):457-74

Oxidants

- Accept electrons
- Involved in production of deoxyribonucleotides, prostaglandin, oxidation, others
- Reactive Oxygen Species (ROS)
  - **Superoxide (O_2^-)**
  - **Hydroxyl radicals (HO)**
  - Hydrogen peroxide (H_2O_2)
- Reactive Nitrogen Species (RNS)
  - **Nitric oxide (NO)**
  - Peroxynitrite ($ONOO^-$)
- Free radical production required for host defense

Mantzarlis K, et al. Oxid Med Cell Longev 2017; 2017:5985209
Koekkoek WA, et al. Nutr Clin Pract. 2016;31(4):457-74

Antioxidants

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

Mantzarlis K, et al. Oxid Med Cell Longev 2017; 2017:5985209
Koekkoek WA, et al. Nutr Clin Pract 2016;31(4):457-74

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

Kuhn SO, et al. Curr Opin Anesthesiol 2018; 31(1):55-60
Koekkoek WA, et al. Nutr Clin Pract 2016;31(4):457-74

Vitamin C Levels in Critically Ill

Day	Multi-organ Failure	Non-Multi-organ Failure
1	3.8 ± 1	12 ± 3.2
Last Day in ICU	4.1 ± 1.3	11.9 ± 3.6

ADAPTED FROM: Borrelli E, et al. Crit Care Med 1996; 24:392-397

Group	Average Age	Vitamin C Level
ICU (n=62)	60 years	11 µmol/L (8-22 µmol/L)
Healthy (n=29)	29 years	61.8 µmol/L (55-72 µmol/L)

ADAPTED FROM: Schorah CJ, et al. Am J Clin Nutr 1996;63(5):760-765

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 (H_2O_2 -> H_2O)
- Prevents endothelial damage from ROS

Koekkoek WA, et al. Nutr Clin Pract 2016;31(4):457-74
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

Kuhn SO, et al. Curr Opin Anesthesiol 2018; 31(1):55-60
Gao YL, et al. Mediators Inflamm. 2017;2017:4024672
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

Padayatty SJ, et al. Ann Intern Med 2004;140(7):533-537
Burzle M, et al. Curr Top Membr 2012;70:357-375

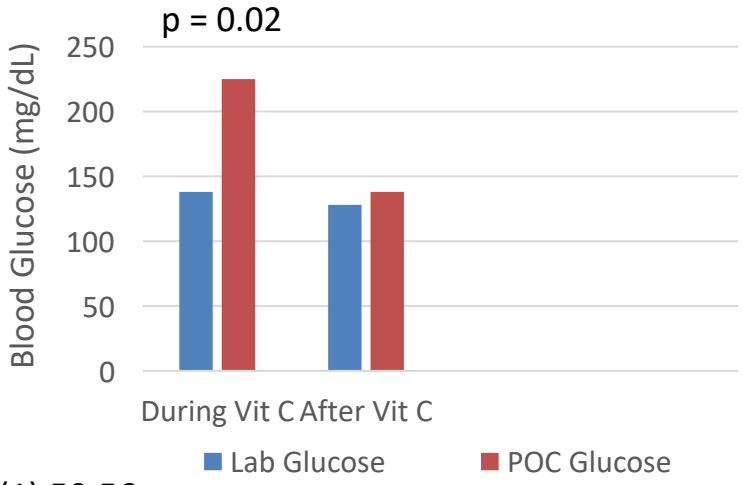
Vitamin C Toxicity

- 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 CO_2
  - Possible renoprotective effect?

Massey LK, et al. J Nutr 2005;135(7):1673-1677
Hoppe B, et al. Kidney Int 2009;75(12):1264-1271

“Fictitious hyperglycemia”

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



Sartor Z, et al. J Burn Care Res 2015;36(1):50-56
Kahn SA, et al. J Burn Care Res 2015;36(2):e67-7

