An Orange a Day to Keep Sepsis at Bay: Hydrocortisone + Vitamin C + Thiamine as Adjunct Treatment of Septic Shock

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UT Health San Antonio
September 5, 2017 and September 8, 2017

At the end of this session, the learner will be able to:
1. Summarize current guideline-indicated treatment strategies for septic shock
2. Describe potential adjunct therapies, including hydrocortisone, thiamine, and ascorbic acid for patients with septic shock
3. Evaluate the effect of triple therapy with hydrocortisone, thiamine, and ascorbic acid on clinical outcomes in septic shock
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Kyllie Shae Ryan-Hummel, PharmD
PGY2 Critical Care Resident
September 5, 2017 at 2:00 and September 8, 2017 at 3:00
University Health System and McDermott Building

Learning Objectives:
At the completion of this activity, the participant will be able to:

1. Summarize current guideline-indicated treatment strategies for septic shock
2. Describe potential adjunct therapies, including hydrocortisone, thiamine, and ascorbic acid, for patients with septic shock
3. Evaluate the effect of triple therapy with hydrocortisone, thiamine, and ascorbic acid on clinical outcomes in septic shock

Assessment Questions:

T  F—Thiamine is added to the triple therapy because all patients have vitamin B deficiency.

Multiple Choice—Current guidelines state all the following agents may be used in septic shock treatment EXCEPT:
   1. Norepinephrine
   2. Empiric antibiotics
   3. Fluid resuscitation with crystalloids
   4. Hydrocortisone
   5. Dexamethasone

T  F—A 2016 clinical trial proposed a novel adjunctive treatment using hydrocortisone, vitamin C, and thiamine for septic shock patients which improved mortality but caused renal toxicity.

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Speaker Disclosure: Kyllie Shae Ryan-Hummel has indicated she has no relevant financial relationships to disclose relative to the content of her presentation.
Sepsis

I. Definitions

a. 1992 American College of Chest Physicians (ACCP)/Society of Critical Care Medicine (SCCM) definitions

i. Systemic Inflammatory Response Syndrome (SIRS): combination of findings resulting from systemic activation of innate immune response (Appendix A)

ii. Sepsis: SIRS plus presumed or proven infection

iii. Severe sepsis: sepsis associated with hypoperfusion, hypotension, or organ dysfunction

iv. Septic shock: sepsis with arterial hypotension after appropriate fluid resuscitation

b. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) definitions

i. Sepsis: life-threatening organ dysfunction caused by a dysregulated host response to infection

1. Organ dysfunction: change in Sequential Organ Failure Assessment (SOFA) score by ≥2 points

   a. Validated scale for grading severity of organ dysfunction in critically ill

   b. Assesses six organ systems and scores them on degree of severity (0-4; 4 being the worst)

   c. Baseline score zero unless preexisting organ dysfunction

   d. Higher scores associated with increased mortality

   i. Score ≥2 and suspected infection have a risk of mortality >10%

   ii. Score >11 points has predictive mortality of 95%

2. Quick SOFA (qSOFA) score (Appendix C)

   a. Used to identify patients with suspected sepsis and high likelihood of prolonged ICU stay or mortality

   b. Sepsis-3 task force suggests that positive qSOFA should prompt clinicians to look for organ dysfunction/infection and initiate or escalate care

   c. Utilized in out of hospital settings, general wards, and emergency departments

ii. Septic shock: subset of sepsis with profound underlying circulatory and cellular metabolic abnormalities; associated with substantially increased mortality

   1. Adequate fluid resuscitation

   2. Persistent hypotension requiring vasopressors to keep mean arterial pressure (MAP) ≥65 mmHg

   3. Serum lactate >2 mmol/L (18 mg/dL)

II. Epidemiology

a. Associated with high morbidity and mortality even with optimal therapy

i. Sepsis-related mortality is ≥10%

ii. Septic shock-related mortality is ≥40%

b. Accounted for $23.7 billion in healthcare costs in 2013

c. Incidence of “severe sepsis” is 300/100,000 patients in United States

 d. Pneumonia is most common infection leading to sepsis

III. Risk factors associated with sepsis

<table>
<thead>
<tr>
<th>Table 1. Sepsis risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-modifiable</strong></td>
</tr>
<tr>
<td>African American</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>≥ 65 years old</td>
</tr>
<tr>
<td>Cirrhosis</td>
</tr>
<tr>
<td>Immunosuppression</td>
</tr>
<tr>
<td>Invasive lines</td>
</tr>
</tbody>
</table>

IV. Pathophysiology and clinical manifestations

a. Cellular and molecular level changes

i. Infection triggers proinflammatory signaling via the innate immune system (macrophages, monocytes, granulocytes, natural killer cells, dendritic cells)

1. Activation of innate immune cells stimulates transcription of pro-inflammatory cytokines and type I interferons (tumor necrosis factor-α [TNF-α], interleukins [IL-1, IL-6])

