Hydrocortisone, Ascorbic Acid and Thiamine for the Treatment of Severe Sepsis and Septic Shock

Paul E Marik, MD
Disclosures

- Advisory board
- Stocks
- Grants
- Patents
- Speaker bureau

None
Sepsis in a Global Problem

> 50 Million cases of sepsis / year
Sepsis mortality ~ 60% resource poor countries
Commonest cause of death in children ~ 5 million / year
> 20 Million deaths / year
SEPSIS SEVERITY

Sepsis kills more Americans than AIDS, prostate cancer and breast cancer combined. Number of deaths in 2015 caused by:

- AIDS: 15,000
- Prostate cancer: 29,000
- Breast cancer: 41,000
- Sepsis: 258,000

SOURCE Centers for Disease Control and Prevention, National Center for Biotechnology Information
# National Inpatient Hospital Costs: The Most Expensive Conditions by Payer, 2013

## STATISTICAL BRIEF #204  May 2016

## Table 1. The 20 most expensive conditions treated in U.S. hospitals, all payers, 2013

<table>
<thead>
<tr>
<th>Rank</th>
<th>CCS principal diagnosis category</th>
<th>Aggregate hospital costs, $ millions</th>
<th>National costs, %</th>
<th>Number of hospital stays, thousands</th>
<th>Hospital stays, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Septicemia</td>
<td>23,653</td>
<td>6.2</td>
<td>1,297</td>
<td>3.6</td>
</tr>
<tr>
<td>2</td>
<td>Osteoarthritis</td>
<td>16,520</td>
<td>4.3</td>
<td>1,023</td>
<td>2.9</td>
</tr>
<tr>
<td>3</td>
<td>Liveborn</td>
<td>13,287</td>
<td>3.5</td>
<td>3,765</td>
<td>10.6</td>
</tr>
<tr>
<td>4</td>
<td>Complication of device, implant or graft</td>
<td>12,431</td>
<td>3.3</td>
<td>632</td>
<td>1.8</td>
</tr>
<tr>
<td>5</td>
<td>Acute myocardial infarction</td>
<td>12,092</td>
<td>3.2</td>
<td>602</td>
<td>1.7</td>
</tr>
<tr>
<td>6</td>
<td>Congestive heart failure</td>
<td>10,218</td>
<td>2.7</td>
<td>832</td>
<td>2.5</td>
</tr>
<tr>
<td>7</td>
<td>Spondylosis, intervertebral disc disorders, other back problems</td>
<td>10,198</td>
<td>2.7</td>
<td>555</td>
<td>1.6</td>
</tr>
<tr>
<td>8</td>
<td>Pneumonia</td>
<td>9,501</td>
<td>2.5</td>
<td>951</td>
<td>2.7</td>
</tr>
<tr>
<td>9</td>
<td>Coronary atherosclerosis</td>
<td>9,003</td>
<td>2.4</td>
<td>458</td>
<td>1.3</td>
</tr>
<tr>
<td>10</td>
<td>Acute cerebrovascular disease</td>
<td>8,840</td>
<td>2.3</td>
<td>585</td>
<td>1.6</td>
</tr>
<tr>
<td>11</td>
<td>Cardiac dysrhythmian</td>
<td>7,176</td>
<td>1.9</td>
<td>710</td>
<td>2.0</td>
</tr>
<tr>
<td>12</td>
<td>Respiratory failure, insufficiency, arrest (adult)</td>
<td>7,077</td>
<td>1.9</td>
<td>387</td>
<td>1.1</td>
</tr>
<tr>
<td>13</td>
<td>Complications of surgical procedures or medical care</td>
<td>6,079</td>
<td>1.6</td>
<td>465</td>
<td>1.3</td>
</tr>
<tr>
<td>14</td>
<td>Rehabilitation care, fitting of prostheses, and adjustment of devices</td>
<td>5,373</td>
<td>1.4</td>
<td>390</td>
<td>1.1</td>
</tr>
<tr>
<td>15</td>
<td>Mood disorders</td>
<td>5,246</td>
<td>1.4</td>
<td>836</td>
<td>2.3</td>
</tr>
<tr>
<td>16</td>
<td>Chronic obstructive pulmonary disease and bronchiectasis</td>
<td>5,182</td>
<td>1.4</td>
<td>645</td>
<td>1.8</td>
</tr>
<tr>
<td>17</td>
<td>Heart valve disorders</td>
<td>5,151</td>
<td>1.4</td>
<td>123</td>
<td>0.3</td>
</tr>
<tr>
<td>18</td>
<td>Diabetes mellitus with complications</td>
<td>5,142</td>
<td>1.3</td>
<td>531</td>
<td>1.5</td>
</tr>
<tr>
<td>19</td>
<td>Fracture of neck of femur (hip)</td>
<td>4,851</td>
<td>1.3</td>
<td>303</td>
<td>0.9</td>
</tr>
<tr>
<td>20</td>
<td>Biliary tract disease</td>
<td>4,722</td>
<td>1.2</td>
<td>405</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>Total for top 20 conditions</td>
<td>181,752</td>
<td>47.7</td>
<td>15,554</td>
<td>43.7</td>
</tr>
<tr>
<td></td>
<td>Total for all stays</td>
<td>381,439</td>
<td>100.0</td>
<td>35,598</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Abbreviation: CCS, Clinical Classifications Software
Source: Agency for Healthcare Research and Quality (AHRQ), Center for Delivery, Organization, and Markets, Healthcare Cost and Utilization Project (HCUP), National Inpatient Sample (NIS), 2013
William Osler...