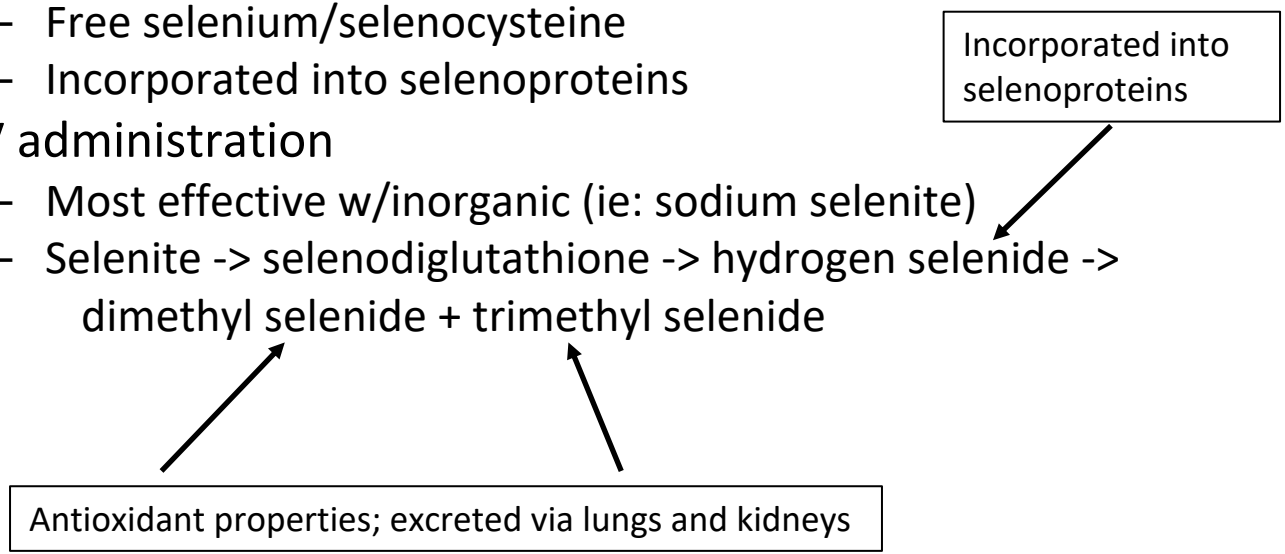
Selenium

- 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%

Koekkoek WA, et al. Nutr Clin Pract 2016;31(4):457-74
Rech M, et al. Nutr Clin Pract 2014;29:78-89

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



Koekkoek WA, et al. Nutr Clin Pract 2016;31(4):457-74
Rech M, et al. Nutr Clin Pract 2014;29:78-89

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

Koekkoek WA, et al. Nutr Clin Pract 2016;31(4):457-74
Rech M, et al. Nutr Clin Pract 2014;29:78-89

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

Koekkoek WA, et al. Nutr Clin Pract 2016;31(4):457-74
Rech M, et al. Nutr Clin Pract 2014;29:78-89
Forceville X, et al. Crit Care Med 1998;26(9):1536-1544
Forceville X, et al. Eur Surg Res 2009;43(4):338-347

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

Peh HY, et al. Pharmacol Ther 2016;162:152-69
Swift SN, et al. Int J Toxicol 2014;33(6):450-8
O'Byrne D, et al. Free Radic Biol Med 2000;29:834-845
Koekkoek WA, et al. Nutr Clin Pract 2016;31(4):457-74

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)