ii. Cellular damage from overproduction of inflammatory markers
1. Reactive oxygen species (ROS) (e.g., nitric oxide, hydroxyl radicals)
   a. Damage essential molecules
   b. Disrupt normal actions of cellular proteins, lipids, DNA, and mitochondria
2. Complement activation
   a. Increase ROS formation
   b. Enzyme release from granulocytes
   c. Increased endothelial permeability
   d. Tissue factor expression
   e. Adrenal medullary cell apoptosis
3. Immunothrombosis leading to disseminated intravascular coagulopathy (DIC)
   a. Impaired microvascular function and organ injury
   b. Increased activation of inflammatory pathways
   iii. Metabolic dysfunction
1. Cell death mainly confined to lymphatic tissues
2. Mitochondrial dysfunction results primarily from high levels of ROS
   a. Adenosine triphosphate (ATP) levels drop causing viable cells to enter “hibernation” state
      i. Decreased cellular function which promotes widespread organ dysfunction
      ii. Myocardial depression
      iii. Hepatic dysfunction
      iv. Acute kidney injury
      v. Acute lung injury
      vi. Encephalopathy
      vii. Decreased function of gastrointestinal tract
3. Muscle catabolism
4. Tissue and organ dysfunction
   i. Cardiovascular
      1. Systemic inflammation causes
         a. Decreased systemic vascular resistance
            i. Hypotension results in poor perfusion of tissues and organs
            ii. Switch to anaerobic metabolism leads to increased lactate levels
      b. After appropriate volume resuscitation, normal or increased cardiac output despite presence of acute ventricular dysfunction
   ii. Endothelial dysregulation alters
      1. Vasomotor tone
      2. Coagulation system
      3. Cell and nutrient movement
      4. Inflammatory and anti-inflammatory signaling
   iii. Widespread tissue edema
      1. Endothelial vasodilation
      2. Loss of barrier function
      3. Increased leukocyte adhesion
      4. Shift to procoagulant state
   iv. Microcirculatory changes
      1. Obstruction of microvessel lumens due to microthrombi, leukocyte, and erythrocyte plugs
      2. Impaired response to local stimulation
      3. Tissue factor expression
      4. Fibrin deposition
      5. Impaired anticoagulant mechanisms leading to DIC
   v. Renal injury
      1. Result of hypoperfusion
      2. Decreased urine output and increased serum creatinine levels
      3. Often requires renal-replacement therapy
V. Management and treatment of septic shock
   a. Initial therapy
      i. Fluid resuscitation
1. Initial bolus of 30 mL/kg of IV crystalloid administered within first three hours of recognition
2. Goals of therapy
   a. Target MAP ≥ 65 mmHg
   b. Normalize lactate levels
ii. Vasopressors (Appendix D)
   1. First line: norepinephrine
   2. Second line: vasopressin
   3. Initiation and titration of vasopressors should be individualized based on patient response
b. Early initiation of broad spectrum antibiotics
   i. Broad spectrum IV antibiotic therapy within one hour of recognition
      1. Each hour delay in treatment increases mortality 7.6% \(^{11}\)
   ii. Obtain blood cultures prior to broad spectrum antibiotics
      1. Do not delay initiation of antibiotics to obtain blood cultures
c. Procalcitonin \(^{12,13}\)
   i. Biomarker used to identify presence of infection
      1. Should not be used to identify/diagnose sepsis
      2. Higher value is associated with increased mortality
      3. Can be helpful for de-escalation of antimicrobial therapy
   ii. Cannot reliably or accurately differentiate between SIRS and sepsis in critically ill patients
      1. Sensitivity 77%
      2. Specificity 39%

**Hydrocortisone**

I. **Mechanism and pathophysiology** \(^{14}\)
   a. High doses suppress production of excessive inflammatory signals
      i. Decrease damage associated with high inflammatory states
   b. Low dose steroids (<300 mg/day)
      i. Increase responsiveness of vascular smooth muscle to exogenous and endogenous vasopressors
      ii. May improve balance of innate immune system
      iii. Replenish anti-inflammatory effects (cytokine suppression)
      iv. Have minimal immunosuppressive effects
      v. May reverse endothelial activation and sepsis-related clotting disorders

II. **Critical illness related corticosteroid insufficiency (CIRCI)** \(^{15}\)
   a. Inadequate cellular corticosteroid activity in relation to the severity of illness \(^{15}\)
      i. Insufficient down-regulation of proinflammatory transcription factors
      ii. Persistent elevations of proinflammatory mediators
   b. Pathophysiology \(^{15}\)
      i. Reversible decrease in adrenal steroid production or tissue resistance to adrenal steroids
      ii. Adrenal insufficiency can occur at any level on hypothalamic-pituitary-adrenal axis
      iii. Effects on metabolic, immune, vascular, and organ functions
      iv. Diagnosis \(^{15-17}\)
         1. Objective diagnosis
            a. Delta cortisol < 9 mcg/dL after administration of 250 mcg IV cosyntropin
            b. Random total cortisol < 10 mcg/dL
         2. Clinical application \(^{15}\)
            a. Cosyntropin stimulation test should not be used to identify septic shock patients
            b. Critically ill patients have a disconnect between total cortisol and free cortisol levels
            c. May not be representative of the amount of useable free cortisol
   c. **Treatment** \(^{15}\)
      i. Clinical criteria dictates use of glucocorticoids in septic patients
         1. Consider hydrocortisone in septic shock who have poor response to fluid resuscitation and vasopressor therapy
      ii. Dosing strategy: IV hydrocortisone 200 mg/day divided into four daily doses (50 mg every 6 hours)
Ill. Rationale for use in septic shock
a. Decreased mortality
b. Reversal of CIRCI
c. No immunosuppression seen with low-dose
d. Vasopressor duration decreased

IV. Efficacy and safety of hydrocortisone in septic shock patients\textsuperscript{18-20}

<table>
<thead>
<tr>
<th>Design</th>
<th>Annane 2002\textsuperscript{21}</th>
<th>CORTICUS 2008\textsuperscript{17}</th>
<th>HYPRESS 2016\textsuperscript{18}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Multicenter, placebo-controlled, double-blind, randomized</td>
<td>Multicenter, placebo-controlled, double-blind, randomized</td>
<td>Multicenter, placebo-controlled, double-blind, randomized</td>
</tr>
<tr>
<td>28-day mortality</td>
<td>Severe sepsis—not shock (n=353)</td>
<td>Severe sepsis (n=499)</td>
<td>Septic shock (n=299)</td>
</tr>
<tr>
<td>Baseline</td>
<td>SAPS II 61% placebo</td>
<td>60 vs 57</td>
<td>34.3% hydrocortisone 31.5% placebo</td>
</tr>
<tr>
<td>Timing</td>
<td>3-8 hours</td>
<td>&lt;72 hours</td>
<td>n/a</td>
</tr>
<tr>
<td>Vasopressor</td>
<td>Duration</td>
<td>Duration</td>
<td>n/a</td>
</tr>
<tr>
<td>Mortality</td>
<td>Mortality in non-responders</td>
<td>No difference &amp; NOT powered</td>
<td>No difference &amp; NOT powered</td>
</tr>
<tr>
<td>Shock reversal</td>
<td>Time to reversal</td>
<td>Time to reversal</td>
<td>No septic shock prevention</td>
</tr>
</tbody>
</table>


Objectives
- Identify impact of early hydrocortisone initiation on the clinical course of septic shock and cytokine release

