Sepsis Treatment: Is There a Role For Vitamins?

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Associate Editor, Critical Care Medicine
Disclosures

Financial

• Grant Support Current
  – FDA/BARDA
  – Marcus Foundation

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Intellectual

• Medical Advisor to Project Hope (ARDS Advocacy Group)
Talk Outline

• Review Treatment of Patients with Sepsis

• Review the Benefits and Limitations of Single Center vs Multicenter Clinical Trials

• Discuss the evidence supporting use of Vitamin C, Thiamine, and Steroids in Sepsis

• To Describe the Design of the VICTAS study (Vitamin C, Thiamine and Steroids in Sepsis)
Patient JM

- 66 year old with CML - extra lymphatic involvement S/P ABMT 60 days prior to admission
  - Admitted with GVHD with GI symptoms
  - Noted to have tachypnea to 30’s B/P 90/55 pulse 108 T 38.5 wbc 1.2 lactate 4
  - Blood cultures oxidase positive gram negative rods
  - Started on ceftazidime
  - Transferred to ICU when required non-rebreather

Infection
Organ failure
Sepsis is a Medical Emergency

Concept Highlighted by Manny Rivers
Proper Orientation is Important

Sepsis Care Must Center Around the Patient
Sepsis is a Medical Emergency

- Treatment

- Similar conditions
Sepsis is…

- Life-threatening organ dysfunction caused by a dysregulated host response to infection\textsuperscript{1}
- **Common**: 0.9-3 million cases/yr\textsuperscript{2,3}
- **Life-threatening**: 15-30% mortality\textsuperscript{2}
- **Time-sensitive**: 8% mortality increase for every hour delay in initiation of antibiotics\textsuperscript{4}
- **A major public health concern**: most expensive reason for US hospitalization\textsuperscript{5,6}

\textsuperscript{1} Singer et al. JAMA 2016
\textsuperscript{2} Gaieski et al. CCM 2013
\textsuperscript{3} Martin et al. NEJM 2003
\textsuperscript{4} Kumar et al. CCM 2006
\textsuperscript{5} Elixhauser et al. AHRQ Report 2011
\textsuperscript{6} Torio and Andrews. AHRQ Report 2013
Sepsis is a Syndrome

- Disease
- Known Biomarker
- Diagnostic Test that enables identification

- Syndrome
- Constellation of signs and syndromes that lead to diagnosis
Sepsis Diagnosis- Not Always Simple
 Partnering with Patients and Advocacy Groups
What is in the Sepsis Treatment Toolbox?

- Early Recognition of Sepsis
- Early Antibiotics and Fluids
- Performance Improvement Projects
Timing of Antibiotics in Sepsis Induced Hypotension

- 2731 Patients with septic shock
- 44% Admissions From ED
  - Lung, Intra-abdominal and Urine most common sites of infection
- Mortality Rate 21% if Effective Antibiotics given within 1 hour
- Mortality Rate 58% if Effective Antibiotics given within 6 hours

Kumar et al Crit Care Med 2006;34:1589-1596
Following Sepsis Guidelines Helps Patients

Not every patient gets treatment consistent with guidelines

Timeliness of Antibiotics associated with mortality

Timeliness of Fluids Not associated with mortality

New Engl J Med 2017;23:2335-44
Small Increase in Process Measures

Table 5. Impact of the Educational Program on Process-of-Care Measurement and Outcome Depending on Hospital Categorization According to Baseline Compliance With the Guidelines

