Vitamin C in sepsis

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It is about feelings not facts
30 studies in clinicaltrials.gov

- **ORANGES** (140 participants, US) Fowler AA
  - ESICM 2019
- **HYVCTTSSS** China (80 participants)
  - Vitamin C (1.5 g every 6 h for 4 days or until ICU discharge), hydrocortisone (50 mg every 6 h for 7 days or until ICU discharge followed by a taper over 3 days), as well as intravenous thiamine (200 mg every 12 h for 4 days or until ICU discharge).
  - Completed January 2019
- **NCT02734147** USA (20 participants) 67 mg/kg every 8 hours for 28 days
  - Completed 2017
- **VICTAS** USA (2000 participants)
  - Intravenous vitamin C (1.5 grams every 6 hours) for 4 days or until ICU discharge.
  - Intravenous thiamine (100 mg every 6 hours) for 4 days or until ICU discharge.
  - Intravenous hydrocortisone (50 mg every 6 hours) for 4 days or until ICU discharge.
- **NCT01590303** Canada (20 participants) 1 gram every 8 hours for 28 days
  - Completed 2012
- **LOVIT** Canada (800 participants) 50 mg/kg every 6 hours for 4 days
- **CITRIS-ALI** USA (170 participants) 50mg/kg/day every 6 hours for 4 days.
  - Completed January 2018
- **NCT03592277** USA (120 participants)
  - Intravenous vitamin C (1.5 grams every 6 hours) for 4 days or until ICU discharge.
  - Intravenous thiamine (200 mg every 12 hours) for 4 days or until ICU discharge.
- **ACTS** NCT03389555 USA (200 participants)
  - Intravenous vitamin C (1.5 grams every 6 hours) for 4 days or until ICU discharge.
  - Intravenous thiamine (100 mg every 6 hours) for 4 days or until ICU discharge.
  - Intravenous hydrocortisone (50 mg every 6 hours) for 4 days or until ICU discharge.
- + more RCTs (Korea, Mexico, Greece, Netherlands, Egypt,
Vitamin C

• Cofactor for redox reactions
• Deficiency within 4 weeks if body contents decrease below 300 mg
  • 10 mg / day reverses scurvy
• Low toxicity: LD$_{50}$ 15 g/kg
• Water soluble but enters cells
• Low levels in sepsis patients

Pemberton J. Int J Epidemiol. 2006
Toxnet: L-ascorbic acid
Marik PE. Pharmacol Ther. 2018
Radicals
Healthy volunteers

SIRS (Burn)

Severe sepsis

Septic shock

Healthy Vol  Day 1  Day 2  Day 3  Day 5-6

Plasma H$_2$O$_2$ (µmol/L)

Vitamin C – Apart from curing common cold, cancer and HIV...

• Biochemical effects
  • Antioxidant – limits mitochondrial oxidative stress caused cell injury
  • Antioxidant recycler
  • Inhibits iNOS activation
  • Noradrenalin synthesis

• Cellular effects
  • Limits endothelial leak
  • Improved vasopressor response
  • Macrophage activation
  • Collagen synthesis
  • Decreases bacterial growth

• Circulatory effects
  • Restored macrocirculation in sepsis models
  • Improved microcirculation

• ...

### Study or Subgroup

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Experimental Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2.1.1 Higher methodological quality</strong></td>
<td></td>
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<tr>
<td>Beale 2008</td>
<td>7</td>
<td>27</td>
<td>7</td>
<td>26</td>
<td>9.8%</td>
<td>0.95 [0.28, 3.22]</td>
</tr>
<tr>
<td>Berger 2008</td>
<td>14</td>
<td>102</td>
<td>9</td>
<td>98</td>
<td>13.4%</td>
<td>1.57 [0.65, 3.82]</td>
</tr>
<tr>
<td>van Zanten 2014</td>
<td>38</td>
<td>152</td>
<td>33</td>
<td>149</td>
<td>18.1%</td>
<td>1.17 [0.69, 2.00]</td>
</tr>
<tr>
<td>Zabet 2016</td>
<td>2</td>
<td>14</td>
<td>9</td>
<td>14</td>
<td>5.6%</td>
<td>0.09 [0.01, 0.59]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>295</td>
<td>287</td>
<td></td>
<td></td>
<td>46.9%</td>
<td>0.88 [0.40, 1.94]</td>
</tr>
</tbody>
</table>