“Except for a few occasions patients' appear to die from the body's response to infection rather than from it”
A network-based analysis of systemic inflammation in humans

- Pro-inflammatory cytokines
- Anti-inflammatory cytokines
- Chemokines
- Adhesion molecules
- Transcription factors
- Enzymes
- Clotting factors
- Stress proteins
- Etc, etc

3714 unique genes

Unifying Pathophysiology
Pro-Inflammatory cytokines and ROS
Association between mitochondrial dysfunction and severity and outcome of septic shock

David Brealey, Michael Brand, Iain Hargreaves, Simon Heales, John Land, Ryszard Smolenski, Nathan A Davies, Chris E Cooper, Mervyn Singer

Lancet 2002;360:219
Why Patients with Sepsis Die?

Cellular Bioenergetic (Metabolic) Failure

Tissue Hypoxia
Failed “Novel Pharmacologic Agents” for Sepsis

> 100 Phase II and III clinical trials

- *E. Coli* J5 antisera
- Anti-lipid A E5 mAb
- Anti-lipid A HA1A mAB
- Anti-TNF mAB
- Chimeric TNF mAB
- Humanized TNF mAB
- sTNFR1:Fc
- sTNFR2:Fc
- Anti-CD 14 mAB
- Tissue factor pathway inhibitor
- Platelet activating factor receptor antagonist
- IL-1 receptor antagonist
- Bactericidal permeability increasing protein
- Selenium
- Immunoglobulins
- rHDL and phospholipid complexes
- Activated Protein C
- N-acetyl cysteine
- Antithrombin III
- Statins
- NOS inhibitors
- Phospholipase A-II inhibitor
- Granulocyte stimulating factor
- Bradykinin antagonist
- Elastase inhibitor
- TAK-242, Toll-4 inhibitor
- Eritoran, MD2-TLR4 antagonist
- Anti-β2 integrin
- Lactoferrin
- RT-123, r-human soluble
- Thrombomodulin
- Ibuprofen
“…the best hope for therapeutic advances [in sepsis] will depend on broad-base targeting, in which multiple components are targeted at the same time.”

Aird, W.C., Blood, 2003
Steps to the Cure……

- Early Diagnosis
- Early administration of the correct antibiotics, in the correct dose
- Source Control
- Conservative, individualized, physiologic approach to fluid resuscitation
- Early use of Norepinephrine
- The “Metabolic Resuscitation Protocol” (HAT)
  - Hydrocortisone, Ascorbic Acid & Thiamine
- Multidisciplinary, team approach to patient care
- State-of-the-art evidence based supportive care
The changing paradigm of Sepsis: Early diagnosis, Early antibiotics, Early pressors and Early adjuvant treatment

Traditional time-course of therapies

- Antibiotics
- Fluid
  - Norepinephrine
  - Vasopressin
  - Epinephrine
  - Stress-dose steroids