<table>
<thead>
<tr>
<th>Type of Measure</th>
<th>Preintervention Cohort</th>
<th>Postintervention Cohort</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1 hospitals (n = 20)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of tasks completed, mean (SD) [56% CI]</td>
<td>3.25 (1.56) [3.0-3.4]</td>
<td>4.42 (1.97) [4.2-4.6]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Resuscitation bundle completed, No. (%) [56% CI]</td>
<td>1 (0.5) [0-1]</td>
<td>16 (4.7) [2-7]</td>
<td>.006</td>
</tr>
<tr>
<td>Management bundle completed, No. (%) [56% CI]</td>
<td>13 (6.4) [3-10]</td>
<td>36 (10.6) [7-14]</td>
<td>.10</td>
</tr>
<tr>
<td>Hospital mortality, No. (%) [56% CI]</td>
<td>96 (48.0) [41-55]</td>
<td>134 (50.3) [34-44]</td>
<td>.05</td>
</tr>
<tr>
<td>APACHE II, mean (SD) [95% CI]</td>
<td>20.6 (7.4) [19.6-21.6]</td>
<td>20.0 (7.3) [19.2-20.8]</td>
<td>.37</td>
</tr>
<tr>
<td>Category 2 hospitals (n = 19)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of tasks completed, mean (SD) [56% CI]</td>
<td>4.85 (1.72) [4.46-4.85]</td>
<td>5.22 (1.98) [5.06-5.38]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Resuscitation bundle completed, No. (%) [56% CI]</td>
<td>11 (3.6) [2-6]</td>
<td>47 (7.9) [6-10]</td>
<td>.02</td>
</tr>
<tr>
<td>Management bundle completed, No. (%) [56% CI]</td>
<td>24 (7.9) [6-11]</td>
<td>67 (11.2) [9-14]</td>
<td>.13</td>
</tr>
<tr>
<td>Hospital mortality, No. (%) [56% CI]</td>
<td>135 (44.7) [39-50]</td>
<td>245 (40.9) [37-45]</td>
<td>.28</td>
</tr>
<tr>
<td>APACHE II, mean (SD) [56% CI]</td>
<td>20.7 (7.3) [19.8-21.6]</td>
<td>21.6 (8.1) [20.9-22.0]</td>
<td>.07</td>
</tr>
<tr>
<td>Category 3 hospitals (n = 20)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of tasks completed, mean (SD) [56% CI]</td>
<td>5.90 (1.92) [5.70-6.11]</td>
<td>6.45 (2.00) [5.27-6.62]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Resuscitation bundle completed, No. (%) [56% CI]</td>
<td>33 (6.9) [8-13]</td>
<td>84 (16) [13-19]</td>
<td>.006</td>
</tr>
<tr>
<td>Management bundle completed, No. (%) [56% CI]</td>
<td>56 (16.1) [12-20]</td>
<td>127 (24.2) [21-28]</td>
<td>.004</td>
</tr>
<tr>
<td>Hospital mortality, No. (%) [56% CI]</td>
<td>143 (41.1) [36-48]</td>
<td>201 (38.3) [34-42]</td>
<td>.41</td>
</tr>
<tr>
<td>APACHE II, mean (SD) [56% CI]</td>
<td>21.5 (7.3) [20.7-22.3]</td>
<td>21.6 (7.7) [21.0-22.0]</td>
<td>.87</td>
</tr>
</tbody>
</table>

Decreased Mortality Rate

Table 3. Performance of Outcome Measurements

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Preintervention Cohort</th>
<th>Postintervention Cohort</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality, No. (%) [56% CI]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital</td>
<td>376 (44.9) [41-47]</td>
<td>500 (50.7) [47-53]</td>
<td>.04</td>
</tr>
<tr>
<td>28-d</td>
<td>311 (38.6) [33-40]</td>
<td>496 (51.1) [39-53]</td>
<td>.006</td>
</tr>
<tr>
<td>Mean (SD) [56% CI]</td>
<td>315 (38.6) [34-40]</td>
<td>474 (32.4) [30-35]</td>
<td>.03</td>
</tr>
<tr>
<td>ICU stay, d*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) [56% CI]</td>
<td>28.7 (23.4) [25-30.3]</td>
<td>30.7 (25.7) [29.0-32.4]</td>
<td>.16</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>23.9 (13.5-23.7)</td>
<td>22.8 (13.3-21.4)</td>
<td>.25</td>
</tr>
<tr>
<td>Hospital mortality, No. (%) [56% CI]</td>
<td>13.4 (16.0) [11.0-14.0]</td>
<td>13.6 (16.3) [12.5-14.7]</td>
<td>.67</td>
</tr>
<tr>
<td>Mean (SD) [56% CI]</td>
<td>7.5 (4.5-15.0)</td>
<td>7.7 (4.0-15.9)</td>
<td>.63</td>
</tr>
</tbody>
</table>