Design & Methods
- Non-randomized, prospective, longitudinal study
- Septic shock patients, admitted to ICU or internal medicine departments over a two-year period

Patient Population
- ≥18 years old
- Septic shock defined as adequate fluid resuscitation, SBP <90 mmHg and need for vasopressors
- NE >0.5 mcg/kg/min
- Hydrocortisone 50 mg IV q6h for 7 days
- Antimicrobials within 48 hours of hydrocortisone

Exclusion
- Vasopressor other than NE
- Immunosuppression (e.g., HIV, neutropenia, corticosteroid use)
- Severe immunosuppression
  - Solid tumor or hematologic malignancy
  - Antineoplastic chemotherapy
- Palliative treatment only or withdrawal of therapy decision

Study Groups
- Early initiation of hydrocortisone: less than nine hours post-vasopressor initiation (n=46)
- Late initiation of hydrocortisone: more than nine hours post-vasopressor initiation (n=124)
- 34 patients were sampled for peripheral blood mononuclear cells and cytokine stimulation 24-hours post hydrocortisone initiation

Outcomes
- Primary endpoint
  - Effect of delaying hydrocortisone therapy after initiating norepinephrine on final clinical outcomes
- Secondary endpoints
  - Effect of delaying hydrocortisone therapy after initiating norepinephrine on cytokine stimulation of circulating monocytes

Statistics
- Baseline characteristics compared using Student T test for continuous variables and chi-square for nominal variables
- OR and 95% CI calculated using Mantel-Haenszel’s statistics
- Kaplan-Meier analysis assessed survival and time on vasopressors; compared using log-rank tests
- Univariate analysis compared to analyze effect of nominal variables on outcome
  - Significant variables entered with APACHE II score as a marker for disease severity using forward stepwise cox and logistic regression analyses; HR and 95% CI calculated
- TNF-α produced by PBMCs and monocytes compared between patients in different quartiles using analysis of variance
- ROC curve analysis performed to confirm early vs late initiation was correct selection to make
- Significance was determined by p <0.05

Baseline Characteristics (n=170)

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Early initiation (n=46)</th>
<th>Late initiation (n=124)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>26 (56.5)</td>
<td>84 (67.7)</td>
<td>0.207</td>
</tr>
<tr>
<td>Age in years, mean ± SD</td>
<td>65.2 ± 19.7</td>
<td>62.8 ± 16.9</td>
<td>0.432</td>
</tr>
<tr>
<td>APACHE II score, mean ± SD</td>
<td>26.3 ± 9.9</td>
<td>23.9 ± 11.5</td>
<td>0.229</td>
</tr>
<tr>
<td>SOFA score, mean ± SD</td>
<td>11.5 ± 3.8</td>
<td>10.7 ± 3.6</td>
<td>0.307</td>
</tr>
<tr>
<td>Infection, n (%)</td>
<td>14 (30.4)</td>
<td>63 (50.8)</td>
<td>0.144</td>
</tr>
<tr>
<td>Ventilator-associated pneumonia</td>
<td>13 (28.3)</td>
<td>33 (26.6)</td>
<td></td>
</tr>
</tbody>
</table>

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Vitamin C

I. Mechanism and pathophysiology
   a. Electron reducing agent and antioxidant
      i. Scavenges ROS
      ii. Inhibits NADPH oxidase and superoxide synthesis in microvascular endothelial cells
   b. Infection triggers a systemic inflammatory response leading to vitamin C depletion
   c. Vitamin C protects arteriolar responsiveness and capillary blood flow
      i. Inhibits oxidative stress
      ii. Reduces ROS; decreases further damage to endothelium and organs
      iii. Modulates intracellular signaling pathways
      iv. Maintains homeostatic nitric oxide levels
   d. Accumulates in neutrophils, monocytes, lymphocytes, and platelets which suggests it may be a vital component of appropriately functioning immune cells

II. Rationale for use in septic shock
   a. Essential water-soluble exogenous micronutrient
   b. Highest concentrations in brain and adrenal glands, where catecholamines are synthesized
   c. Low vitamin C levels (hyposcorbia) often seen in septic and critically ill patients
      i. Increased vitamin C requirement leads to total body depletion
         1. Increased ROS causes oxidation
         2. Decreased transport into cells via vitamin C-specific transporters (SVCT1 and SVCT2)
         3. Suboptimal levels associated with higher rates of organ dysfunction and mortality
      ii. Administration of IV vitamin C
         1. Attenuates development and effects of multiple organ dysfunction syndrome (MODS)

V. Current indications
   a. Low dose hydrocortisone reverses steroid deficiency due to relative adrenal insufficiency caused by CIRCI
   b. Guidelines state hydrocortisone can be considered in patients with septic shock who require vasopressor therapy for at least one hour

Conclusions
   - Early initiation of hydrocortisone in septic shock patients is associated with improved survival
   - TNF-α production by PBMCs and monocytes was reduced in patients receiving earlier hydrocortisone administration
   - Early initiation of hydrocortisone in septic shock patients is associated with improved survival
   - Vasopressor discontinuation (early vs late): 4 vs 15 days (p<0.0001)
   - Early initiation (n=46) had lower TNF-α production

Secular outcomes

Primary outcomes

<table>
<thead>
<tr>
<th>Pathogen, n (%)</th>
<th>Early initiation (n=46)</th>
<th>Late initiation (n=124)</th>
<th>p-value</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klebsiella pneumonia</td>
<td>11 (23.9)</td>
<td>25 (20.2)</td>
<td>0.673</td>
<td></td>
</tr>
<tr>
<td>Acinetobacter baumannii</td>
<td>4 (8.7)</td>
<td>32 (25.8)</td>
<td>0.019</td>
<td></td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>5 (10.9)</td>
<td>15 (12.1)</td>
<td>0.532</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>9 (19.6)</td>
<td>13 (10.5)</td>
<td>0.128</td>
<td></td>
</tr>
<tr>
<td>Appropriateness of antimicrobials, n (%)</td>
<td>27 (93.1)</td>
<td>68 (80.0)</td>
<td>0.149</td>
<td></td>
</tr>
</tbody>
</table>