Escalation–deescalation strategy

- Antibiotics
- Fluid
  - Norepinephrine
  - Vasopressin
  - Epinephrine
  - Metabolic resuscitation (Hydrocortisone/Ascorbate/Thiamine)

Marik & Fargas, Crit Care Med 2018;46:1690
In the beginning
53 female presents with AMS (per family)

In ER:
- 47/20 mmHg, HR 122, Temp 38.5, jaundice, tender RUQ
- WBC 24 000 with 9% bandemia,
- Cr 3.2 mg/dl
- Lactate 4.4 mmol/l
- PCT 59 ng/ml
- T-Bili 7.8 mg/dl, AST 140 U/l, ALT 170 U/l
- Ab U/S + CT: acute cholecystitis
- Zosyn and vancomycin
- Rapid diagnosis and admission to ICU
Pivotal First Case

- In ICU - Day 1
  - Escalating doses of pressors; fluid non-responsive
  - Intubation
  - IR: percutaneous cholecystotomy tube
  - ARF – CRRT commenced
  - ECHO: EF 15% previously 55%
The Metabolic Resuscitation Protocol

- Hydrocortisone
  - Anti-inflammatory
  - Increases pressor sensitivity
  - Preserves/restores endothelial integrity
  - Cheap
  - Safe

- Vitamin C
  - Anti-inflammatory
  - Increases pressor sensitivity
  - Preserves/restores endothelial integrity
  - Cheap
  - Safe
Pivotal First Case

- In ICU - Day 1
  - Escalating doses of pressors; fluid non-responsive
  - Intubation
  - IR: percutaneous cholecystotomy tube
  - ARF – CRRT commenced
  - ECHO: EF 15% previously 55%
- *Vitamin C + Hydrocortisone*
Pivotal First Case

- In ICU - Day 2
  - Pressors weaned off
  - Extubated (awake and alert)
  - Increase U/O
- In ICU - Day 3
  - CRRT stopped
  - BC: *E.coli* + *Clostridia perfringens*
  - EF 40%
- Day 4 – transfer to medical floor
- Day 8 – sent home; to return for cholecystectomy
Pivotal First Case (n=1)

With Consent from patient
Philosophy of the Hydrocortisone, Ascorbic Acid and Thiamine (HAT) Protocol

- Targets the host's response to infection
  - Anti-inflammatory + antioxidant
- Multiple agents with overlapping and synergistic actions
- SAFE – No side effects
- CHEAP and readily available
Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock
A Retrospective Before-After Study

Paul E. Marik, MD, FCCP; Vikramjit Khangoora, MD; Racquel Rivera, PharmD; Michael H. Hooper, MD; and John Catravas, PhD, FCCP
Methods

- **Treatment Group**
  - January 2016 to July 2016 (7 months)
  - All consecutive pts adm. to MICU with primary diagnosis of sepsis
  - Procalcitonin (PCT) > 2ng/ml
  - Rx: Vitamin C protocol within 24 hours ICU admission

- **Control Group**
  - June 2015 to December 2015 (7 months)
  - All consecutive pts adm. to MICU with primary diagnosis of sepsis
  - Same inclusion criteria (as above)
  - Standard evidence based management strategy during both time periods

- **Exclusion Criteria**
  - Age < 18 yrs
  - Pregnancy
  - Limitations of care
## Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment n=47</th>
<th>Control * n=47</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>58.3 ± 16.3</td>
<td>62.2 ± 16.5</td>
</tr>
<tr>
<td>Male</td>
<td>27 (57%)</td>
<td>23 (49%)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>22 (47%)</td>
<td>26 (55%)</td>
</tr>
<tr>
<td>Vasopressors</td>
<td>22 (46%)</td>
<td>22 (46%)</td>
</tr>
<tr>
<td>PCT (&lt;0.05 ng/ml)</td>
<td>25.8 (5.8-93.4)</td>
<td>15.2 (5.9-39.0)</td>
</tr>
<tr>
<td>Day 1 SOFA</td>
<td>8.3 ± 2.8</td>
<td>8.7 ± 3.7</td>
</tr>
<tr>
<td>APACHE II</td>
<td>22.1 ± 6.3</td>
<td>22.6 ± 5.7</td>
</tr>
<tr>
<td>APACHE IV</td>
<td>79.5 ± 16.4</td>
<td>82.0 ± 27.4</td>
</tr>
<tr>
<td>Predicted Mortality*</td>
<td>39.7 ± 16.7</td>
<td>41.6 ± 24.2</td>
</tr>
<tr>
<td>Vitamin C (40-60 umol/l) n=22</td>
<td>14.1 ± 11.8</td>
<td>-</td>
</tr>
</tbody>
</table>

* No significant differences between groups
Outcome

The graph illustrates the mortality rates for the Control and Treatment groups. The predicted mortality is indicated by black bars, while the actual mortality is represented by gray bars.

