IV Vitamin C as an adjunctive treatment for COVID19 patients is promising and based on literature on the use of IV vitamin C for patients with sepsis. However, the evidence is not conclusive and inconsistencies may result from differences in patient populations studied, doses administered and concurrent use of thiamin as well as a variety of medications, including steroids.

Based on the brief literature review below, possible inclusion of micronutrient supplement for a COVID19 treatment plan is suggested for recommendation.

- 1.5 g of IV ascorbic acid every 6 hours until ICU discharge
  - when high dose vitamin C provided need lab glucose values as Accu-check POC glucose levels will be spuriously high
- 200 mg of thiamin every 12 hours until ICU discharge
- Standard IV multivitamin with minerals as most patients are not meeting nutrient needs via po diet nor from tube feedings (patients tend not to tolerate rate that meets needs); this is especially important to meet micronutrient needs, such as copper when giving zinc supplementation with hydroxychloroquine.

**Background information**: IV ascorbic acid doses commonly studied and resulting dosing by weight are shown in the table below for reference (associated total daily dose and quantity if dosed 4 times a day); literature supports minimum of 50 mg/kg/day of IV ascorbic acid divided in 4 doses; 200 mg/kg/day may be associated with excess oxalate production.

<table>
<thead>
<tr>
<th>wt lbs</th>
<th>wt kg</th>
<th>30 mg/kg/day total and by QID dose</th>
<th>50 mg/kg/day total and by QID dose</th>
<th>100 mg/kg/day total and by QID dose</th>
<th>200 mg/kg/day total and by QID dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>120</td>
<td>54.5</td>
<td>1.6</td>
<td>0.4</td>
<td>2.7</td>
<td>0.7</td>
</tr>
<tr>
<td>130</td>
<td>59.1</td>
<td>1.8</td>
<td>0.4</td>
<td>3.0</td>
<td>0.7</td>
</tr>
<tr>
<td>140</td>
<td>63.6</td>
<td>1.9</td>
<td>0.5</td>
<td>3.2</td>
<td>0.8</td>
</tr>
<tr>
<td>150</td>
<td>68.2</td>
<td>2.0</td>
<td>0.5</td>
<td>3.4</td>
<td>0.9</td>
</tr>
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<td>160</td>
<td>72.7</td>
<td>2.2</td>
<td>0.5</td>
<td>3.6</td>
<td>0.9</td>
</tr>
<tr>
<td>170</td>
<td>77.3</td>
<td>2.3</td>
<td>0.6</td>
<td>3.9</td>
<td>1.0</td>
</tr>
<tr>
<td>180</td>
<td>81.8</td>
<td>2.5</td>
<td>0.6</td>
<td>4.1</td>
<td>1.0</td>
</tr>
<tr>
<td>190</td>
<td>86.4</td>
<td>2.6</td>
<td>0.6</td>
<td>4.3</td>
<td>1.1</td>
</tr>
<tr>
<td>200</td>
<td>90.9</td>
<td>2.7</td>
<td>0.7</td>
<td>4.5</td>
<td>1.1</td>
</tr>
</tbody>
</table>

**Proposed Mechanisms:**

**Vitamin C**

- Antioxidant – scavenges intracellular and mitochondrial free radicals
- Anti-inflammatory – inhibits activation of NFkB, prevents NETosis
- Immune support – supports neutrophil chemotaxis and bacteriocidal action
- Anti-thrombotic – decreases platelet activation, increases thrombomodulin
- Microcirculation – increases endothelial NOS and decreases inducible NOS (inducible); preserves tight junctions
- Support for synergistic effect of steroids and vitamin C: “Oxidation of cysteine thiol groups of the glucocorticoid receptor affects ligand and DNA binding, reducing the efficacy of glucocorticoids. Vitamin C has been demonstrated to reverse these changes and restore glucocorticoid function. The transport of vitamin C into the cell is mediated by the sodium-
vitamin C transporter-2 (SVCT2). Proinflammatory cytokines have been demonstrated to decrease expression of SVCT2.” (Marik, Chest. 2017; 151((6):p1235)

Thiamine

- With high dose vitamin C there can be in increased conversion to glyoxylate and subsequently to oxalate, which leads to a concern for a negative impact on kidney function. Thiamine pyrophosphate is a coenzyme for glyoxylate aminotransferase, and thiamine availability can drive conversion of glyoxylate away from oxalate to glycine.

- Precursor of thiamine pyrophosphate which is a coenzyme for several decarboxylases necessary for the Krebs cycle and pentose phosphate pathway; thereby supports production of ATP and NADPH

4 studies supporting a positive impact of IV ascorbic acid (especially with thiamine) and 1 study indicating no impact are summarized below with key findings; at doses up to 100 mg/kg/day or less no negative effects have been identified.


- Study on pharmacokinetics (2 g/day or 10 g/day in either 2 boluses/day or continuous over 24 hr/day) n=20 patients with severe sepsis or after major trauma or surgery with a SOFA score>6 and expected ICU stay >96hrs; 5 subjects per dosing strategy; randomized)
  - 2 g IV dose (either continuous over 24 hours or twice daily boluses) required to normalize vitamin C levels in patients who are critically ill
  - 10 g IV dose led to supra-normal plasma concentrations >1,000 mmol/l; considered optimal for fast cellular uptake and increased radical scavenging
  - Bolus doses associated with highest concentrations within 1 hour followed by troughs that with the 2 g dose led to plasma concentrations that approached the hypovitaminosis cutoff
o Twelve-hour oxalate excretion was higher in the 10 g/d dose compared with the 2 g/d dose and in the last (36-48 h) sampling period compared with the first (0-12 h) sampling period.
o Found a varying decline in plasma concentrations across all groups 48 h after the end of therapy (96 h),
o In all, the findings indicate that supplementation > 48 h is needed to maintain plasma concentrations in the normal range, possibly as long as patients remain critically ill.