Secondary outcomes

- Kaplan-Meier survival analysis had better overall survival (AUC=0.613; p=0.014)
- ROC analysis showed early administration had better overall survival (p=0.018)
- Vasopressor discontinuation (early vs late): 4 vs 15 days (p<0.0001)
- Early initiation (n=46) had lower TNF-α production

APACHE II=acute physiology and chronic health evaluation II score; AUC=area under the curve; BP=blood pressure; CRD=chronic renal disease; CVP=central venous pressure; DM=diabetes mellitus; h=hours; HIV=human immunodeficiency virus; HR=hazard ratio; ICU=intensive care unit; NE=norepinephrine; Neutropenia=WBC <1,000 neutrophils/mm³; OR=odds ratio; PBMC=peripheral blood mononuclear cells; q=every; ROC=receiver operator characteristics; SOFA=sequential organ failure assessment score; TNF-α=tumor necrosis factor alpha; WBC=white blood cell.
2. Reverses arteriolar hypo-responsiveness to endogenous vasoconstrictors (angiotensin, vasopressin, norepinephrine)\textsuperscript{25}

3. Acts as a cofactor for copper-containing enzymes and increases formation of vitamin-C dependent vasopressors\textsuperscript{24,26}
   a. Synthesis of norepinephrine
      i. Enzyme uses oxygen to add a hydroxyl group to dopamine (Figure 1)
      ii. Dopamine β-hydroxylase

![Figure 1. Biosynthesis of norepinephrine](image)

b. Synthesis of vasopressin
   i. Enzyme converts glycine-extended peptide into intermediate products to be broken down into active hormone and glyoxylate (Figure 2)
   ii. Peptidylglycine α-amidating monooxygenase (PAM)

![Figure 2. Biosynthesis of vasopressin](image)
4. Successful administration without nephrotoxicity
   a. IV doses exceeding recommended dietary allowances of vitamin C have been given without adverse renal toxicities
   b. Studies commonly utilize 50-200 mg/kg/day which were not associated with renal toxicity or adverse effects

III. Rationale for vitamin C
   a. Essential micronutrient that is depleted in septic shock
   b. Increase arteriolar response to endogenous vasoconstrictors
   c. Cofactor for synthesis of norepinephrine & vasopressin
   d. Improved outcomes in septic shock patients
   e. Safety & efficacy have been described in septic shock patients
   f. Early repletion through supra-physiologic doses necessary

IV. Efficacy and safety of vitamin C in septic shock patients

<table>
<thead>
<tr>
<th></th>
<th>Long 2003(^{28})</th>
<th>Zabet 2016(^{29})</th>
<th>Baharara 2016(^{30})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Pharmacokinetic study</td>
<td>Multicenter, placebo-controlled, double-blind, randomized</td>
<td>Case report</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>Critically ill; no renal failure (n=14)</td>
<td>Septic shock (n=28)</td>
<td>Sepsis-associated ARDS (n=1)</td>
</tr>
<tr>
<td><strong>28-day mortality</strong></td>
<td>n/a</td>
<td>14.28% vs 64.28%</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>IV vitamin C 300 mg (2 days) IV vitamin C 1000 mg (2 days) IV vitamin C 3000 mg (2 days)</td>
<td>IV vitamin C 25 mg/kg q6h x 72h</td>
<td>IV vitamin C 50 mg/kg q6h On day 4 on two separate admissions</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td>Injury severity score: 26±3</td>
<td>APACHE II SOFA 19.07 vs 23 11.78 vs 12.35</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Achieved normal plasma vitamin C levels on days 5, 6</td>
<td>↓ Norepinephrine doses ↓ duration of norepinephrine ↓ mortality</td>
<td>Improved chest x-ray and subsequent extubation</td>
</tr>
</tbody>
</table>


**Objective**
- Determine safety of IV ascorbic acid in patients with severe sepsis
- Determine if ascorbic acid infusions impact organ failure measured by biomarkers

**Design & Methods**
- Randomized, double-blind, placebo-controlled, phase I trial
- Screened and enrolled upon admission to the medical ICU at VCU Medical Center

**Patient Population**

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe sepsis within 48 hours of ICU admission:</td>
<td>Not meeting inclusion criteria</td>
</tr>
<tr>
<td>- SIRS</td>
<td></td>
</tr>
<tr>
<td>- Suspected or proven infection</td>
<td></td>
</tr>
<tr>
<td>- Sepsis-induced organ dysfunction</td>
<td></td>
</tr>
</tbody>
</table>

**Intervention**
- Treatment groups
  - Placebo (n=8)
  - Low-dose ascorbic acid (Lo-AscA): 50 mg/kg/day ascorbic acid (n=8)
  - High-dose ascorbic acid (Hi-AscA): 200 mg/kg/day ascorbic acid (n=8)
- Study drug initiated within 2-4 hours of informed consent and randomization
- Ascorbic acid divided in 4 equal doses administered in 50 mL D5W over 30 minutes q6h for 4 days

**Outcomes**
- Primary endpoint
  - Assess ascorbic acid safety and tolerability by monitoring severity and frequency of treatment related adverse effects
  - Arterial hypotension, tachycardia, hypernatremia, nausea, vomiting
- Secondary endpoints
  - Vasopressor days
  - Ventilator-free days
  - ICU LOS
  - 28-day mortality

**Statistics**
- Results expressed as mean ± SE
- Differences between groups analyzed using two-factor analysis of variance with Tukey’s studentized range test
- Summary data reported as mean ± SEM
- Statistical significance reported as p-value <0.05
- SOFA scores based on the evolution of the delta daily SOFA score compared with day 0 over the 4 study days through comparison of regression coefficients using Student’s T test
V. Current indications
   a. No mention in guidelines

Thiamine

I. Mechanism and pathophysiology
   a. Water-soluble vitamin essential to cellular metabolism, existing in the human body in various forms
   b. Essential for converting glucose into energy
      i. Depletion of thiamine decreases activity of pyruvate dehydrogenase (Figure 3)
         1. Decreased decarboxylation of pyruvate into acetyl coenzyme A
         2. Decreased initiation of Krebs cycle