*Abbreviations: IQR, interquartile range; d*, days at discharge; CI, confidence interval.
Increasing Compliance with Sepsis Bundle is Associated with Decreasing Patient Mortality

Compliance with early bundles was associated with decreased need for later intervention

Lung protective Mechanical Ventilation, inotropes, and steroids were interventions independently associated with mortality

**Multicenter Implementation of a Severe Sepsis and Septic Shock Treatment Bundle**

**Figure A**
- Mortality (%)
- Total Bundle Compliance (%)
- Year: 2004 to 2010
- Control: 4.9% to 87.4%

**Figure B**
- Mortality (%)
- Total Bundle Compliance (%)
- Year: 2004 to 2010
- Control: 7.0% to 68.4%

*Am J Resp Crit Care Med 2013:188:77-82*
Following Sepsis Guidelines Helps Patients

Not all sepsis patients get desired treatment

Time to Completion of 3 hour bundle associated with in hospital mortality

New Engl J Med 2017;23:2335-44
7.5 year Evaluation of a PI project on Sepsis (SSC)

<table>
<thead>
<tr>
<th>Model</th>
<th>Risk factors</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Continuous compliance, either resuscitation or management bundle, as a site-level variable and measured in last 2 quarters of site's SSC participation</td>
<td>For every additional quarter of site participation</td>
<td>0.96 (0.95–0.97)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>10% increase in resuscitation compliance</td>
<td>0.95 (0.94–0.97)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>10% increase in management compliance</td>
<td>0.97 (0.96–0.98)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>2. Compliance as a patient-level variable and measuring whether patient’s ICU visit was compliant with resuscitation or with management bundle</td>
<td>For every additional quarter of site participation</td>
<td>0.97 (0.96–0.98)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Resuscitation compliance, yes vs. no</td>
<td>0.82 (0.76–0.88)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Management compliance, yes vs. no</td>
<td>0.76 (0.71–0.81)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Resuscitation Compliance includes among other things 30 cc/kg /IVF
Serum Tumor Necrosis Factor Levels After Endotoxin Challenge

- Monoclonal antibodies to TNF given to animals challenged with endotoxin
  - reverse hemodynamic embarrassment
  - improve mortality

Tracey et. al Science 1987;330:662-4
Clinical Sepsis Trials of Monoclonal Antibodies Directed Against TNF

Treatment Directed at Modulating Inflammation: Not Effective

Table 1. Clinical trials of anti-TNF MAbs

<table>
<thead>
<tr>
<th>Therapy (Company)</th>
<th>Study design</th>
<th>Inclusion criteria</th>
<th>Control arm deaths/Total (%)</th>
<th>Treatment arm deaths/Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAK 109F (Knoll) 12</td>
<td>Open-label, phase II</td>
<td>Severe sepsis or septic shock (69%)</td>
<td>44/93</td>
<td>4/93</td>
</tr>
<tr>
<td>MAK 109F (Knoll) 13</td>
<td>Open-label, phase II</td>
<td>Severe sepsis or septic shock</td>
<td>6/12</td>
<td>2/12</td>
</tr>
<tr>
<td>MAK 109F (Knoll) 14</td>
<td>Double-blind, phase III</td>
<td>Sepsis and high IL-6 levels</td>
<td>12/21</td>
<td>20/21</td>
</tr>
<tr>
<td>CD1771 (Cellthera) 15</td>
<td>Open-label, phase II</td>
<td>Severe sepsis or septic shock</td>
<td>6/12</td>
<td>2/12</td>
</tr>
<tr>
<td>CD800 (Cellthera) 16</td>
<td>Open-label, phase II</td>
<td>Severe sepsis or septic shock</td>
<td>6/12</td>
<td>2/12</td>
</tr>
<tr>
<td>RAYs1055 (Bayer/Milex) 17</td>
<td>Double-blind, phase III</td>
<td>Severe sepsis or septic shock (94%)</td>
<td>19/21</td>
<td>30/21</td>
</tr>
<tr>
<td>RAYs1055 (Bayer/Milex) 18</td>
<td>Double-blind, phase III</td>
<td>Severe sepsis or septic shock (94%)</td>
<td>19/21</td>
<td>30/21</td>
</tr>
<tr>
<td>RAYs1055 (Bayer/Milex) 19</td>
<td>Double-blind, phase III</td>
<td>Severe sepsis</td>
<td>19/21</td>
<td>30/21</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>112/100</td>
<td>19/20</td>
</tr>
</tbody>
</table>