- **Control**
  - Predicted Mortality: 0%
  - Actual Mortality: 0%

- **Treatment**
  - Predicted Mortality: 40%
  - Actual Mortality: 10%

The p-value for the comparison between the predicted and actual mortality rates is less than 0.001, indicating a statistically significant difference.
Propensity Adjusted Outcome

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin C Protocol</td>
<td>0.13</td>
<td>0.04 - 0.48</td>
<td>0.002</td>
</tr>
<tr>
<td>Propensity Score</td>
<td>1.26</td>
<td>0.11 - 14.98</td>
<td>0.86</td>
</tr>
</tbody>
</table>
Time to pressor discontinuation

Treatment Group

Mean time to discontinuation of all pressors 18.3 ± 9.8
Sofa Score Over Time

- **TREATMENT**
- **CONTROL-ALIVE**
- **CONTROL-DEAD**
S-Cr over time – Treatment Group

Excluding CRF

S-Creatinine mg/dl

Day

0 1 2 3 4 5 6

Discharge
s-Lactate over time

Days: 0 1 2 3 4 5
Lactate mmol/l: 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0

- Lactate - Treatment
- Lactate - Control
Procalcitonin Over Time

![Procalcitonin Over Time Graph]

- **Y-axis**: Procalcitonin ng/ml
- **X-axis**: Day
- **Legend**:
  - **Black filled circle**: Treatment
  - **Red open circle**: Control

The graph shows the concentration of procalcitonin over time for the treatment and control groups. The concentration peaks on Day 2 for the control group and has a similar trend for the treatment group with a slight increase on Day 2.
Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock
A Retrospective Before-After Study

**CONCLUSIONS:** Our results suggest that the early use of intravenous vitamin C, together with corticosteroids and thiamine, are effective in preventing progressive organ dysfunction, including acute kidney injury, and in reducing the mortality of patients with severe sepsis and septic shock. Additional studies are required to confirm these preliminary findings.

CHEST 2017; 151(6):1229-1238
The Impact of Social Media

Very Cool

Snake oil
Fairy dust
Utter “crap”
Highly visible sepsis publications from 2012 to 2017: Analysis and comparison of altmetrics and bibliometrics

Table 1
Title – Top 50 Publications by Overall Altmetric.com Attention Score.

<table>
<thead>
<tr>
<th>Altmetric Attention Rank (Score)</th>
<th>Title</th>
<th>Journal</th>
<th>Year Published (Days Until Extraction)</th>
<th>Mainstream Media Mentions</th>
<th>Twitter Rank of 50 (User Count)</th>
<th>Web of Science Citations</th>
<th>Scopus Citations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (2629)</td>
<td>The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)</td>
<td>JAMA</td>
<td>2016 (710)</td>
<td>77</td>
<td>1 (2248)</td>
<td>1272</td>
<td>1373</td>
</tr>
<tr>
<td>2 (1811)</td>
<td>Time to treatment and mortality during mandated emergency care for sepsis</td>
<td>N Engl J Med</td>
<td>2017 (255)</td>
<td>123</td>
<td>2 (1132)</td>
<td>41</td>
<td>41</td>
</tr>
<tr>
<td>3 (1086)</td>
<td>Recognizing sepsis as a global health priority — a WHO resolution</td>
<td>N Engl J Med</td>
<td>2017 (218)</td>
<td>60</td>
<td>4 (850)</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>4 (1012)</td>
<td>A randomized synbiotic trial to prevent sepsis among infants in rural India</td>
<td>Nature</td>
<td>2017 (170)</td>
<td>68</td>
<td>10 (663)</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>5 (998)</td>
<td>Hydrocortisone, vitamin C and thiamine for the treatment of severe sepsis and septic shock: a retrospective before-after study</td>
<td>CHEST</td>
<td>2016 (428)</td>
<td>70</td>
<td>16 (427)</td>
<td>35</td>
<td>33</td>
</tr>
</tbody>
</table>
SGEM#174: Don’t Believe the Hype – Vitamin C Cocktail for Sepsis

Click on the names below to hear what these skeptics have to say about Dr. Marik’s study or listen to the whole SGEM podcast on iTunes.

