Metabolic resuscitation in sepsis

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Declaration

• Financial support and sponsorship
  Nil

• Conflicts of interest
  There are no conflicts of interest
Outlines

• Very brief overview of the scientific rationale
• Why does Vitamin C help?
• Why does Thiamine help?
• Vitamin C deficiency causes clinical disease
• Thiamine deficiency causes clinical disease
• Clinical studies of IV Vitamin C:
• Clinical studies of Thiamine:
• Marik protocol
• Take home message
Very brief overview of the scientific rationale

- Septic patients are invariably deficient in Vitamin C, and frequently deficient in thiamine.
- Deficiencies in Vitamin C and thiamine might explain many of the abnormalities seen in sepsis.
- Vitamin C and thiamine have an outstanding track record of safety, proven over decades of experimentation and clinical experience.
• Many RCTs have suggested benefit from Vitamin C or thiamine in critically ill patients, with no evidence of toxicity.
• A recent before-after study found a substantial mortality benefit from the combination of stress-dose steroid, IV vitamin C, and IV thiamine. Although this isn't an RCT, the results are quite striking.
• Further research is required, but in the interim this is a reasonable intervention given the excellent safety profile of these agents.
Vitamin C
Why does Vitamin C help?
Why does Vitamin C help?

• Antioxidant:
  - Scavenges ROS and RNS,
  - prevents endothelial damage
  - maintaining microvascular integrity
Why does Vitamin C help?

• **Synthesis of catecholamines**
  
  Acts as cofactor in synthesis of epinephrine, dopamine, and vasopressin allowing for maintenance of vascular tone and cardiac output
  
  - **dopamine beta-hydroxylase**, This enzyme converts dopamine into epinephrine
  
  - Rate-limiting step of synthesising L-DOPA, the precursor of dopamine
Why does Vitamin C help?

- Essential co-factor for iron and copper-containing enzymes

*Figure 2* Vitamin C reactions: A, Hydroxylation of proline. Ascorbic acid (AA) is a cofactor involved in regenerating ferrous iron. \(\alpha\)-KG, \(\alpha\)-ketoglutaric acid; B, hydroxylation of dopamine. (From Ref. 1.)
Why does Vitamin C help?

• **Immune function**
  - Supports lymphocytic proliferation,
  - Assists in neutrophilic killing of bacteria,
  - Improves chemotaxis
  - Inhibits NF-KB activation
Why does Vitamin C help?

**Journal Name:** Biofactors

**Review Article Title:** Mechanism of action of vitamin C in sepsis: Ascorbate modulates redox signaling in endothelium

**Authors:** Wilson et al. 2009

- **Conclusion / Recommendation:**
  - Vitamin C deficiency correlates with multiorgan failure and death
  - microvascular function may be improved in sepsis by parenteral administration of ascorbate as an adjuvant therapy
Why does Thiamine help?
Why does Thiamine help?

- Thiamine deficiency is common in sepsis, occurring in perhaps one-third of patients. This is associated with increased mortality ([Manganese 2011](#)).
- is a critical co-factor in the glycolysis and oxidative decarboxylation of carbohydrates for energy production.
- Shunts metabolism of vitamin C away from oxalate (potential for renal crystallisation)
depletion is frequently unrecognised and underdiagnosed by clinicians.

Potentially deleterious consequences of thiamine depletion should be avoided by early and appropriate supplementation.
Why does Thiamine help?
Why does Thiamine help?

An example is the conversion of pyruvate to acetyl-CoA, which is irreversible, during CHO metabolism.

- **Oxidative decarboxylation** reactions are oxidation reactions in which a carboxylic group is removed, forming CO₂.
Why does Thiamine help?

- Shunts metabolism of vitamin C away from oxalate (potential for renal crystallisation)
Vitamin C deficiency causes clinical disease
Vitamin deficiency causes clinical disease

- Vitamin C deficiency causes scurvy.
- Vitamin C is important for the maintenance of endothelial boundaries, with edema noted in scurvy.
- Vitamin C is also required for the synthesis of catecholamines and cortisol, so deficiency causes failure of the sympathetic nervous system.
scurvy

Symptoms of Scurvy

Stage I
Lethargy & Fatigue

Stage II
Bleeding in the gums

Stage III
Anemia

Stage IV
High fever

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Thiamine deficiency causes clinical disease
Vitamin deficiency causes clinical disease

- Thiamine deficiency may cause
  - Delirium
    - (Wernicke's encephalopathy)
  - and
  - cardiac dysfunction
    - (Beriberi).