Odds Ratio for Treatment Effects of Mediator-Specific Anti-inflammatory Agents

- TNF MAb
- sTNFα
- IL-1ra
- PAFra
- Bradykinin Antagonist
- Anti-Prostaglandin

Increasing Harm → No Effect → Increasing Benefit
Clinical Sepsis Trials That Did Not Show Beneficial Treatment Effect

Albumin Replacement in Patients
Goal-Directed Resuscitation for Patients
High versus Low Blood-Pressure Target

Early, Goal-Directed Therapy for Septic Shock
Lower versus Higher Hemoglobin Threshold for Transfusion
Hydrocortisone Therapy for Patients with Septic Shock
TREATMENTS

Doctor Turns Up Possible Treatment For Deadly Sepsis

March 23, 2017 · 12:01 AM ET
Heard on Morning Edition

RICHARD HARRIS
Biologic Rationale Vitamin C in Sepsis

• Antioxidant and enzyme co-factor
  – Activates Nrf2
  – Restores cellular antioxidants
  – Catecholamines

• Anti-inflammatory
  – ↓ NF-κB

• Necessary for tight junctions and microcirculatory flow
Thiamine

• Essential for aerobic metabolism:
  – Pyruvate dehydrogenase
  – Alpha ketoglutarate dehydrogenase
Thiamine and Vitamin C

Vitamin C → Glyoxalic acid → Oxalic Acid

Thiamine

Carbon Dioxide
Phase I Study of Vitamin C in Sepsis

• Patients- 26 Patients with severe sepsis (1.0) at VCU randomized 1:1:1
• Intervention Vitamin C 50 mg/kg/day in divided doses every 6 hours for 96 hours
• Or
• Vitamin C 200 mg/kg/day in divided doses every 6 hours for 96 hours

• Comparator Placebo

• Outcome measure- Sequential Organ Failure Assessment (SOFA scores) and Vitamin C Levels
Phase I Study of Vitamin C in Sepsis

![Graph showing Delta SOFA score over time. The graph includes lines for Placebo, Lo-AscA, and Hi-AscA, with slopes indicated for each group.]

![Graph showing Plasma Ascorbate (μM) over time. The graph includes lines for Placebo, Lo-AscA, and Hi-AscA, with concentrations at 15 μM, 300 μM, and 3,000 μM indicated.]

Journal of Translational Medicine 2014, 12:32
Thiamine in Sepsis

- Patients - Adult patients with septic shock and elevated (> 3 mmol/L) lactate between 2010 and 2014 at 2 hospitals
- Intervention — Thiamine 200 mg twice daily for 7 days or until hospital discharge.
- Comparator - Placebo treated patients
- Outcome Lactate level 24 hours after first study dose

Thiamine in Sepsis

Complete group (n = 88)

<table>
<thead>
<tr>
<th>Days</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent survival</td>
<td>100</td>
<td>80</td>
<td>60</td>
<td>40</td>
<td>20</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Thiamine deficient group (n = 28)

<table>
<thead>
<tr>
<th>Days</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent survival</td>
<td>100</td>
<td>80</td>
<td>60</td>
<td>40</td>
<td>20</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

p = 0.85

p = 0.047

Triple Therapy for Sepsis

Original Research

Hydrocortisone, Vitamin C and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study