   Figure 3. Metabolic role of thiamine
c. Daily repletion is necessary due to a short half-life and limited body stores\textsuperscript{32,33}
d. Thiamine deficiency associated with a variety of clinical syndromes\textsuperscript{32,33}
   i. Cardiovascular disease
   ii. Beriberi syndrome
   iii. Peripheral neuropathy
   iv. Wernicke-Korsakoff syndrome
   v. Refeeding syndrome
   vi. Oxidative stress
   vii. Lactic acidosis
   viii. Sepsis

II. Rationale for use in septic shock\textsuperscript{32}
   a. Subclinical deficiency is highly prevalent in critically ill patients
      i. 20% of ICU admissions
      ii. 21% of emergency department admissions
   b. Despite higher rates of morbidity and mortality seen with thiamine deficiency in critically ill, routine supplementation is not used
   c. Unrecognized “relative thiamine deficiency syndrome” leads to lactic acid production
   d. Patients at highest risk for thiamine deficiency
      i. Alcoholics
      ii. Chronic malnutrition or starvation
      iii. Chemotherapy
      iv. Receiving diuretics
      v. Parenteral or enteral nutrition with inadequate supplementation

III. Efficacy and safety of thiamine in septic shock patients
   a. Donnino et al. studied prevalence of thiamine deficiency in critically ill septic patients and association with lactic acidosis\textsuperscript{34}
      i. Prospective observational study in patients with evidence of tissue hypoperfusion requiring vasopressor support (n=30) versus placebo (n=30)
         1. Absolute thiamine deficiency upon admission to the ICU (n=3)
         2. Thiamine deficiency developed within 72 hours (n=3)
      ii. Found no correlation between lactic acidosis and thiamine deficiency (p=0.83)
   b. de Andrade et al. evaluated effects of thiamine deficiency on oxidative stress, cellular recruitment, and inflammation in a murine sepsis model\textsuperscript{35}
      i. Postulated that thiamine deficiency
         1. Further compounds oxidative stress
         2. Associated with increased inflammation
      ii. Findings
         1. Thiamine deficiency occurred within 10 days in study mice fed thiamine deficient (TD) chow
         2. TNF-\(\alpha\) in peritoneal fluid significantly greater in cecal ligation and puncture (CLP) + thiamine deficient (TD) chow group
         3. Blood mononuclear cell counts increased in CLP+TD chow group (p<0.05)
         4. Peritoneal bacterial colony forming units lower in the CLP+TD chow group
      iii. Thiamine deficiency is associated with greater bacterial clearance, oxidative stress, and inflammatory response changes

## Table

<table>
<thead>
<tr>
<th>Objective</th>
<th>Determine if IV thiamine reduces lactate levels in septic shock patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design &amp; Methods</td>
<td>Randomized, double-blind, placebo-controlled, pilot study; DSMB evaluated for drug safety</td>
</tr>
<tr>
<td>Two tertiary care hospitals in Massachusetts between January 2010-October 2014; randomized in 1:1 ratio; stratified by participation site</td>
<td></td>
</tr>
</tbody>
</table>

### Inclusion

- \(\geq 18\) years old
- Sepsis with the presence of \(\geq 2\) SIRS criteria
  - Documented or suspected infection
- Lactate \(\geq 3\) mmol/L
- Hypotension: SBP <90 mmHg after \(\geq 2\) L fluid bolus
- Vasopressor dependence

### Exclusion

- Liver injury/dysfunction (e.g., AST or ALT >240 units/L, cirrhosis)
- Current thiamine supplementation
- Clinical need for thiamine (e.g., alcohol abuse, beriberi)
- Comfort measures only
- Inability to provide consent
- Alternative reason for elevated lactate levels
### Characteristics

| LT= |  |  |

### Intervention
- Placebo: 50 mL D5W q12h for 7 days or until hospital discharge
- Thiamine: 200 mg in 50 mL D5W q12h for 7 days or until hospital discharge

### Outcomes
- Primary endpoint
  - Lactate level at 24-hours post dose
- Secondary endpoints
  - Lactate levels at 6 and 12-hours post dose and the change at 24 hours
  - Lactate ≥4 mmol/L at 24 hours
  - Time to shock reversal (>24 hours off all vasopressors)
- SOFA score at 24 hours
- APACHE II score at 24 hours
- SOFA score at 24 hours
- ICU and hospital LOS
- In-hospital mortality with classification of the mode of death

### Statistics
- Study population summarized using descriptive statistics
  - Continuous variable presented as means (SD) or medians (1st quartile, 3rd quartile) depending on data normality
  - Wilcoxon rank sum tests and t-tests were used to compare continuous data between the groups
- Categorical variable presented as frequencies or compared using Fisher’s exact tests
- All data based on modified intention to treat principle
- Kaplan Meier curves created for survival and compared with the log-rank test
- Patients censored at hospital discharge
- All hypotheses were two sided with significance at p<0.05
- No adjustments made for multiple testing and all secondary outcomes considered exploratory

### Baseline Characteristics (n=88)

<table>
<thead>
<tr>
<th>Age in years, mean (SD)</th>
<th>70 (14)</th>
<th>65 (17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>17 (40)</td>
<td>19 (42)</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>36 (84)</td>
<td>40 (89)</td>
</tr>
<tr>
<td>APACHE II score, mean (SD)</td>
<td>25.7 (9.1)</td>
<td>26.5 (9.2)</td>
</tr>
<tr>
<td>SOFA score, mean (SD)</td>
<td>10.1 (3.7)</td>
<td>10.2 (3.7)</td>
</tr>
</tbody>
</table>

### Results (n=88)

<table>
<thead>
<tr>
<th>Primary outcomes</th>
<th>Thiamine (n=43)</th>
<th>Placebo (n=45)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate levels at 24 hours in mmol/L, median (quartiles)</td>
<td>2.5 (1.5-3.4)</td>
<td>2.6 (1.6-5.1)</td>
<td>0.40</td>
</tr>
<tr>
<td>Decrease in lactate levels from baseline to 24-hours was higher with significantly lower lactate concentrations in thiamine (p=0.048)***</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