Beriberi in particular can mimic sepsis, by causing distributive shock and lactic acidosis.
Wernicke's encephalopathy

Dr Carl Wernicke
A Polish neurologist, who described this neuropsychiatric syndrome in 1881 as a triad of acute mental confusion, ataxia, and ophthalmoplegia.
Beriberi

Classification of Beri-Beri

- Dry Beriberi
- Cardiovascular (Wet Beriberi)
- Infantile Beriberi
- Shoshin Beriberi
- Wernicke-Korsakoff syndrome
Beriberi

Common symptoms
- Loss of tendon reflexes
- Burning or tingling
- Numbness of feet
- Painful, tender muscles
- Foot drop

Dry beriberi
- Emaciation
- Confusion
- Inability to speak
- Great weakness
- Wrist drop
Beriberi

Wet Beriberi

Dyspnea, Orthopnea
Slight Cyanosis

Dilatation of Right Heart, Heart Failure

Edema
Confusion
Coma
Death

Wernicke's Syndrome

Ophthamoplegia (6th Nerve Palsy)
Clinical studies of IV Vitamin C:
Intestinal absorption of vitamin C is **saturable**

**Intestinal absorption of water-soluble vitamins in health and disease**

Hamid M. Said

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Clinical studies of IV vitamin C in cardiac patients

Table 2 Controlled studies on the effect of vitamin C in cardiac surgery patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Intervention</th>
<th>Number of patients</th>
<th>Incidence of new POAF (%)</th>
<th>P value</th>
<th>Other clinical benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dingchao and colleagues [101]</td>
<td>Controlled; patients undergoing cardiopulmonary bypass</td>
<td>i.v. vitamin C; 250 mg/kg i.v. before</td>
<td>45</td>
<td></td>
<td></td>
<td>MDA ↓, CK, CK-MB ↓, postbypass defibrillation 0 vs. 12.5% CI ↑, LOS ICU ↓, LOS hospital ↓</td>
</tr>
<tr>
<td>Carnes and colleagues [82]</td>
<td>Matched control; CABG</td>
<td>Control</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eslami and colleagues [98]</td>
<td>RCT; CABG</td>
<td>Matched control</td>
<td>43</td>
<td>16.3</td>
<td>0.048</td>
<td></td>
</tr>
<tr>
<td>Eslami and colleagues [98]</td>
<td>RCT; CABG</td>
<td>Oral vitamin C; 2 g night before, 500 mg daily for 5 days</td>
<td>43</td>
<td>34.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papioulidou and colleagues [100]</td>
<td>RCT; CABG</td>
<td>β-Blocker alone</td>
<td>50</td>
<td>26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bjordahl and colleagues [99]</td>
<td>RCT; CABG</td>
<td>Oral vitamin C; 2 g night before, 1 g twice daily for 5 days</td>
<td>50</td>
<td>30.3</td>
<td>0.985</td>
<td>Shorter time on ventilator, 1.2 vs. 1.4 days, P = 0.032</td>
</tr>
<tr>
<td>Papoulidou and colleagues [100]</td>
<td>RCT; CABG</td>
<td>i.v. vitamin C; 2 g 3 hours before CPB</td>
<td>89</td>
<td>30.2</td>
<td>0.041</td>
<td>Time to SR conversion ↓, LOS hospital ↓, LOS ICU ↓</td>
</tr>
<tr>
<td>Rodrigo and colleagues [95]</td>
<td>RCT</td>
<td>Preoperative PUFA; 2 g/day for 5 days; vitamin C 1 g/day + vitamin E 400 IU/day for 2 days preoperatively and postoperatively until discharge</td>
<td>103</td>
<td>9.7</td>
<td>&lt;0.001</td>
<td>Oxidative stress-related biomarkers in atrial tissue ↓</td>
</tr>
<tr>
<td>Placeboa</td>
<td>100</td>
<td></td>
<td></td>
<td>32</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Clinical studies of IV vitamin C in critically ill patients:

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Intervention</th>
<th>Number of patients</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nathens and colleagues [104]</td>
<td>RCT; trauma and MOF</td>
<td>i.v. vitamin C 1 g three times daily; enteral vitamin E 1,000 IU three times daily</td>
<td>301</td>
<td>Pulmonary morbidity ↓, new MOF ↓, LOS ventilation ↓, LOS ICU ↓</td>
</tr>
<tr>
<td>Crimi and colleagues [107]</td>
<td>RCT; critically ill (mainly trauma, cardiogenic shock)</td>
<td>With TPN, vitamin C 100 mg and vitamin E 10 IU daily; with EN, vitamin C 240 mg/I, vitamin E 60 IU/I</td>
<td>294</td>
<td></td>
</tr>
<tr>
<td>Collier and colleagues [103]</td>
<td>Prospective vs. retrospective 1-year cohort; trauma</td>
<td>Vitamin C 500 mg/day and vitamin E (400 IU/day) in EN Saline solution for 10 days</td>
<td>105</td>
<td>Ventilator-free days ↓, 28-day mortality ↓</td>
</tr>
<tr>
<td>Collier and colleagues [103]</td>
<td>RCT; complicated cardiac surgery, trauma, SAB</td>
<td>l.v. or oral vitamin C 1 g three times daily + oral vitamin E 1,000 IU three times daily + selenium 200 µg i.v.</td>
<td>2,272</td>
<td>LOS ICU ↓, LOS hospital ↓, mortality ↓ OR 0.32, 95% CI 0.22 to 0.46</td>
</tr>
<tr>
<td>Berger and colleagues [105]</td>
<td>RCT; complicated cardiac surgery, trauma, SAB</td>
<td>Selenium 540 i.v. day 1, 270 µg days 2 to 5; zinc 60 mg i.v. day 1, 30 mg days 2 to 5; vitamin B1 305 mg i.v. day 1, 205 mg days 2 to 5; vitamin C 27 g i.v. day 1, 16.5 g days 2 to 5; vitamin E 600 mg i.v. day 1, 300 mg days 2 to 5</td>
<td>2022</td>
<td>New organ failure ND, new infections ND, LOS shorter in trauma, CRP ↓ in cardiac surgery and trauma, recovery of health after discharge ↑</td>
</tr>
<tr>
<td>Heyland and colleagues [106]</td>
<td>RCT, 2 × 2 factorial; critically ill adults with multiple organ failure</td>
<td>Vitamin B1 100 mg i.v. days 1 to 3 (both groups); vitamin C 500 mg i.v. days 1 to 5 (both groups)</td>
<td>98</td>
<td>No difference in 28-day mortality or length of stay</td>
</tr>
<tr>
<td>Burn</td>
<td>RCT; severe burn &lt;2 hours</td>
<td>Selenium 500 µg i.v., selenium 300 µg or dnc 20 mg or β-carotene 10 mg; vitamin E 500 mg or vitamin C 1,500 mg</td>
<td>307</td>
<td>Fluid requirements ↓, body weight gain ↓, PF ratio ↑, days on mechanical ventilation ↓</td>
</tr>
<tr>
<td>Tanaka and colleagues [84]</td>
<td>RCT</td>
<td>Ringer lactate + 66 mg/kg/hour vitamin C Ringer lactate for 24 hours</td>
<td>19</td>
<td></td>
</tr>
</tbody>
</table>
Reduction of resuscitation fluid volumes in severely burned patients using ascorbic acid administration

Authors: Tanaka H et al, 2000

- Study type, number: N37
  A prospective RCT
  involving patients with major burns (>30% body surface area).
- Methodology:
  Patients were randomized regarding whether or not to receive
  An infusion of IV vitamin C, 66 mg/kg/hr
  for the first 24 hours of hospitalisation.
Tanaka H et al, 2000

• **Results**: patients in the vitamin C group required
  - less fluid resuscitation,
  - had higher urine output, and
  - developed less wound edema

• **Conclusion / Recommendation:**

• this translated into
  - improved oxygenation and
  - less time on mechanical ventilation among the Vitamin C group
  (average of 12 vs. 21 days of ventilation, \( p=0.03 \)).
Journal Name: Ann Surg