1. Andrew Worster (BEEM): Retrospective Study
2. Salim Rezaie (REBEL EM): Association vs. Causation
4. Lauren Westafer (FOAMCast): Lack of Blinding
5. Chris Carpenter (EMA): Hawthorne/Observer Effect
6. Chris Nickson (LITFL): External Validity
7. Daniel Horner (St. Ellyn's): Cost Effectiveness:
8. Anand Swaminathan (EM Rap): Attention
9. Chip Lange (TOTAL EM): Harm
10. Meghan Groth (EM Pharm Girl): Synergistic Effects
11. Jerome Hoffman (EMA): 30,000 Foot View
I killed a person, what did you do to get sent here?

I said my Observational trial was so good, we didn't need a RCT.
Simon Finfer @icuresearch · Mar 24

It's snake oil quality evidence. No funding body would touch. Historical control trials "always" +ve. Crap news articles don't = science

It amazes and worries me that people genuinely think these data mean something and are strong enough to advocate treating patients.

First, the argument that it can't do harm is intellectually destitute. There are loads of things that we don’t think harm patients until we study them properly. There is also the harm that results from getting our nurses to spend their time giving useless treatments.

International Sepsis Forum
Simon Finfer, Chair
Surviving Sepsis Campaign: Research Priorities for Sepsis and Septic Shock

Craig M. Coopersmith, MD, FCCM (Co-chair)¹; Daniel De Backer, MD, PhD (Co-chair)²; Clifford S. Deutschman, MS, MD, MCCM³; Ricard Ferrer, MD, PhD⁴; Ishaq Lat, PharmD⁵; Flavia R. Machado, MD, PhD⁶; Greg S. Martin, MD, MSc, FCCM⁷; Ignacio Martin-Loeches, MD⁸; Mark E. Nunnally, MD, FCCM⁹; Massimo Antonelli, MD¹⁰; Laura E. Evans, MD, MSc, FCCM¹¹; Judith Hellman, MD¹²; Sameer Jog, MD, IDCCM¹³; Jozef Kesecioglu, MD, PhD¹⁴; Mitchell M. Levy, MD, MCCM¹⁵; Andrew Rhodes, MB BS, MD (Res)¹⁶

Methods: Each committee member independently gave their top five priorities for sepsis research. A total of 88 suggestions (Supplemental Table 1, Supplemental Digital Content 2, http://links.lww.com/CCM/D636) were grouped into categories by the committee co-chairs, leading to the formation of seven subgroups:
The Experience of other!

> 2000 e-mails

Josh from NH

neat case right now in my unit: Elderly man with ischemic cardiomyopathy, EF 15% pace/AICD at baseline presented to outside hospital with shock and Bp 60/30. Given 2-3 liters fluid and immediately went into respiratory failure requiring intubation. Shipped to us intubated on four pressors with AKI (Cr 3). Eventually he ended up growing Group B Strep from his blood with procalcitonin 43. Started on cocktail and within a day his pressor requirements melted away and he was extubated. His kidneys have improved and he is walking around the ICU. Tomorrow he will probably leave the ICU with no residual organ dysfunction, no volume overload, no ICU complications.
Gerald from SC.
Post-chemo septicemia.
Semi comatose.
Given three days to live.

Dr. Says it’s in Gods hands...nothing can be done.
24 hours later; Rx with “HAT”
Combined vitamin C, hydrocortisone, and thiamine therapy for patients with severe pneumonia who were admitted to the intensive care unit: Propensity score-based analysis of a before-after cohort study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment n=53</th>
<th>Control n=46</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>73</td>
<td>74</td>
</tr>
<tr>
<td>Pressors</td>
<td>62%</td>
<td>48%</td>
</tr>
<tr>
<td>Mechanical Ventilation</td>
<td>81%</td>
<td>78%</td>
</tr>
<tr>
<td>APACHE II</td>
<td>28</td>
<td>27</td>
</tr>
<tr>
<td>SOFA</td>
<td>11</td>
<td>11</td>
</tr>
</tbody>
</table>
Combined vitamin C, hydrocortisone, and thiamine therapy for patients with severe pneumonia who were admitted to the intensive care unit: Propensity score-based analysis of a before-after cohort study.