***All pair-wise tests were performed without adjustment for multiple comparisons

<table>
<thead>
<tr>
<th>Secondary outcomes</th>
<th>Thiamine (n=43)</th>
<th>Placebo (n=45)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate change at 24 hours, % (quartiles)</td>
<td>42 (17-51)</td>
<td>25 (-12-47)</td>
<td>0.16</td>
</tr>
<tr>
<td>Lactate ≥4 mmol/L at 24 hours, n (%)</td>
<td>9 (21)</td>
<td>17 (38)</td>
<td>0.10</td>
</tr>
<tr>
<td>Time to shock reversal (&gt;24 hours off all vasopressors), %</td>
<td>74</td>
<td>71</td>
<td>0.81</td>
</tr>
<tr>
<td>APACHE II score at 24 hours, mean (SD)</td>
<td>23.8 (8)</td>
<td>26.1 (10)</td>
<td>0.15</td>
</tr>
<tr>
<td>SOFA score at 24 hours, mean (SD)</td>
<td>8.1 (3.5)</td>
<td>8.9 (5)</td>
<td>0.41</td>
</tr>
<tr>
<td>Time to ICU discharge in days, mean (SD)</td>
<td>8.4 (13)</td>
<td>7.3 (18)</td>
<td>0.70</td>
</tr>
<tr>
<td>Hospital LOS in days, mean (SD)</td>
<td>13 (8-20)</td>
<td>13 (7-24)</td>
<td>0.86</td>
</tr>
<tr>
<td>Inpatient mortality, %</td>
<td>42</td>
<td>44</td>
<td>1.00</td>
</tr>
<tr>
<td>Lactate levels at 6, 12, and 24-hours post-dose were non-significant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate change at 24 hours in TD patients mmol/L, median (quartiles)</td>
<td>2.1 (1.4-2.5)</td>
<td>3.1 (1.9-8.3)</td>
<td>0.03</td>
</tr>
<tr>
<td>Time to death in favor of thiamine group</td>
<td>log-rank test, p=0.047</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Conclusions
- Thiamine did not improve lactate levels or other secondary outcomes but did significantly improve lactate levels at 24 hours in patients with a baseline deficit

### Critique

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk for Wernicke’s encephalopathy excluded</td>
<td>Inclusion/exclusion criteria likely led to uneven cohorts</td>
</tr>
<tr>
<td>Included a critically ill population</td>
<td>Small sample sizes; enrollment primarily from one site</td>
</tr>
<tr>
<td>Baseline characteristics similar between groups</td>
<td>Epinephrine patients were not excluded</td>
</tr>
<tr>
<td>Adverse effects were not mentioned</td>
<td>Lack of adjustment for multiple comparisons</td>
</tr>
<tr>
<td></td>
<td>No information about how sepsis was treated</td>
</tr>
<tr>
<td></td>
<td>Kaplan Meier survival curve only reflects 28 of 88 total patients</td>
</tr>
</tbody>
</table>

### Rational for thiamine
- Decreases lactic acid production in deficient patients
- Increases use of aerobic metabolism
- Decreases oxalic acid formation
- Improved outcomes in deficient patients
- High prevalence of thiamine deficiency in critically ill patients

**ALT=alanine transaminase; APACHE=acute physiology and chronic health evaluation II score; AST=aspartate transaminase; bpm=beats per minute; D5W=5% dextrose in water; DSMB=data safety monitoring board; ED=emergency department; ICU=intensive care unit; INR=international normalized ratio; IV=intravenous; LOS=length of stay; n/a=not applicable; nr=not reported; ns=not significant; q=every; SBP=systolic blood pressure; SIRS=systemic inflammatory response syndrome; SOFA=sequential organ failure assessment score; TD=thiamine deficient**

IV. Rational for thiamine

a. Decreases lactic acid production in deficient patients
b. Increases use of aerobic metabolism
c. Decreases oxalic acid formation
d. Improved outcomes in deficient patients
e. High prevalence of thiamine deficiency in critically ill patients
Is triple therapy a successful adjunct for septic shock patients?

I. Triple therapy 37,37-39
a. Combination therapy has additive effects that protect the vascular endothelium and reversed the lipopolysaccharide (LPS)-induced barrier dysfunction compared to either agent used alone 37
b. Vitamin C has been shown to reverse the oxidation of glucocorticoid receptors leading to increased glucocorticoid activity 38

c. Administration of glucocorticoids increases the sodium vitamin C transporter-2 expression which is essential for vitamin C to be transported intracellularly 39

d. Thiamine decreases the production of oxalic acid from the metabolism of vitamin C

<table>
<thead>
<tr>
<th>Objective</th>
<th>Determine if administration of vitamin C, hydrocortisone, and thiamine as adjunctive septic shock therapy is associated with improved survival rates</th>
</tr>
</thead>
</table>
| Design & Methods | Retrospective, before-after study comparing outcomes of septic patients before and after implementation of new practice protocol
Consecutive septic patients treated with IV vitamin C, hydrocortisone, and thiamine (triple therapy) between January 2016 to July 2016 compared to control group treated between June 2015 to December 2015 |
| Patient Population Inclusion | Severe sepsis or septic shock diagnosis
Procalcitonin >2 ng/mL |
| Patient Population Exclusion | <18 years old
Pregnant
DNR or DNR + limitations of care |
| Intervention | Control group
Hydrocortisone (50 mg q6h) administered at the discretion of the attending physician

