The Use of Metabolic Resuscitation in Sepsis

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Disclosures

• No conflicts of interest to disclose
Objectives

Define the use of metabolic resuscitation in the critically ill

Discuss evidence evaluating resuscitation & clinical outcomes in critically ill patients
Background

- 15-19 million cases of sepsis worldwide annually
- Septic shock mortality as high as 50%
- Reduced quality of life persists in sepsis survivors
- Clinical research has failed to produce novel pharmacologic treatments for sepsis

Current guideline-based resuscitation

- Fluid resuscitation
- Norepinephrine
- Vasopressin &/or Hydrocortisone
Defining Metabolic Resuscitation

“We can deliver all the oxygen we want to the tissues, but if the mitochondria are failing, it won’t work.” ~ Dr. Johsua Farkas
Mitochondrial Function

- Generation of energy through Krebs cycle
- Thermoregulation
- Calcium homeostatis
- Production of reactive oxygen species
- Biosynthesis
  - Cortisol
  - Vascular endothelium growth factor
- Regulation of cell death
Role of Metabolic Resuscitation in Sepsis

Sepsis

Depletion of essential vitamins

Mitochondrial dysfunction + Endothelial barrier disruption

Septic shock +/- Multiple organ dysfunction

Role of Vitamin C

- Antioxidant/
  Anti-inflammatory
- Catecholamine/
  Vasopressin/
  Cortisol synthesis
- Endothelial
  integrity/
  Nitric oxide
  regulation
- Immune modulator

## Vitamin C Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fowler, et al 2014</td>
<td>Sepsis Organ dysfunction Medical ICU- US</td>
<td>Low dose Vit C- 50 mg/kg/d IV x4d (n=8) vs High dose Vit C- 200 mg/kg/d IV x4d (n=8) vs placebo (n=8)</td>
<td>Primary: safety (tachycardia, hypotension, hypernatremia, nausea/vomiting) Secondary: SOFA, ascorbic acid levels, CRP, PCT, thrombomodulin</td>
<td>No adverse safety events Ascorbic acid levels rapidly improved with Vit C Decline in SOFA scores, CRP &amp; PCT with Vit C</td>
</tr>
<tr>
<td>Zabet, et al 2016</td>
<td>Septic shock Organ dysfunction Vasopressor(s) Excluded: other antioxidants, steroids, chronic HD Surgical ICU- Iran</td>
<td>Vit C 25m/kg IV q6h x3d (n=14) vs placebo (n=14)</td>
<td>Primary: vasopressor dose &amp; duration Secondary: ICU LOS, 28d mortality</td>
<td>Vitamin C ➔ decreased norepinephrine dose &amp; duration No change in ICU LOS Vitamin C ➔ decreased 28d mortality</td>
</tr>
</tbody>
</table>

Role of Thiamine

- Component of aerobic metabolism (Kreb’s cycle)
- Deficiency → cardiac dysfunction
- Deficiency → delirium
- Role in mitochondrial metabolism

References:
# Thiamine Studies

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| Donnino, et al 2016    | Sepsis Lactate > 3 Vasopressor(s)               | Thiamine 200mg IV q12h x7d (n=43) vs placebo (n=45) | Primary: lactate at 24h Secondary: change in lactate, shock reversal, change in SOFA/APACHE II, ICU & hospital LOS, in-hospital mortality | No difference in lactate at 24h overall  
Lower lactate at 24h in thiamine deficient group  
No difference in shock reversal, LOS or mortality |
|                        | Excluded: liver injury/dysfunction, indication for thiamine, ischemia | Two centers- US |                                                                           |                                                                         |
|                        |                                                 |                                                  |                                                                           |                                                                         |
| Woolum, et al 2018     | Septic shock Lactate > 2 Vasopressor(s)         | Thiamine IV within 24h of admission (n=123) vs matched controls (n=246) | Primary: time to lactate clearance Secondary: 28d mortality, vasopressor-free days, change in SOFA, AKI/RRT | Thiamine associated with improved lactate clearance & 28d mortality  
No difference in vasopressor-free days, SOFA, AKI/RRT |
|                        | 65% baseline liver disease                      | Thiamine 100mg q24h-500mg q8h, median 3d        |                                                                           |                                                                         |
|                        | Single center- US                               |                                                  |                                                                           |                                                                         |
|                        |                                                 |                                                  |                                                                           |                                                                         |
Role of Hydrocortisone

- Anti-inflammatory
- Reverses relative adrenal insufficiency
- Improved blood volume
- Improved systemic vascular resistance
Hydrocortisone

Surviving Sepsis Campaign Guidelines, 2016:

We suggest against using IV hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If this is not achievable, we suggest IV hydrocortisone at a dose of 200 mg per day. (weak recommendation, low quality of evidence).