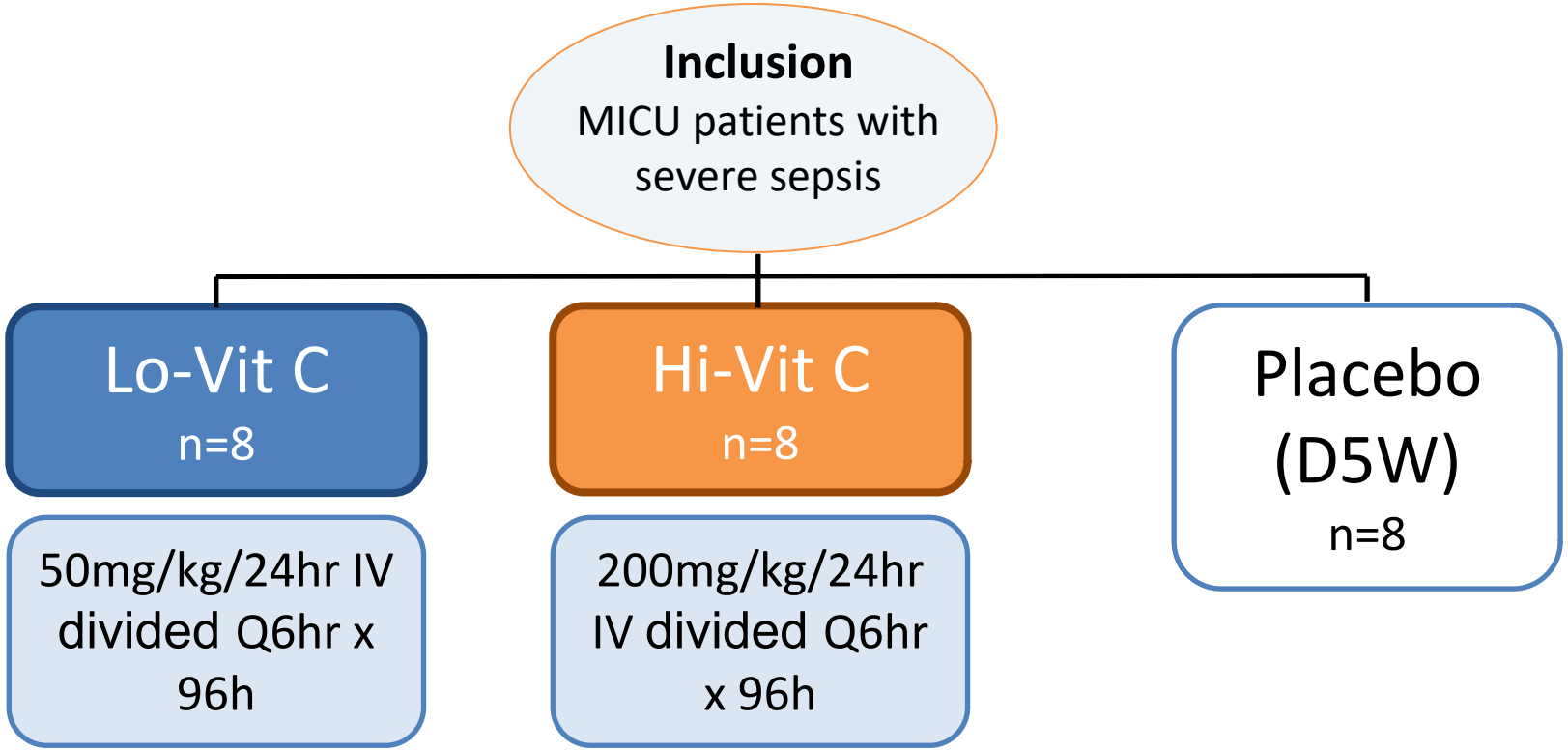
Walravens PA. West J Med 1979;130:133-142
Rech M, et al. Nutr Clin Pract 2014;29:78-89

Primary Literature for Antioxidants in Sepsis

Rationale for Primary Literature Inclusion

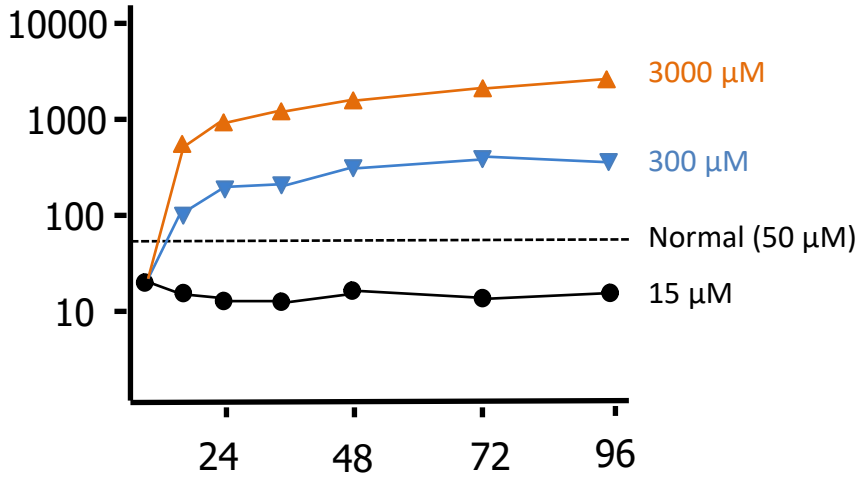
- Studies of antioxidants in humans with sepsis
  - Antioxidants
    - Vitamins C, E
    - Trace minerals selenium, zinc, and copper
    - Antioxidant combinations or ‘cocktails’
  - Excluded
    - Animal studies
    - Studies in ‘critically ill’ patients without sepsis
- Evaluated clinical outcomes