Triple therapy group
Vitamin C: 1.5 g IV q6h for 4 days or until ICU discharge in 100 mL D5W or NS over 30-60 minutes
Hydrocortisone: 50 mg IV q6h for 7 days or until ICU discharge followed by a 3-day taper
Thiamine: 200 mg IV q12h for 4 days or until ICU discharge in 50 mL D5W or NS over 30 minutes
Standard practice protocol utilized in both groups
Empiric initiation of broad spectrum antibiotics; deescalated as clinically relevant
Physiologically based vasopressor and fluid therapy
Norepinephrine 1st choice titrated to 20 mcg/min; 2nd vasopressin 0.04 units/min; 3rd phenylephrine or epinephrine
Lung-protective strategy while intubated
Limited sedation (preferred dexmedetomidine)
Enteral nutrition: whey-based formula and intermittent bolus within 24 hours post-ICU admission; allow permissive hyperglycemia
Deep vein thrombosis prophylaxis with enoxaparin (heparin if CrCl <30 mL/min) and sequential compression devices
Routine stress ulcer prophylaxis is not practiced |
| Outcomes | Primary endpoint
Hospital survival
Secondary endpoints
Duration of vasopressor therapy
Renal replacement therapy requirement for acute kidney injury
ICU LOS
Change in serum procalcitonin
ΔSOFA score over 72 hours |
| Statistics | Summary statistics used to describe clinical data: presented as means, SD, percentages and interquartile ranges
Analysis using Fisher’s exact test and Student’s t test (Mann-Whitney U test if non-normal distribution)
Statistical significance p<0.05
Logistic discriminant analysis performed to determine independent predictors of survival
Propensity scores to control for likelihood to receive vitamin C protocol; help adjust potential baseline differences between groups
Binary logistic regression with propensity score adjustment performed to assess odds ratio for mortality by treatment group |
| Baseline Characteristics (n=94) | | Triple therapy (n=47) | Control (n=47) | p-value |
| Age in years, mean ± SD | | 58.3 ± 14.1 | 62.2 ± 14.3 | ns |
| Male, n (%) | | 27 (57) | 23 (49) | ns |
| Vasopressors, n (%) | | 22 (46) | 22 (46) | ns |
| Hydrocortisone treatment, n (%) | | 47 (100) | 28 (59.6) | ns |
| Acute kidney injury, n (%) | | 31 (66) | 30 (64) | ns |
| Renal replacement therapy, n (%) | | 3 (10) | 11 (37) | p=0.02 |
Lactate in mM, mean ± SD 2.7 ± 1.5 3.1 ± 2.8 ns
Creatinine in mg/dL, mean ± SD 1.9 ± 1.4 1.9 ± 1.1 ns
Procollactin in ng/mL, median (IQR) 25.8 (5.8-93.4) 15.2 (5.9-39.0) ns
Day 1 SOFA, mean ± SD 8.3 ± 2.8 8.7 ± 3.7 ns
APACHE II, mean ± SD 22.1 ± 6.3 22.6 ± 5.7 ns
APACHE IV, mean ± SD 79.5 ± 16.4 82.0 ± 27.4 ns
Predicted mortality, mean ± SD 39.7 ± 16.7 41.6 ± 24.2 ns

Results (n=94)

Hospital mortality, n (%) 4 (8.5) 19 (40.4) <0.001
ICU LOS in days, median (IQR) 4 (3-5) 4 (4-10) ns
Duration of vasopressors in hours, mean ± SD 18.3 ± 9.8 54.9 ± 28.4 <0.001
RRT for AKI, n (%) 3 of 31 (10%) 11 of 30 (33%) 0.02
ΔSOFA, 72 hours 4.8 ± 2.4 0.9 ± 2.7 <0.001
Procollactin clearance 72 hours, median % (IQR) 86.4 (80.1 to 90.8) 33.9 (-62.4 to 64.3) <0.001

Conclusions
- Early use of IV vitamin C with thiamine and hydrocortisone appear to be effective in preventing progressively worsening organ dysfunction and reduce mortality associated with sepsis and septic shock

Critique

- Propensity score to adjust for likelihood of triple therapy
- No control patients received IV thiamine or vitamin C
- Safety of individual agents previously described
- Plausible biochemical mechanisms can explain effects; both vitamin C and hydrocortisone are necessary for endogenous catecholamine production and utilization
- Septic patients often have depletion of triple therapy components

Limitations
- Small sample sizes
- Single-center design
- Control subjects not enrolled concurrently
- Did not assess typical volume resuscitation protocol
- Time to antimicrobials and agent used not commented on
- Did not provide vasopressor breakdown explicitly
- Vasopressor escalation differs from most published data

II. Rational for use in septic shock
   a. Decreased mortality using triple therapy
   b. Decreased vasopressor requirements with triple therapy
   c. Improved organ function in septic shock patients
   d. Reversal of metabolic derangements

III. Current indications
   e. No mention in guidelines

Conclusions

I. Overall
   a. Treat septic shock per the Sepsis-3 guidelines and ensure that all normal therapies are provided for every patient
   b. Combination adjunct therapy using hydrocortisone + vitamin C + thiamine in septic shock patients is associated with improved outcomes in septic shock patients when added to standard septic shock treatment
      i. Decreased time on vasopressor therapy
      ii. Decreased mortality
   c. Adverse drug reaction not identified with single agent or in combination
   d. With all adjunct therapies, treatment has proven beneficial when therapies are not delayed and when they are used in combination due to the synergism between the three agents

II. Safety
   a. Hydrocortisone has a long history of use in septic shock and is regarded safe at low doses (e.g. 50 mg q6h)
   b. Vitamin C has been administered safely in critically ill patients at doses of 12.5-50 mg/kg/dose q6h
   c. Thiamine is associated with improved outcomes when administered to deficient patients and is safe at levels of 200 mg q12h

III. Efficacy
   a. Hydrocortisone decreases mortality and time on vasopressor therapy
   b. Vitamin C decreases SOFA score and markers of inflammation
   c. Thiamine decreases mortality in patients who are thiamine deficient
   d. Triple cocktail decreases mortality, time on vasopressor therapy, SOFA score, and markers of inflammation

AKI=acute kidney injury; APACHE=acute physiology and chronic health evaluation; Δ=delta/change; D5W=dextrose 5% in water; DNR=do not resuscitate; ICU=intensive care unit; IV=intravenous; LOS=length of stay; NS=normal saline; RRT=renal replacement therapy SOFA=sepsis-related organ failure assessment
### Design