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<tr>
<td>Keh D, et al 2016</td>
<td>Severe sepsis NOT septic shock</td>
<td>HC 50mg bolus, 200mg/24h continuous infusion x 5d, then tapered (n=170) vs placebo (n=170)</td>
<td>Primary: septic shock within 14d</td>
<td>No difference in development of septic shock</td>
</tr>
<tr>
<td>HYPRESS trial</td>
<td>Excluded: other indication for steroids</td>
<td></td>
<td>Secondary: time until septic shock, mortality- ICU, hospital, up to180d, secondary infections, hyperglycemia, muscle weakness</td>
<td>No difference in secondary outcomes</td>
</tr>
<tr>
<td></td>
<td>34 centers- Germany</td>
<td></td>
<td></td>
<td><strong>More episodes of hyperglycemia in HC group</strong></td>
</tr>
</tbody>
</table>
# Hydrocortisone Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Decreased Vasopressors</th>
<th>Improved Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annane, et al 2002</td>
<td>HC 50mg q6h +fludro x7d vs placebo; n=300</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>CORTICUS 2008</td>
<td>HC 50mg q6h x5d (then tapered) vs placebo; n=499</td>
<td>✔</td>
<td>✗</td>
</tr>
<tr>
<td>ADRENAL 2018</td>
<td>HC 200mg/day (continuous) x7d vs placebo; n=3658</td>
<td>✔</td>
<td>✗</td>
</tr>
<tr>
<td>APROCCHSS 2018</td>
<td>HC + fludro x 7d vs placebo; n=1241</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Systematic Review &amp; Meta-Analysis 2018</td>
<td>42 RCTS ➔ 27 used HC, most &lt; 3d; n=6922</td>
<td>✔</td>
<td>+/-</td>
</tr>
</tbody>
</table>

“On the basis of experimental & emerging clinical data, we decided to administer intravenous Vitamin C... as a life saving measure... All three... patients made a dramatic recovery & were discharged from the ICU within days with no residual organ dysfunction.” ~Dr. Paul Marik
Role of combination

Vitamin C + Hydrocortisone work synergistically as antioxidants/anti-inflammatory agents

Vitamin C restores glucocorticoid function & preserves endothelial function

Thiamine decreases production of oxalate

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<tr>
<td>Marik, et al 2016</td>
<td>Severe sepsis or septic shock PCT ≥ 2</td>
<td>Vit C + Thiamine + HC (n=47) vs control (n=47)</td>
<td>Primary: hospital survival</td>
</tr>
<tr>
<td>Retrospective, before-after, propensity-matched</td>
<td>Consecutive patients during specified 7-month time periods</td>
<td>*60% of control group received hydrocortisone</td>
<td>Secondary: duration of vasopressors, RRT for AKI, ICU LOS, change in PCT &amp; SOFA</td>
</tr>
<tr>
<td></td>
<td>Medical ICU</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exclusion: limitations of care</td>
<td></td>
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Vitamin C 1.5gm IV q6h x 4 days
Thiamine 200mg IV q12h x 4 days
Hydrocortisone 50mg IV q6h x 7 days

## Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable (%)</th>
<th>Treated (n=47)</th>
<th>Control (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, years</td>
<td>58.3 ± 14.1</td>
<td>62.2 ± 14.3</td>
</tr>
<tr>
<td>Sex, 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>Acute kidney injury</td>
<td>31 (66)</td>
<td>30 (64)</td>
</tr>
<tr>
<td>WBC, mean ± SD, x10⁹</td>
<td>20.6 ± 13.5</td>
<td>17.1 ± 13.4</td>
</tr>
<tr>
<td>Lactate, mean ± SD, mM</td>
<td>2.7 ± 1.5</td>
<td>3.1 ± 2.8</td>
</tr>
<tr>
<td>Procalcitonin, median &amp; IQR, ng/mL</td>
<td>25.8 (5.8-93.4)</td>
<td>15.2 (5.9-39)</td>
</tr>
<tr>
<td>Positive blood cultures</td>
<td>13 (28)</td>
<td>13 (28)</td>
</tr>
<tr>
<td>Day 1 SOFA, mean ± SD</td>
<td>8.3 ± 2.8</td>
<td>8.7 ± 3.7</td>
</tr>
<tr>
<td>APACHE II/IV, mean ± SD</td>
<td>22.1 ± 6.3/79.5 ± 16.4</td>
<td>22.6 ± 5.7/82 ± 27.4</td>
</tr>
<tr>
<td>Predicted mortality, mean ± SD</td>
<td>39.7 ± 16.7</td>
<td>41.6 ± 24.2</td>
</tr>
</tbody>
</table>
## Results

<table>
<thead>
<tr>
<th>Variable (%)</th>
<th>Treated (n=47)</th>
<th>Control (n=47)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital mortality</td>
<td>4 (8.5)</td>
<td>19 (40.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ICU LOS, median &amp; IQR, d</td>
<td>4 (3-5)</td>
<td>4 (4-10)</td>
<td></td>
</tr>
<tr>
<td>Duration of vasopressors, mean ± SD, h</td>
<td>18.3 ± 9.8</td>
<td>54.9 ± 28.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>RRT for AKI</td>
<td>3 of 31 (10)</td>
<td>11 of 30 (33)</td>
<td>0.02</td>
</tr>
<tr>
<td>Change in SOFA, 72h</td>
<td>4.8 ± 2.4</td>
<td>0.9 ± 2.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PCT clearance, median &amp; IQR, 72h</td>
<td>86.4 (80.1-90.8)</td>
<td>33.9 (-62.4-64.3)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
Results: Primary Outcome

- Propensity adjusted odds of mortality with Vitamin C protocol 0.13 (95% CI, 0.04-0.48, P = 0.002)
- Independent mortality predictors
  - APACHE IV score
  - Mechanical ventilation
- “No patients in treatment group died of complications related to sepsis”

(Predicted mortality based on APACHE IV scores)
Results: Secondary Outcomes

Vasopressor Duration

Change in SOFA Score

Study Critique

(+) • First study to evaluate this combination of therapies
  • Enrolled consecutive patients
  • High predicted mortality
  • Propensity score matching
  • Procalcitonin utilized as screening tool
  • High predicted mortality
  • Baseline characteristics similar
  • Sepsis “standard of care” outlined in methods

(-) • Study design: single center, retrospective, not randomized
  • Provider/selection bias
  • Hawthorne effect
  • Study periods not concurrent
  • Procalcitonin clearance multifactorial
  • Adverse events not addressed
  • Death data not well described
  • Hospital mortality endpoint
  • Interventions studied as bundle
  • 60% of controls received steroids
  • Steroid use not guideline based
## Practical Considerations

### Fluid volume
- ≥ 300-500 mL IV fluid per day of therapy

### Dispensing
- Product availability
- Compounding challenges

### Glucose monitoring concerns
- Vitamin C may interfere with meters that utilize glucose dehydrogenase

### Cost
- Relatively low, but not negligible
Discussion

- Results show association, not causation.
- Sepsis data historically hard to replicate.

- Therapies seemingly safe, relatively low cost.
Conclusions

Metabolic resuscitation offers an exciting, potential new mechanism for treatment of sepsis

Quality of currently published literature is limited & should be interpreted with caution

Future studies are needed to confirm efficacy & safety of metabolic resuscitation components
Learning Assessment Question #1

• Metabolic resuscitation in sepsis focuses on which of the following:
  A. Restoring volume loss
  B. Repleting endogenous vasopressin
  C. Improving mitochondrial function
  D. Reversing the hypercoaguable state
Learning Assessment Question #2

• Which of the following regarding metabolic resuscitation in sepsis is true?
  A. Thiamine improves shock reversal
  B. Thiamine decreases production of oxylate
  C. Vitamin C is depleted in sepsis & levels increase when repleted intravenously
  D. **B & C**
The Use of Metabolic Resuscitation in Sepsis

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