Propensity adjusted OR 0.15 (0.04-0.56), p=0.005
### Updated Meta-analysis

#### 1.1.1 Observational Studies

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Vitamin C Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marik 2017</td>
<td>4</td>
<td>47</td>
<td>19</td>
<td>47</td>
<td>13.6%</td>
<td>0.21 [0.08, 0.57]</td>
<td>2017</td>
</tr>
<tr>
<td>Kim 2018</td>
<td>6</td>
<td>36</td>
<td>14</td>
<td>36</td>
<td>17.0%</td>
<td>0.43 [0.19, 0.99]</td>
<td>2018</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>83</strong></td>
<td><strong>83</strong></td>
<td><strong>14</strong></td>
<td><strong>83</strong></td>
<td><strong>30.6%</strong></td>
<td><strong>0.32 [0.16, 0.64]</strong></td>
<td></td>
</tr>
</tbody>
</table>

- **Total events**: 10
- **33**
- **Heterogeneity**: Tau² = 0.04; Chi² = 1.17, df = 1 (P = 0.28); I² = 14%
- **Test for overall effect**: Z = 3.23 (P = 0.001)

#### 1.1.2 Randomized Studies

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Vitamin C Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fowler 2014</td>
<td>7</td>
<td>16</td>
<td>5</td>
<td>8</td>
<td>18.6%</td>
<td>0.70 [0.32, 1.52]</td>
<td>2014</td>
</tr>
<tr>
<td>Zabet 2016</td>
<td>2</td>
<td>14</td>
<td>9</td>
<td>14</td>
<td>8.9%</td>
<td>0.68 [0.45, 1.00]</td>
<td>2018</td>
</tr>
</tbody>
</table>

- **Total events**: 38
- **63**
- **Heterogeneity**: Tau² = 0.09; Chi² = 4.58, df = 3 (P = 0.20); I² = 35%
- **Test for overall effect**: Z = 2.53 (P = 0.01)

- **Total (95% CI)**: 226
- **217**
- **100.0%**
- **0.44 [0.28, 0.69]**

- **Total events**: 48
- **96**
- **Heterogeneity**: Tau² = 0.13; Chi² = 8.93, df = 5 (P = 0.11); I² = 44%
- **Test for overall effect**: Z = 3.55 (P = 0.0004)
- **Test for subgroup differences**: Chi² = 1.38, df = 1 (P = 0.24), I² = 27.4%

### NNT = 4.3

### NNH = ∞
The annual incidence of sepsis in the United States is 1.5m cases suggesting a total expected cost saving of $74.5bn USD. Over the same 5-year period, patients gain an additional 1.26 QALY per case, or 1.9m QALYs per year for the population. Given the reduced costs and improved outcomes, the Marik bundle dominates standard care, as it both saves costs and increase health outcomes at the same time. The probabilistic sensitivity analysis shows this conclusion arises 98.0% of the time.

~ -$10 000 QALY
Vitamin C – Ascorbic acid
Ascorbic Acid → Ascorbate Radical → Dehydroascorbate → 2,3-Diketo-1-gulonic acid → Oxalate
The Genetics of Vitamin C Loss in Vertebrates
Ascorbic Acid

70 kg goat synthesizes 2-4 g/day
Ascorbic Acid Injection

Dosage Form: injection, solution

500 mg/mL

For intravenous, intramuscular or subcutaneous use. Contains no preservatives.