Study Title: Randomized, prospective trial of antioxidant supplementation in critically ill surgical patients

Authors: Nathens AB et al. 2002

• Study type, number:
  595
  Randomized, prospective trial

• Methodology:
  They randomised patients shortly after admission to the ICU to no therapy vs. a combination of enteral vitamin E plus IV vitamin C 1000 mg q8hr until ICU discharge
Nathens AB et al. 2002

- **Results**: patients treated with vitamins E and C fared better on a variety of secondary endpoints including:
  - less time on the ventilator and
  - less multi organ failure

- **Conclusion / Recommendation**: prophylactic antioxidants provided to surgical ICU patients could reduce pulmonary complications
Study Title: Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis

Authors: Fowler A et al. 2014

- Study type, number: N 24
  Single Centre, PRDPCT
  Involving patients with severe sepsis in a medical ICU

- Methodology:
  Patients were randomised to receive
  - placebo,
  - low-dose vitamin C (12.5 mg/kg IV q6hr), or
  - high-dose vitamin C (50 mg/kg IV q6hr).
<table>
<thead>
<tr>
<th>Fowler A et al. 2014</th>
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</table>

- **Results:**
  The primary endpoint was safety and tolerability, with no adverse events noted.

- **Conclusion / Recommendation:**
  Patients treated with vitamin C experienced a
  - dose-dependent improvement in SOFA score over time
  - Improved inflammatory markers
Journal Name: J Pulm Respir Med,

Study Title: Impact of intravenous ascorbic acid infusion on novel biomarkers in patients with severe sepsis

Authors: Natarajan et al 2014

- **Study type, number:** N24
  - Single centre, retrospective randomized

- **Methodology:**
  - 50 mg/kg or 200 mg/kg IV infusion every 24 h
Natarajan et al 2014

• Results:

• Conclusion / Recommendation:
  - Decrease in biomarkers of sepsis (cf-DNA and mtDNA) and
  - Decrease in RDW
Study Title: Effect of high-dose ascorbic acid on vasopressor requirement in septic shock

Authors: Zabet MH et al 2016

• Study type, number: N28
  Single centre, DBRCT

• Methodology:
  A surgical ICU with vasopressor-dependent septic shock were randomized to receive placebo vs. Vitamin C 25 mg/kg IV q6hr.
• Results:

• Conclusion / Recommendation:

Reduction in

- vasopressor dose and
- vasopressor duration
- mortality

among patients treated with Vitamin C.
Clinical studies of Thiamine:
Journal Name: Crit Care Med

Study Title
Randomized, double-blind, placebo-controlled trial of thiamine as a metabolic resuscitator in septic shock: A pilot study

Authors: Donning MW 2016

- Study type, number
  88 patients with septic shock
  Randomised, double-blind, placebo-controlled trial

Methodology:
Investigating the effect of thiamine (200 mg IV q12hr)
Endpoint: Lactate levels, time to shock reversal, SOI, mortality
• **Results:**
  – No difference in overall groups
  – In patients with baseline thiamine deficiency (35% of total):
    • Lower lactate
    • Decreased mortality

**Conclusion / Recommendation:**
Within this pre-specified subgroup, thiamine administration did reduce lactate levels and mortality
Clinical studies of Thiamine:

Figure 3. Kaplan Meier survival curves. Survival curves for the thiamine and placebo groups in the full study group (left) and the thiamine deficient group (right). Patients were censored at hospital discharge. The graph is truncated at 30 days for illustrative purposes. Vertical lines represent censored patients and the p-value is from the log-rank test.
Marik Cocktail:

Vitamin C 1.5g IV q6h
Hydrocortisone 50 mg IV q6h
Thiamine 200mg IV q12h

Infused, not stirred.
• Paul Marik, MBBCh
• Chief of Pulmonary and Critical Care Medicine
Marik Protocol

- **IV Vitamin C 1.5g q6hr**
  - x4d or ICU DC

- **IV Hydrocortisone 50mg q6hr**
  - x7d or ICU DC + 3d Taper

- **IV Thiamine 200mg q12hr**
  - x4d or ICU DC
What He Did:

- Electronic Heath Record (EHR)
  - Retrospective before-after clinical study
- Compared the clinical course and outcome of consecutive severe sepsis (maybe clarify that this is the new definition?) and septic shock patients and a procalcitonin (PCT) $\geq 2\text{ng/mL}$:
Marik Protocol cont’d

<table>
<thead>
<tr>
<th>Design</th>
<th>Retrospective observational study</th>
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<tr>
<td></td>
<td>Single centred</td>
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<table>
<thead>
<tr>
<th>Setting</th>
<th>Single centre in US</th>
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<tr>
<td></td>
<td>January – July 2016</td>
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</table>
Marik Protocol cont’d

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Control Group:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Treated with <strong>standard sepsis care</strong></td>
<td>• Treated with <strong>standard sepsis care</strong> only.</td>
</tr>
<tr>
<td>+</td>
<td></td>
</tr>
<tr>
<td>- Intravenous <strong>vitamin C</strong></td>
<td></td>
</tr>
<tr>
<td>- <strong>Hydrocortisone</strong> and</td>
<td></td>
</tr>
<tr>
<td>- <strong>Thiamine</strong></td>
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<tr>
<td>within 24 hours of ICU admission</td>
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</tbody>
</table>
Standard ICU Care:

- **Empiric broad spectrum antibiotics** giving initially, which were de-escalated according to microbiological data and clinical progress
- Conservative physiologic **fluid** based therapy
- Intravenous **hydrocortisone** 50mg q6hr
- **Lung protective strategy** and avoidance of hyperoxia
- Limited use of **sedative agents** (dexmedetomidine was the preferred agent)
Marik Protocol cont’d

- **Norepinephrine** was the vasopressor of choice (titrated to a dose of 20ug/min targeting a MAP >65mmHg)
- If needed, the next vasopressor added was **vasopressin** at 0.04 U/min, followed next with by phenylephrine or epinephrine
- **Enteral nutrition** was initiated 24 hours after ICU admission and clinical stability achieved
- **DVT prophylaxis** with enoxaparin (or heparin in patients with creatinine clearance <30ml/min) and sequential compression devices
Vitamin C (Marik) Treatment Protocol:

- Standard ICU care plus:
- Intravenous vitamin C 1.5g q6hr x4d or until ICU discharge
- Hydrocortisone 50mg q6hr x7d or until ICU discharge followed by a taper over 3d
- Intravenous thiamine 200mg q12hr x4 or until ICU discharge
Outcomes:

- **Primary:** Hospital survival
- **Secondary:**
  - Duration of vasopressor therapy
  - Requirement for renal replacement therapy (RRT) in patients with AKI
  - ICU length of stay
  - Change in serum procalcitonin (PCT)
  - Change in SOFA score over the first 72 hours
### Outcomes:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treated</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital mortality, No. (%)</td>
<td>4 (8.5)</td>
<td>19 (40.4)</td>
</tr>
<tr>
<td>ICU LOS, median and IQR, d</td>
<td>4 (3-5)</td>
<td>4 (4-10)</td>
</tr>
<tr>
<td>Duration of vasopressors, mean ± SD, h</td>
<td>18.3 ± 9.8</td>
<td>54.9 ± 28.4</td>
</tr>
<tr>
<td>RRT for AKI, No. (%)</td>
<td>3 of 31 (10%)</td>
<td>11 of 30 (33%)</td>
</tr>
<tr>
<td>ΔSOFA, 72 h</td>
<td>4.8 ± 2.4</td>
<td>0.9 ± 2.7</td>
</tr>
<tr>
<td>Procalcitonin clearance, median % and IQR, 72 h</td>
<td>86.4 (80.1-90.8)</td>
<td>33.9 (–62.4 to 64.3)</td>
</tr>
</tbody>
</table>
NNT for death was 3.1 in this study, rounded up to 4 treated patients to avoid one death.
Strengths:

• No difference in baseline characteristics between groups
• Consecutive patients enrolled
• The studied interventions were cheap, seemingly safe and readily available. However, vitamin C toxicity can cause renal failure and the safety profile would be best evaluated in the context of an RCT
Strengths cont’d