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>Intervention</th>
<th>Baseline</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katsenos 2014</td>
<td>Non-randomized, prospective, longitudinal</td>
<td>Septic shock adults; norepinephrine &gt;0.5 mcg/kg/min</td>
<td>IV hydrocortisone 50 mg q6h x 7d Early &lt;9 hours (n=46) Late &gt;9 hours (n=124) IV vitamin C divided q6h Placebo (n=8) Lo-AscA: 50 mg/kg/d (n=8) Hi-AscA: 200 mg/kg/d (n=8)</td>
<td>APACHE II 26.3 vs 23.9 SOFA 11.5 vs 10.7</td>
<td>† vasopressor duration † mortality † c-reactive protein † procalcitonin</td>
</tr>
<tr>
<td>Fowler 2014</td>
<td>Placebo-controlled, double-blind, randomized, phase I trial</td>
<td>Severe sepsis</td>
<td>Thiamine 200 mg q12h x 7d Placebo (n=45) Thiamine (n=43)</td>
<td>APACHE II 20.4 vs 20.4 vs 24 SOFA 13.3 vs 10.1 vs 10.8</td>
<td>† mortality in deficient patients</td>
</tr>
<tr>
<td>Donnino 2016</td>
<td>Two-center, placebo-controlled, double-blind, randomized, pilot</td>
<td>Sepsis + lactate &gt;3 mmol/L + hypotension + vasopressors</td>
<td>Triple therapy</td>
<td>APACHE II 26.5 vs 25.7 SOFA 10.2 vs 10.1</td>
<td>† mortality in deficient patients</td>
</tr>
<tr>
<td>Marik 2016</td>
<td>Retrospective, before-after study</td>
<td>Severe sepsis or septic shock + procalcitonin &gt;2 ng/mL</td>
<td>Control (n=47) Triple therapy (n=47)</td>
<td>APACHE II 22.6 vs 22.1 SOFA 8.7 vs 8.3</td>
<td></td>
</tr>
</tbody>
</table>

*Triple therapy = IV hydrocortisone 50 mg q6h x 7d + IV vitamin C 50 mg q6h x 4d + IV thiamine 200 mg q12h x 4*

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### Treatment recommendations

**I. Patient with septic shock**

- Appropriate fluid resuscitation based on patient specific parameters with a goal MAP &gt;65 mmHg
- If MAP &gt;65 mmHg not achieved, initiate norepinephrine and titrate to MAP &gt;65 mmHg
- If not at goal with norepinephrine &gt;0.5 mcg/kg/min for &gt;1 hour then add further therapy
- Add vasopressin and triple therapy to norepinephrine drip
  - Vasopressin 0.04 units/min
  - Hydrocortisone IV 50 mg every 6 hours for 7 days
  - Vitamin C IV 1.5 g every 6 hours for 4 days
    1. Reconstitute in 100 mL D5W or NS over 30 to 60 minutes
  - Thiamine IV 200 mg every 12 hours for 4 days
    1. Reconstitute in 50 mL D5W or NS over 30 minutes

**II. Further consideration should be provided for the following patients; must outweigh risks**

- Chronic immunosuppression
- Glucose-6-phosphate dehydrogenase deficiency
- Underlying/previous identified chronic kidney disease
- 72 hours after septic shock onset
- A diagnosis of “severe sepsis” and not septic shock
References


Appendices

I. Appendix A. SIRS criteria (range 0-4 points)\textsuperscript{1,2}

- T >38° C or T <36° C
- RR >20 breaths/min or PCO\textsubscript{2} < 32 mmHg
- WBC >12,000/mm\textsuperscript{3} or WBC <4,000/mm\textsuperscript{3} or bands >10%
- HR >90 beats/min

*C=degrees Celsius; HR=heart rate; PCO\textsubscript{2}=partial pressure of carbon dioxide; RR=respiratory rate; WBC=white blood cell count
**SIRS criteria met when at least two of the criteria are present

II. Appendix B. SOFA score (range 0-24 points)\textsuperscript{4,5}

<table>
<thead>
<tr>
<th>Organ failure score</th>
<th>Respiratory</th>
<th>Neurological</th>
<th>Cardiovascular</th>
<th>Hepatic</th>
<th>Coagulation</th>
<th>Renal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PaO\textsubscript{2}/FiO\textsubscript{2} (mmHg)</td>
<td>GCS</td>
<td>Vasopressor (mcg/kg/min)</td>
<td>Bilirubin (mg/dL)</td>
<td>Platelets (x10\textsuperscript{11}/µL)</td>
<td>Creatinine (mg/dL)</td>
</tr>
<tr>
<td>0</td>
<td>≥400</td>
<td>15</td>
<td>MAP ≥70 mmHg</td>
<td>&lt;1.2</td>
<td>≥150</td>
<td>&lt;1.2</td>
</tr>
<tr>
<td>1</td>
<td>&lt;400</td>
<td>13-14</td>
<td>MAP &lt;70 mmHg</td>
<td>1.2-1.9</td>
<td>&lt;150</td>
<td>1.2-1.9</td>
</tr>
<tr>
<td>2</td>
<td>&lt;300</td>
<td>10-12</td>
<td>D &lt;5; DO</td>
<td>2.0-5.9</td>
<td>&lt;100</td>
<td>2.0-3.4</td>
</tr>
<tr>
<td>3</td>
<td>&lt;200+MV/</td>
<td>6-9</td>
<td>D 5.1-15; E ≤0.1; NE ≤0.1</td>
<td>6.0-11.9</td>
<td>&lt;50</td>
<td>3.5-4.9</td>
</tr>
<tr>
<td>4</td>
<td>&lt;100+MV/</td>
<td>&lt;6</td>
<td>D &gt;15; E &gt;0.1; NE &gt;0.1</td>
<td>&gt;12.0</td>
<td>&lt;20</td>
<td>&gt;5.0</td>
</tr>
</tbody>
</table>

D=dopamine; DO=dobutamine; E=epinephrine; GCS=Glasgow coma scale; MAP=mean arterial pressure; MV=mechanically ventilated; NE=norepinephrine; PaO\textsubscript{2}/FiO\textsubscript{2}=fraction of inspired oxygen

III. Appendix C. qSOFA criteria (range 0-3)\textsuperscript{4,5}

- Altered mental status (GCS £13)
- RR ≥22 breaths/min
- SBP ≤100 mmHg

GCS=Glasgow coma scale; RR=respiratory rate; SBP=systolic blood pressure

IV. Appendix D. Vasopressor administration in septic shock\textsuperscript{10}

- MAP <65 mmHg
  - Titrate norepinephrine to 0.5-1.3 mcg/kg/min
  - Add vasopressin 0.03 units/min
  - Consider IV hydrocortisone

- MAP <65 mmHg
  - Titrate epinephrine to 0.3-0.7 mcg/kg/min
  - Add IV hydrocortisone

- MAP <65 mmHg
  - Titrate phenylephrine 2.9-4.3 mcg/kg/min

IV=intravenous; MAP=mean arterial pressure