Paul E. Marik, MD, FCCM, FCCP1, Vikramji Khangoora, MD1, Racquel Rivera, Pharm D1, Michael H. Hooper, M.D., MSc1, John Cattevash, PhD, FAHA, FCCP1,2

Rationale for Marik study

- Preliminary data
  - Patients with sepsis have low serum levels of Vitamin C
  - Patients with sepsis have low serum levels of thiamine
- Small studies have shown feasible to give supplemental Vitamin C and thiamine without obvious harm
- Potential synergistic effect of steroids and Vitamin C
Before-After Study

- Patients – 47 consecutive patients admitted to the ICU at Sentara Norfolk General Hospital with a primary diagnosis of severe sepsis or septic shock and a procalcitonin \( \geq 2\text{ng/ml} \)

- Intervention: intravenous vitamin C (1.5 gm q 6 hourly for 4 days or until ICU discharge), hydrocortisone (50 mg q 6 hourly for 7 days or until ICU discharge followed by a taper over 3 days), intravenous thiamine (200 mg q 12 hourly for 4 days or until ICU discharge).

- Comparator Patients with severe sepsis and septic shock with procalcitonin \( \geq 2\text{ng/ml} \) treated during previous year without vitamin C or thiamine, but who could receive hydrocortisone per physicians orders

- Outcome Measure Hospital Survival
Additional analysis

• Propensity score:
  – Probability (0-1) of receiving treatment based on covariates

• Logistic regression for OR mortality
  1. Propensity score
  2. Propensity score + age

<table>
<thead>
<tr>
<th>Covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Weight</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>APACHE IV Score</td>
</tr>
<tr>
<td>Mechanical Ventilation</td>
</tr>
<tr>
<td>Vasopressors</td>
</tr>
<tr>
<td>WBC</td>
</tr>
<tr>
<td>Lactate</td>
</tr>
<tr>
<td>Procalcitonin</td>
</tr>
<tr>
<td>Serum Creatinine</td>
</tr>
</tbody>
</table>
# Before-After Study

<table>
<thead>
<tr>
<th></th>
<th>Treated (n=47)</th>
<th>Control (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>58.3 ± 4.1</td>
<td>62.2 ± 14.3</td>
</tr>
<tr>
<td><strong>Sex (male)</strong></td>
<td>27 (57%)</td>
<td>23 (49%)</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>2 (4%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>16 (34%)</td>
<td>20 (42%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20 (43%)</td>
<td>25 (53%)</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>15 (32%)</td>
<td>16 (34%)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>5 (11%)</td>
<td>7 (15%)</td>
</tr>
<tr>
<td>COPD</td>
<td>8 (17%)</td>
<td>7 (15%)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>6 (13%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>CVA</td>
<td>8 (17%)</td>
<td>5 (11%)</td>
</tr>
<tr>
<td>CRF</td>
<td>7 (15%)</td>
<td>8 (17%)</td>
</tr>
<tr>
<td>Morbid Obesity</td>
<td>6 (13%)</td>
<td>8 (17%)</td>
</tr>
<tr>
<td>Immunocompromised</td>
<td>6 (13%)</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>Drug addiction</td>
<td>5 (11%)</td>
<td>5 (11%)</td>
</tr>
</tbody>
</table>
Study Limitations

Single Center before and after study

Complex intervention

Steroids used in comparator arm

Little information about contemporaneous therapies (antibiotics, fluids etc)

Confirmation bias

Large effect size
Highly Polarizing Results

• A significant number of professionals immediately began prescribing this as a cure for sepsis
• A significant number of professionals criticized the study very vociferously
• Much of this discussion has been high-level intellectual discourse
• Some of it has not been
Pneumococcal Bacteremia with Especial Reference to Bacteremic Pneumococcal Pneumonia

ROBERT AUSTRIAN, M.D., and JEROME GOLD, M.D.