• This was the first study to evaluate the combination of intravenous vitamin C, hydrocortisone, and thiamine

• An interesting hypothesis generating study which has some biologically plausible explanations for benefit in sepsis
Limitations:

- Not a RCT
- Small sample size
- Only a single center study
- Use of non-concurrent controls (i.e., patients were not evaluated during the same timeframe)
- PCT is not readily available at every hospital
Limitations cont’d

- **Multiple interventions** and therefore not possible to determine which, if any, are associated with improved outcome
- **60% of patients** in the control group were treated with **corticosteroids**
- **Details** are provided for the underlying reason for death (including advanced dementia, severe heart failure, advanced sarcoidosis and severe COPD) but not for the control group
Discussion:

- **Sepsis related death**

  No patients in the treatment group died from complications related to sepsis, rather their mortality was secondary to complications of their underlying disease.
• **PCT**

  PCT typically decreases in a linear fashion in patients with severe sepsis (sepsis?) and septic shock, reaching about 30% of their baseline value within 72 hours.

  • A fall greater than 30% over 72 hours usually indicates improved survival
Discussion cont’d

• **Synergistic effects:**

  • Combination of
    - Vitamin C
    - Thiamine and
    - Hydrocortisone

  ↓ Vaso-plegic shock
  ↓ Vasopressor duration
Discussion cont’d

• **Vit C dose**

  The exact dosing strategy for Vitamin C is unknown, as it is not been well studied.

  The authors conclude that up to 6 grams daily should be enough without running the risk of conversion to oxalate and potentially causing worsening renal impairment from oxalate crystal formation and renal deposition.
The Bottom Line

- This study is hypothesis generating.
- An RCT is required to determine the efficacy of vitamin C, steroids and thiamine in severe sepsis and septic shock.
Are there potential harms?

Vitamin C

- calcium oxalate nephropathy
- pro-oxidant effect
Are there potential harms?

- **Calcium oxalate nephropathy**
  - Dose-dependent toxicity
  - Higher doses >40 grams/day; 
    - *(Buehner 2016)*
  - Concurrent use of thiamine should reduce the conversion of vitamin C into oxalate
Are there potential harms?

- pro-oxidant effect.
  - This was shown not to occur even at a dose of 7.5 grams IV daily (Muhlhofer 2004).
Are there potential harms?

Thiamine

- Thiamine: Rare reports of
  - hypersensitivity or
  - anaphylaxis,
  especially with repeated injections
Are there potential harms?

**Steroids**

- Steroids
  - HYPRESS Trial
  - CORTICUS Trial
  - Annane Trial
  - The VANISH trial
  - The ADRENAL trial
Journal Name: *Journal of the American Medical Association*.

**Study Title:** "Effect of hydrocortisone on development of shock among patients with severe sepsis"

**Authors:** Keh D, et al, 2016

**Study type:** number: N=380

- Multicenter, placebo-controlled, double-blind RCT
- Setting: 34 sites in Germany
- Enrollment: January 13, 2009 to August 27, 2013

**Methodology:**
- IV hydrocortisone (n=190)
- Placebo (n=190)
Results: Conclusion / Recommendation:

Subgroup Analysis

There was no significant difference regarding the primary and secondary end points between those with and without relative adrenal insufficiency who received hydrocortisone versus placebo.

Adverse Events

- **Secondary infection**: 40 (21.5%) vs. 32 (16.9%) (P=0.26)
- **Hyperglycaemia**: 169 (90.9%) vs. 154 (81.5%) (P=0.009)

**Study Title**: "Hydrocortisone therapy for patients with septic shock"

**Authors**: Sprung CL, et al

**Study type: number:**
- N=499
- Multicenter, double-blind, parallel-group, randomized, placebo-controlled trial

**Methodology**:
- N=499
  - Hydrocortisone (n=251)
  - Placebo (n=248)

Mean follow-up: 28 days
CORTICUS

• Adverse Events
• New sepsis or septic shock OR 1.37; 95% CI 1.05-1.79; NNH 26
• New shock 6% vs. 2%
  (OR 2.78; 95% CI 1.02-7.58; NNH 25)
• Hyperglycemia 85% vs. 72%
  (OR 1.18; 95% CI 1.07-1.31; NNH 8)
• Hypernatremia 29% vs. 18%
  (OR 1.59; 95% CI 1.13-2.22; NNH 9)
Journal Name: *Journal of the American Medical Association.*