There are no contraindications to the administration of ascorbic acid. Its parenteral administration is desirable for patients with an acute deficiency or for those whose absorption of orally ingested ascorbic acid is uncertain. 1 gram daily are recommended. However, as much as 6 grams have been administered parenterally to normal adults without evidence of toxicity.
Ascor® is the only FDA approved injectable ascorbic acid (vitamin C) indicated for the short term (up to 1 week) treatment of scurvy.
Ascorbic Acid

- An essential vitamin for humans who lack L-gulono-lactone oxidase, the final enzyme in the biosynthetic pathway
- Vitamin C acts as a free radical scavenger and co-enzyme in multiple reactions
- Absorbed by gut by sodium-dependent transporters (SVCT1)
- Vitamin C circulates in human plasma at 40–60 µM
- Transported into cells by SVCT2 reaches mM concentrations
Sodium-Vitamin C Transporters - SVCT

Intestine/kidney → Lung → Liver → Muscle → Blood → Intestine/kidney

Choroid plexus:

- SVCT1: Asc [40-60 μM]
- SVCT2: Asc [500 μM]

Brain:

- Neuron: Asc [10 mM]
- Astrocyte: Asc [1 mM]

Molecular structures:

- N-glycosylation site
- PKC site
- PKA site
Vitamin C Pharmacokinetics: Implications for Oral and Intravenous Use

Sebastian J. Padayatty, MRCP, PhD; He Sun, PhD, CBS; Yaohui Wang, MD; Hugh D. Riordan, MD; Stephen M. Hewitt, MD, PhD; Arie Katz, MD; Robert A. Wesley, PhD; and Mark Levine, MD
Ascorbic Acid

- All mammals except primates and Guinea Pigs increase Vitamin C synthesis during stress
- Vitamin C levels are typically very low in critically ill patients
  - Low levels likely due to enhanced metabolic turnover (oxidant stress)
  - Decreased GI absorption (dec. expression of SVCT1)
  - Urinary loss
- 100% septic patients levels < 23 umol/l (Vitamin C deficient)
- ~40% septic patients levels < 11.3 umol/l - Scurvy
- Low levels despite PO supplementation 1500 mg/day
Key Roles of Vitamin C in Sepsis

<table>
<thead>
<tr>
<th>Key Role</th>
<th>Mechanism</th>
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<tr>
<td>Free radical scavenger</td>
<td>Scavenges extracellular, intracellular and mitochondrial ROS; limits oxidation of mitochondrial proteins, enzymes, lipoproteins, cell membrane, etc</td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td>Inhibits activation of NFκB, decreases HMGB1, inhibits histamine, prevents NETosis, inactivates HIF-1α</td>
</tr>
<tr>
<td>Microcirculation</td>
<td>Increases eNOS, decreases iNOS, preserves tight junctions</td>
</tr>
<tr>
<td>Immune function</td>
<td>Supports lymphocyte proliferation, increases neutrophil bacteriocidal action, improves chemotaxis, stimulates interferon production, decreases T regulatory cells (Tregs)</td>
</tr>
<tr>
<td>Anti-thrombotic</td>
<td>Decreases platelet activation and tissue factor expression, increases thrombomodulin</td>
</tr>
<tr>
<td>Synthesis of catecholamines</td>
<td>Acts cofactor in synthesis of epinephrine, dopamine and vasopressin. Increases adrenergic sensitivity</td>
</tr>
<tr>
<td>Wound Healing</td>
<td>Hydroxylation of procollagen, increased expression of collagen mRNA</td>
</tr>
</tbody>
</table>
Thiamine, Oxalate and Vitamin C
Randomized, Double-Blind, Placebo-Controlled Trial of Thiamine as a Metabolic Resuscitator in Septic Shock: A Pilot Study

Donnino MW et al. Crit Care Med 2016; 44; 360
Thiamine as a Renal Protective Agent in Septic Shock: A Secondary Analysis of a Randomized, Double-Blind, Placebo-Controlled Trial
Ari Moskowitz MD¹, Lars W. Andersen MD²,³,⁴, Michael N. Cocchi MD²,⁵, Mathias Karlsson BS²,³, Parth V. Patel RN², Michael W. Donnino MD¹,²
Thiamine and Oxidative Phosphorylation
The Synergy Between Glucocorticoids and Vitamin C
Protective Effects of Hydrocortisone, Vitamin C and E Alone or in Combination against Renal Ischemia-Reperfusion Injury in Rat

I/R + placebo

I/R + Vitamin C (50 mg/kg)

I/R + hydrocortisone

I/R + Combination

Iran J Pathol 2015;10:272
Hydrocortisone and Ascorbic Acid Synergistically Prevent and Repair Lipopolysaccharide-Induced Pulmonary Endothelial Barrier Dysfunction