Figure 6. Numbers in parentheses indicate size of each group of patients. Data for untreated and serum-treated patients (capsular Types I and II only) from Tilghman and Finland (1).
Single Vs Multicenter Trials

**Phase II Single Center Trials**
- Test potential novel therapies
- Show potential risks and benefits
- Easier to do/Cheaper
- May change practice at one site or with some physicians
- May have large treatment effects

**Phase III Multicenter Trials**
- Test Potential new therapies
- Show potential risks and benefits
- Harder to do/More expensive
- The gold standard for changing clinical practice
- Usually with smaller treatment effects
Vitamin C Is Not Ready for Prime Time in Sepsis but a Solution Is Close

To the Editor:

We read with interest the report by Marik et al\textsuperscript{1} published in CHEST (June 2017). However, the study lacked blinding, randomization, concurrent control subjects, and case-control propensity matching; it also had a small sample size, thus substantially increasing the risk of false benefits due to confounding combined with selection and ascertainment biases. Many

resolution in an even shorter time.\textsuperscript{5} Considering this poor evidence on the safety and efficacy of vitamin C and how swiftly an adaptive RCT can be done, we believe that there is no ethical or scientific justification to use vitamin C outside of a clinical trial at this time.

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DOI: http://dx.doi.org/10.1016/j.chest.2017.05.025
Why We Need a Clinical Trial

Viewpoint 1

• To my knowledge, we have had zero patients treated at Vanderbilt. But Jon, you should emphasize this does not reflect any lack of enthusiasm for conducting a proper study, it reflects Vanderbilt’s long-standing conservatism regarding “new” or “exciting” therapies, i.e., we believe it is proper to wait until there is sufficient high quality data to begin routinely using these treatments on everyday patients.

• Gordon Bernard MD

Viewpoint 2

• “It might help- that’s why I used it”

• I’m on service right now and thought I’d relay an event that occurred simultaneous to the foundation presentation. We have a patient who was found down and seems to have acute on chronic liver disease with septic shock, AKI, DIC and ARDS. She was given thiamine because of the alcoholism and steroids because of refractory shock (vasopressin and 50+ mcg of norepinephrine). Because she was doing poorly despite a couple of days of maximal therapy the resident (all credit due) decided to add Vitamin C to the steroids and thiamine already being given. Within 24 hours her vasopressin was turned off and her norepinephrine was 2-5mcg. In full disclosure she also got NAC and albumin because of liver disease and possible HRS, but still!
What Kind of Evidence Should Change Practice?

1- Single Physician and Single Patient
   • Clinical Experience, Literature

2- Single Institution
   • Clinician Agreement + Data Showing that Practice Change Works in that Institution
   • >1 RCT in a similar patient population

3- Most Patients
   • >1 RCT in similar patient population + evaluation of quality of RCT + cost and downside of intervention

4- Treatment Guidelines
Phase III Multicenter Trials Change Practice
An Analogy For Multicenter vs. Single Center Trials

New York Knicks vs Cleveland Cavaliers Oct 30th 2017 NY 114 –Cleveland 95

• A multicenter trial is more likely to be reproduced than is a single center trial, just as a 7 or 82 game series is more likely to give the same result if repeated.
Trial Design - What Patient Population to Pick

Critically Ill Patients: Mortality Endpoint

• More likely to immediately change practice
• Simpler Enrollment Criteria
• Fewer patients
• More sites required
• May take longer to complete

Very Sick but Not Yet Critical: Rates & Speed of Improvement Endpoint

• Preventing progression to Critically Ill - May be appealing to Patients
• Applies to More Patients
• More complicated enrollment criteria
• Could be less compelling for immediate practice change

Consider nested study including both populations
Design Considerations

• Patients - which patient population are you studying

• Intervention - What are You Giving

• Comparator - What Treatment does the non-intervention arm get

• Outcome – What is the primary outcome measure
Victas PICO Questions

• Patients- Up to 2000 Adult patients with confirmed or suspected infection and evidence of respiratory or cardiovascular organ dysfunction (e.g. adult sepsis)

• Intervention Intravenous vitamin C (1.5 grams every 6 hours), thiamine (100 mg every 6 hours), and hydrocortisone (50 mg every 6 hours), will be administered in divided doses each day for 4 days or until ICU discharge.