**Study Title:** "Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock"

**Authors:** Annane D, et al, 2010

**Annane Trial**

- **Study type: number:** N=300
- Randomized, prospective, double-blind, parallel-group, placebo-controlled trial
- **Sites:** 19 French ICUs
- **Timeline:** 1995-1999

**Methodology:**

- **N=300 patients with septic shock**
  - Corticosteroids (n=151)
  - Placebo (n=149)
Annane Trial

- Adverse Events
  
  There was no difference in the rate of adverse events between the placebo and steroid groups except for a higher rate of surgical wound infection in the placebo group.
Study Title: Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients With Septic Shock

The VANISH Randomized Clinical Trial

Authors: Gordon et al. 2016

- Study type: number: N=400
- Factorial (2×2) multicentre, double blind, RCT
- 18 adult general ICU’s
- February 2013 – May 2015

Methodology:

Patients were randomly allocated to
- vasopressin (titrated up to 0.06 U/min) and hydrocortisone (n = 101),
- vasopressin and placebo (n = 104),
- norepinephrine and hydrocortisone (n = 101), or
- norepinephrine and placebo (n = 103).
VANISH

• Serious adverse events (including digital or mesenteric ischaemia, life-threatening arrhythmia and acute coronary syndrome)
  10.7% in the vasopressin group
  vs
  8.3% in the norepinephrine group;
  difference, 2.5% [95% CI, −3.3% to 8.2%]

• No difference in renal failure –free days

• No difference in mortality
Are there potential harms?

All 3 studies, plus VANISH Trial, showed no mortality increase with steroids.
Journal Name: Estimated Study Completion Date: December 30, 2017

Study Title: ADjunctive coRticosteroid trEatment iN criticAlly iL Patients With Septic Shock (ADRENAL)

Authors: Balasubramanian Venkatesh

- Study type: number: 3800 patients
- a multi-centre, randomised, blinded, placebo controlled trial
- 70 Intensive Care Units recruitment completed.
- Follow up of patients continue.
- Methodology:
  - Eligible patients will be randomised to receive either intravenous hydrocortisone 200mg or placebo per day for seven days.
AN APPROACH TO STEROIDS IN SEPTIC SHOCK

• don’t use in low risk patients
• consider in high risk patients (multi-organ failure) acknowledging that septic shock may reverse more quickly but will not change mortality
• use low dose
• vigilance for super infection
• don’t use a short synACTHem test
• eagerly await the ADRENAL study
Costs

• **IV Vitamin C:**
  ~£ 66 - 196 for 4-day course (drug only)

• **IV Thiamine:**
  ~£ 35 for 4-day course (drug only)

• **Hydrocortisone:**
  ~£60 (drug only)
Implementation Options: A Proposal

- **Patients with Refractory Septic Shock**
  - Already receiving steroids
  - No predicted harm from adding Vitamin C and thiamine
  Reasonable to endorse use in this group

- **Sepsis and Non Refractory Septic Shock**
  - These patients would not otherwise receive steroids per SSC Guidelines
  - Inadequate Evidence-Based literature to justify endorsement
  - Therefore, leave to individual practitioners to choose
Author Conclusion:

- “Our results suggest that the early use of intravenous vitamin C, together with corticosteroids and thiamine may prove to be effective in preventing progressive organ dysfunction including AKI and reducing the mortality of patients with severe sepsis and septic shock.
- Additional studies are required to confirm these preliminary findings.”
Clinical Take Home Point:

• Although the results of this study are very promising, it is important to remember that this was only a hypothesis generating study. We still need an external validation before implementation (How many other treatments in sepsis have been touted as a “cure” and not panned out in subsequent studies?).
References


Br J Anaesth, 81 (3) (1998), pp. 468-470, ArticlePDF (122KB)


[38] V. Yawalkar, M.K. Parashar, J. Punekar *Role of red cell distribution width as a prognostic marker in patients with severe sepsis and septic shock* J Assoc Physicians India, 64 (1) (2016), p. 120


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