Nektarios Barabutis, PhD; Vikramjit Khangoora, MD; Paul E. Marik, MD; and John D. Catravas, PhD
Results: Hydrocort.+ Vitamin C and LPS (post LPS)
Hydrocortisone, Ascorbic acid & Thiamine (HAT) for the treatment of sepsis
Chain of evidence

- Validated mechanistic basis
- Supported by basic science
- Supported by clinical studies
WHAT'S NEXT?
<table>
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<tr>
<th>Study Title</th>
<th>Conditions</th>
<th>Interventions</th>
<th>Locations</th>
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<tbody>
<tr>
<td>Vitamin C, Thiamine, and Steroids in Sepsis</td>
<td>• Sepsis</td>
<td>• Drug: Vitamin C</td>
<td>• Emory University Hospital Atlanta, Georgia, United States</td>
</tr>
<tr>
<td>Ascorbic Acid, Corticosteroids, and Thiamine in Sepsis (ACTS) Trial</td>
<td>• Sepsis</td>
<td>• Drug: Vitamin C, vitamin B1, hydrocortisone</td>
<td>• Mayo Clinic - Arizona Phoenix, Arizona, United States</td>
</tr>
<tr>
<td>Metabolic Resuscitation Using Ascorbic Acid, Thiamine, and Glucocorticoids in Sepsis</td>
<td>• Sepsis, Severe</td>
<td>• Drug: Ascorbic Acid</td>
<td>• Brigham and Women's Hospital Boston, Massachusetts, United States</td>
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<tr>
<td>Thiamine, Vitamin C and Hydrocortisone in the Treatment of Septic Shock</td>
<td>• Septic Shock</td>
<td>• Drug: Thiamine</td>
<td>• Monmouth Medical Center, Southern Campus Lakewood, New Jersey, United States</td>
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<tr>
<td>Vitamin C &amp; Thiamine in Sepsis</td>
<td>• Sepsis</td>
<td>• Dietary Supplement: Thiamine and Vitamin C</td>
<td>• Lakeland Regional Healthcare Saint Joseph, Michigan, United States</td>
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<tr>
<td>Vitamin C and Septic Shock</td>
<td>• Sepsis</td>
<td>• Drug: Vitamin C</td>
<td>• Saint Francis Hospital and Medical Center Hartford, Connecticut, United States</td>
</tr>
<tr>
<td>The Vitamin C, Hydrocortisone and Thiamine in Patients With Septic Shock Trial</td>
<td>• Shock, Septic</td>
<td>• Drug: Vitamin C</td>
<td>• University of Minnesota Medical Center Minneapolis, Minnesota, United States</td>
</tr>
<tr>
<td>Vitamin C, Hydrocortisone and Thiamine for Septic Shock</td>
<td>• Shock, Septic</td>
<td>• Drug: Combined Vitamin C and Stress-Dose Hydrocortisone</td>
<td>• Monash Medical Center Clayton, Victoria, Australia</td>
</tr>
<tr>
<td>Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Sepsis and Septic Shock</td>
<td>• Sepsis</td>
<td>• Drug: Hydrocortisone, Vitamin C, and Thiamine</td>
<td>• Evaggelismos General Hospital Athens, Attica, Greece</td>
</tr>
<tr>
<td>The Effect of Vitamin C, Thiamine and Hydrocortisone on Clinical Course and Outcome in Patients With Severe Sepsis and Septic Shock</td>
<td>• Sepsis</td>
<td>• Other: Normal saline</td>
<td>• Department of Critical Care Medicine of Zhijiang Hospital, Southern Medical University Guangzhou, Guangdong, China</td>
</tr>
<tr>
<td>Evaluation of Hydrocortisone, Vitamin C and Thiamine for the Treatment of Septic Shock</td>
<td>• Septic Shock</td>
<td>• Drug: Vitamin C</td>
<td>• Department of Gastroenterology, UMC Ljubljana Ljubljana, Slovenia</td>
</tr>
<tr>
<td></td>
<td>• Septic Shock</td>
<td>• Drug: Hydrocortisone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Critical Illness</td>
<td>• Drug: Triple therapy group</td>
<td>• Hamad Medical Corporation Doha, Qatar</td>
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Thank you