**Total events** 61 58

Heterogeneity: $\tau^2 = 0.37$; $X^2 = 7.60$, df = 3 ($P = 0.06$); $I^2 = 61$

Test for overall effect: $Z = 0.33$ ($P = 0.74$)

### 2.1.2 Lower-quality trials

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Experimental Total</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Crimi 2004</td>
<td>49</td>
<td>112</td>
<td>76</td>
<td>112</td>
<td>17.9%</td>
<td>0.37 [0.21, 0.64]</td>
</tr>
<tr>
<td>Fowler 2014</td>
<td>7</td>
<td>16</td>
<td>5</td>
<td>8</td>
<td>6.2%</td>
<td>0.47 [0.08, 2.66]</td>
</tr>
<tr>
<td>Nathens 2002</td>
<td>5</td>
<td>301</td>
<td>9</td>
<td>294</td>
<td>10.9%</td>
<td>0.53 [0.18, 1.62]</td>
</tr>
<tr>
<td>Preiser 2000</td>
<td>8</td>
<td>20</td>
<td>6</td>
<td>17</td>
<td>8.8%</td>
<td>1.22 [0.32, 4.66]</td>
</tr>
<tr>
<td>Schneider 2011</td>
<td>6</td>
<td>29</td>
<td>6</td>
<td>29</td>
<td>9.3%</td>
<td>1.00 [0.28, 3.56]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>478</td>
<td>460</td>
<td></td>
<td></td>
<td>53.1%</td>
<td>0.50 [0.32, 0.77]</td>
</tr>
</tbody>
</table>

**Total events** 75 102

Heterogeneity: $\tau^2 = 0.01$; $X^2 = 4.08$, df = 4 ($P = 0.39$); $I^2 = 2$

Test for overall effect: $Z = 3.16$ ($P = 0.002$)

**Total (95% CI)** 773 747 100.0% 0.72 [0.43, 1.20]

**Total events** 136 160

Heterogeneity: $\tau^2 = 0.30$; $X^2 = 18.27$, df = 8 ($P = 0.02$); $I^2 = 56$

Test for overall effect: $Z = 1.26$ ($P = 0.21$)

Test for subgroup differences: $X^2 = 1.48$, df = 1 ($P = 0.22$), $I^2 = 32.6$
Is Vitamin C dangerous?

• It could be pro-oxidant
• Oxidant recycler at high doses
• 500 mg per day for 6 weeks gives DNA damage
• 6 g for weeks gives nausea, vomiting, diarrhea, flushing, headache, fatigue, and disturbed sleep.
• 2 g Vitamin C prior to vascular surgery increased concentrations of ascorbate radical and lipid hydroperoxides
• Who wants kidney stones – the oxalate issue
Would you buy this drug?

• Consider to give Substance E300 to your patients
• There is
  • Experimental data showing improved variables in sepsis models
  • Experimental data showing harm at high doses
  • Small studies suggest better outcome
• Would you start giving E300 to your patients?
Would you buy this drug?

• Consider to give Substance E300 to your patients
• There is
  • Experimental data showing improved variables in sepsis models
  • Experimental data showing harm at high doses
  • Small studies suggest better outcome
• Would you start giving E300 to your patients?
The scientific approach
L-Ascorbic acid $\xrightarrow{e^-, H^+} \text{Monodehydro-L-ascorbic acid} \xrightarrow{e^-, H^+} \text{Dehydro-L-ascorbic acid}$

Oxalic acid $\xrightarrow{\text{2,3-Dioxo-L-gulonic acid}}$

Stable molecule (stable molecule) \hspace{1cm} Free radical (unstable molecule) \hspace{1cm} Antioxidant

unpaired electron