Phase I Vitamin C Study



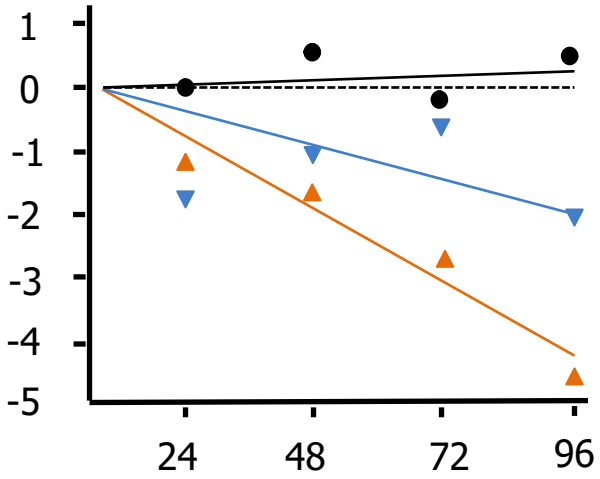
Results

Plasma Ascorbate Level



Lo-Vit C Hi-Vit C Placebo

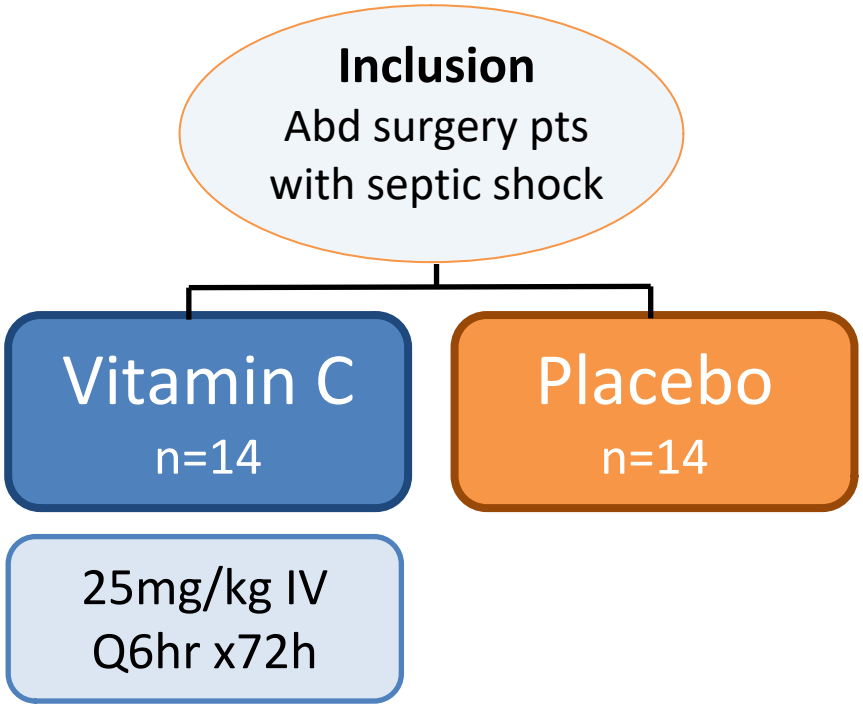
Delta SOFA Score



Lo-Vit C Hi-Vit C Placebo

No adverse safety events observed

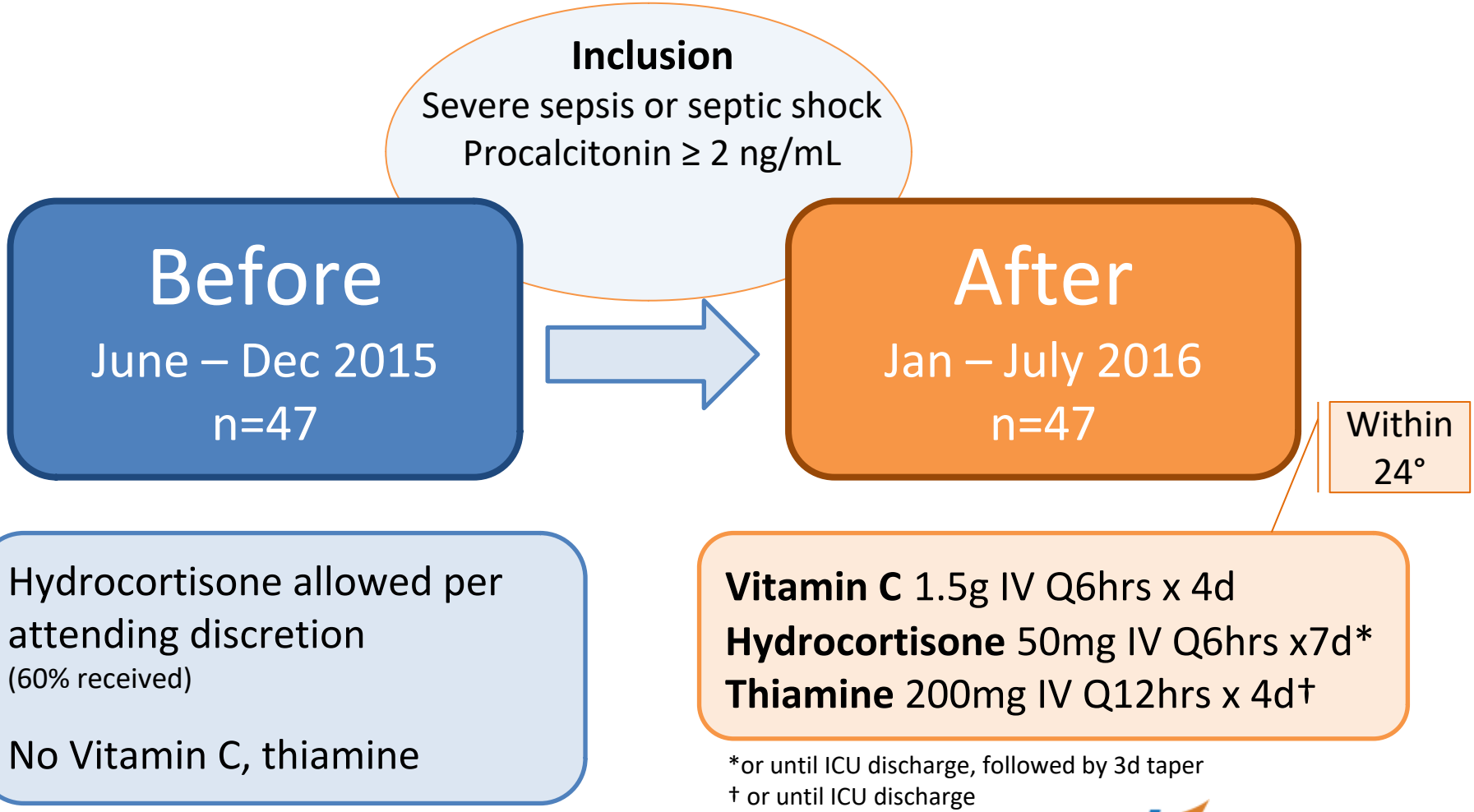
High Dose Vitamin C and Vasopressor Requirement



Baseline Variable	Vit C	Placebo	p
Age, y	64 ± 16	64 ± 14	0.94
APACHE II score	19.1 ± 5	23 ± 6	0.06
SOFA score	11.8 ± 2	12.4 ± 3	0.53
Baseline SCr	1.5± 1.2	2.3 ± 1.7	0.11
Infection Source			0.09
Abdominal	43%	36%	
Pulmonary	29%	29%	
Urinary Tract	14%	21%	

Results

Outcome	Vit C (n=14)	Placebo (n=14)	p
1° Outcomes: NE dose during 72hr study mean ± SD, mcg/min	7.4 ± 3.7	13.8 ± 3.7	0.004
NE duration mean ± SD, h	49.6 ± 25.7	71.6 ± 1.6	0.003
ICU Length of Stay mean ± SD, d	21.5 ± 10.2	20.1 ± 13.0	0.85
28-day mortality	14%	64%	0.009