- Phase I safety trial of IV ascorbic acid in patients with severe sepsis (randomized, double-blinded placebo-controlled; n=26 patients with severe sepsis (systemic inflammation, suspected or proven infection and presence of sepsis-induced organ dysfunction)
o Intervention
  - Placebo: 5% dextrose and water
  - Low dose ascorbic acid (Lo-AscA): 50 mg/kg/24 hours; 4 equal doses administered over 30 minutes every 6 hours
  - High dose ascorbic acid (HiAscA): 200 mg/kg/24 hours; 4 equal doses administered over 30 minutes every 6 hours
- Measured C-reactive protein and procalcitonin as systemic markers of inflammation and thrombomodulin as a marker of vascular injury
Following normalization of the daily SOFA scores, patients treated with either dose of ascorbic acid exhibited descending SOFA scores over the 4-day study period (p < 0.05, slopes significantly non-zero). High dose ascorbic acid patients exhibited significantly faster declines in the regression slopes of delta daily total SOFA scores over time compared to placebo (−0.043 vs. 0.003, p < 0.01).

Serum CRP trended slowly down over the 96 hour period in the placebo group. Patients receiving ascorbic acid exhibited rapid reductions.
PCT levels trended higher in placebo infused patients 24 hours following the onset of sepsis though not reaching statistical significance. Serum PCT levels in patients receiving high dose ascorbic acid declined, becoming significantly lower than baseline by 48 hours (Figure 3B, p < 0.05) and continued to decline over the 96 hr period.

- Plasma TM levels not significantly different however ascorbic acid treated patients did not exhibit the upward trend in TM levels observed in placebo-infused patients.
- No patients were withdrawn due to study-related adverse events.

- Study exploring high dose IV vitamin C on vasopressor requirements in patients in septic shock; n=28 (septic patients requiring vasopressor to maintain mean arterial pressure >65 mm Hg)
  - Intervention (n=14) – 25 mg/kg IV ascorbic acid q 6 hrs for 72 hours (n=14); max dose used in study was 3 g/day
  - Placebo n=14

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Ascorbic acid group (n=14)</th>
<th>Control group (n=14)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean dose of norepinephrine (mcg/min) during the study period (72 h)</td>
<td>7.44±3.65</td>
<td>13.79±6.48</td>
<td>0.004</td>
</tr>
<tr>
<td>Mean dose of norepinephrine (mcg/min) during first 24 h (mcg/min)</td>
<td>6.51±3.53</td>
<td>12.58±5.99</td>
<td>0.003</td>
</tr>
<tr>
<td>Total dose of norepinephrine during the first 24 h (mcg)</td>
<td>156.42±84.81</td>
<td>302.14±143.85</td>
<td>0.003</td>
</tr>
<tr>
<td>Duration of norepinephrine administration (h)</td>
<td>49.64±25.67</td>
<td>71.57±1.60</td>
<td>0.007</td>
</tr>
<tr>
<td>Length of ICU stay (days)</td>
<td>21.45±10.28</td>
<td>20.57±13.04</td>
<td>0.85</td>
</tr>
<tr>
<td>28-day mortality</td>
<td>2 (14.28)</td>
<td>9 (64.28)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

- Outcomes – significantly less norepi needed and significantly lower 28 day mortality
- No adverse events identified in treatment group

- A retrospective observational study, before and after implementing a protocol with hydrocortisone (50 mg q 6 hrs for 7 days or until ICU discharge; then taper down), vitamin C (1.5 g q 6 hrs infused over 30-60 minutes for 4 days or until ICU discharge) and thiamine (200 mg q 12 hrs for 4 days or until ICU discharge); prior to this protocol patient care included hydrocortisone at the physician’s discretion (50 mg q 6 hrs) an no vitamin C or thiamine; n=94 patients with severe sepsis (PCT>2ng/mL) with 47 in each group (in control group 55% vented; 47% met criteria for septic shock; treatment group 47% vented; 47% met criteria for septic shock)
Early use of IV ascorbic acid with thiamin and moderate-dose hydrocortisone may prevent progressive organ dysfunction, including acute kidney injury, and reduce mortality among patients with severe sepsis.

5) **No Impact – Fowler et al. JAMA. 2019; 322(13):1261.**

- A randomized, placebo-controlled, multicenter trial exploring effect of vitamin C on organ failure scores and inflammatory markers among patients with sepsis and ARDS
- Intervention (n=84) – **50mg/kg IV ascorbic acid every 6 hours** for 96 hours; for 180 patient this equals 16 g/day; (placebo n=83)
- There were no significant differences in SOFA scores, CRP or thrombomodulin
In exploratory analysis 43 of 46 secondary outcomes were not significantly different; in these analyses the vitamin C group did have a significantly lower 28 day mortality rate and greater number of ICU free days to day 28 free days (10.7 vs 7.7 (mean difference, 3.2; 95% CI, 0.3 to 5.9; P = .03).
Authors note their results are discordant with previous studies, which supported the role of Vitamin C to prevent sepsis-induces cytokine surges and activate and sequester neutrophils in the lung causing organ damage and vascular damage.

My note –
  - Dose quite high; potential action as a pro-oxidant especially not in presence of other antioxidants is a concern
    - If 180 lbs about 4 grams * 4 doses – 16 grams per day