• Comparator Placebo (unless clinical team desires to give steroids)

• Outcome- Vasopressor and Ventilator Free Days
  - 30 day mortality
Inclusion Criteria

• Patients > 18 with confirmed or suspected infection and evidence of respiratory or cardiovascular organ dysfunction

• Confirmed or suspected infection: ordering of blood cultures and administration of at least one antimicrobial agent

• Respiratory Dysfunction
  – Positive pressure ventilation (invasive or non-invasive)
  – High Flow Nasal Cannula (>=45 L >=45%%)

• Cardiovascular Dysfunction
  – Vasopressors
Exclusion Criteria

Designed to limit exclusions and make the study as pragmatic as possible

• Patients that are too ill from other causes in which the treatment is unlikely to fix the other problems (e.g., end stage cancer)
• Patients who refuse to participate
• Patients who are allergic to any of the treatments
• Patients with medical conditions that would make treatment higher risk (kidney stones, problems metabolizing calcium)
• Patients who are participating in another study
Sample Size
500 Patients- Simulation Data

If the Mortality Difference is 10% between groups, 500 patients would have 80% power to show it.
## Estimates of Patients Needed

According To Differences in Mortality Between Treatment Groups

<table>
<thead>
<tr>
<th>Treatment Effect</th>
<th>Patients Needed to Show Treatment Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>32%</td>
<td>72</td>
</tr>
<tr>
<td>20%</td>
<td>250</td>
</tr>
<tr>
<td>10%</td>
<td>500</td>
</tr>
<tr>
<td>5%</td>
<td>2000</td>
</tr>
</tbody>
</table>

Estimates Dependent Upon Mortality Rates in Control Group

← Marik Manuscript
Pr=Probability
PFVD- vasopressor and ventilator free days (i.e. alive and off vasopressors and ventilators)
Analytic Plan

• Final analysis will be done after all enrolled subjects are followed to Primary Endpoint

• For Vasopressor and Ventilator Free Days will use a Wilcoxon Rank Sum Test, using 1 sided alpha of 0.022 (to adjust to control Type I error rate at 0.025)

• In final analysis, patients who died are treated as though they had zero Ventilator and Vasopressor Free Days

• Managed with DCC, with assistance from Berry Consultants
VICTAS Trial Sites: 46 Enrolling Sites
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500 Patient Milestones

Phase A: Planning
- Jun 1 to Dec 31

Phase B: Initiation, IRB Approval Start-up, 25 Sites
- Jan 1 to Oct 31
  - Obtain IND: Jan 1 to Feb 28
  - Obtain IRB Approval Initial Sites: Jan 1 to Jul 1
  - Prepare Sites for Launch: Jan 1 to Jul 1
  - Enroll Patients (approx. 38/month): Jul 1 to Aug 31
  - Complete Follow-up Data Collection: Jul 1 to Sep 1

Phase C: Completion of Study
- Nov 1 to Dec 31
  - Closeout: Data Analysis and Publications

Kick-off Meeting: 1/10/2018

- 6 Active Sites: 3/31/2018
- 14 Active Sites: 5/31/2018
- 22 Active Sites: 7/31/2018
- 25 Active Sites: 8/31/2018

1st Patient Enrolled: 7/1/2018

- 250th Patient Enrolled: 1/26/2019
- 500th Patient Enrolled: 8/31/2019

Close-out Meeting: 12/1/2019

Submit Final Report and Publication: 12/31/2019

2017
- Jun 1
- Oct 31

2018
- Jan 1
- Oct 31
- Feb 28
- 3 Active Sites
- 4/30/2018
- 10 Active Sites
- 6/30/2018
- 18 Active Sites
- 8/31/2018
- 25 Active Sites

2019
- Jan 1
- Oct 31
- 1/26/2019
- 500 Patient Enrolled
• Thank you

• Jsevran@emory.edu