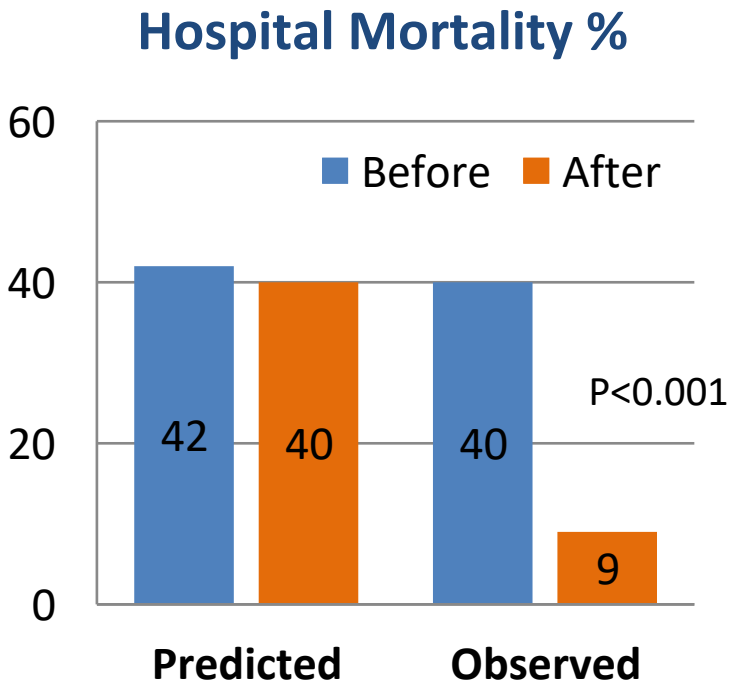

Inclusion
Severe sepsis or septic shock
Procalcitonin ≥ 2 ng/mL
Before
June – Dec 2015
n=47
After
Jan – July 2016
n=47
Within 24°
Hydrocortisone allowed per attending discretion
(60% received)
No Vitamin C, thiamine
Vitamin C 1.5g IV Q6hrs x 4d
Hydrocortisone 50mg IV Q6hrs x7d*
Thiamine 200mg IV Q12hrs x 4d†
*or until ICU discharge, followed by 3d taper
† or until ICU discharge

Baseline Characteristics

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

Illness Severity	Before (n=47)	After (n=47)
Mech Vent	55%	47%
Vasopressors	46%	46%
AKI	64%	66%
Day 1 SOFA mean ± SD	8.7 ± 3.7	8.3 ± 2.8
APACHE II mean ± SD	22.6± 6.3	22.1± 6.3

Results



Outcome	Before	After
ICU Length of Stay median (IQR), d	4 (4-10)	4 (3-5)
Pressor duration* mean ± SD, h	54.9 ± 28.4	18.3 ± 9.8
Δ SOFA, 72 hrs*	0.9 ± 2.7	4.8 ± 2.4
RRT for AKI*	33%	10%

*denotes statistical significance

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

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	Early Trials
• Activated Protein C	• Multicenter, DB, RCT with 1690 pts showing 6% ARR
• G-CSF	• Multicenter, DB, RCT with 18 pts showing 50% ARR
• Intensive Insulin	• 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

	Year	# Studies	# Patients	RR of Mortality	
Huang, et al.	2013	9	965	0.83 (070-0.99)	
Alhazzani, et al.	2013	9	792	0.73 (0.54-0.98)	
Kong, et al.	2013	5	530	0.89 (0.73-1.07)	
ASPEN / SCCM	2016	9	1888	0.94 (0.84-1.06)	

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

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

PCT = Procalcitonin CVT = Conventional (No PCT guidance)

Results

p=0.30

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

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

CVT = Conventional (No PCT guidance)

Primary Literature: Antioxidants in Sepsis

No prospective trials in septic patients

- Vitamin E monotherapy
- Zinc
  - Small studies in burn and trauma patients
  - Often in combination with other antioxidants
- Copper monotherapy

Combination Therapy or "Cocktail"

- Rationale
  - Multiple mechanisms and greater antioxidant effect
  - Regeneration of other antioxidants
- Very limited prospective trials focused on sepsis
  - REDOXS Trial
- "Critically ill"
  - SIGNET Trial
  - MetaPlus Trial

Andrews PJ, et al. BMJ 2011;342:d1542 Zanten van AR, et al. JAMA 2014;312(5):514-524.

REDOXS Trial

40 ICUs in Canada, US, and Europe
Apr 2005 – Dec 2011

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	Antiox	Glut + Antiox	Placebo
n=301	n=307	n=310	n=300
0.35g/kg IV and 30g enterally	**Selenium** 500 mcg IV + 300 mcg enteral **Vitamin C** 1500mg enteral **Vitamin E** 500mg enteral **Zinc** 20 mg enteral **β-carotene** 10 mg enteral		

Heyland D, et al. NEJM 2013;368:1489-97.

REDOXS Trial

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

REDOXS Results

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

*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

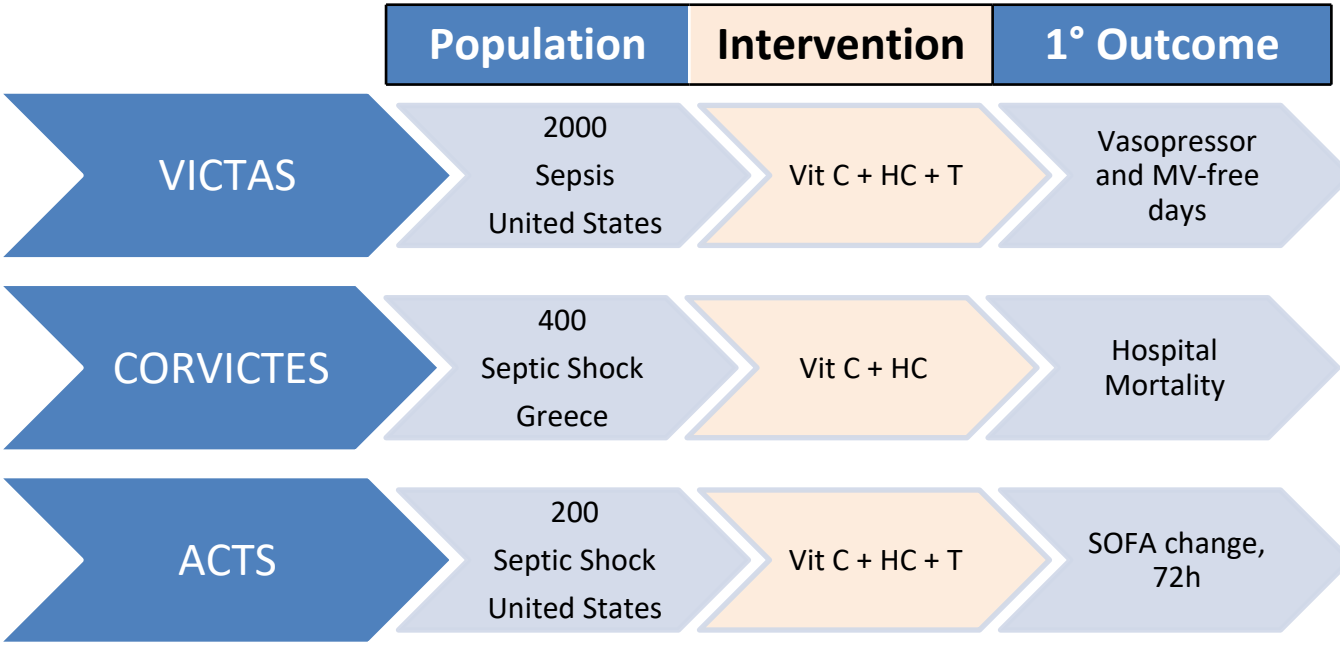
"We recommend against the use of IV selenium to treat sepsis and septic shock"
[Strong recommendation, moderate quality of evidence]

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 equipose exists

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

Ongoing Clinical Trials



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

Information from: clinicaltrials.gov

Patient Case CW Revisited

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 glucoses 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