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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 co-current 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.

- o 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*
- o 200 mg of thiamin every 12 hours until ICU discharge
- o 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.

Vitamin C Dosing Studied									
		30 mg/kg/day total and by QID dose		50 mg/kg/day total and by QID		100 mg/kg/day total and by QID dose		200 mg/kg/day total and by QID dose	
wt lbs	wt kg	g/day	g/dose	g/day	g/dose	g/day	g/dose	g/day	g/dose
120	54.5	1.6	0.4	2.7	0.7	5.5	1.4	10.9	2.7
130	59.1	1.8	0.4	3.0	0.7	5.9	1.5	11.8	3.0
140	63.6	1.9	0.5	3.2	0.8	6.4	1.6	12.7	3.2
150	68.2	2.0	0.5	3.4	0.9	6.8	1.7	13.6	3.4
160	72.7	2.2	0.5	3.6	0.9	7.3	1.8	14.5	3.6
170	77.3	2.3	0.6	3.9	1.0	7.7	1.9	15.5	3.9
180	81.8	2.5	0.6	4.1	1.0	8.2	2.0	16.4	4.1
190	86.4	2.6	0.6	4.3	1.1	8.6	2.2	17.3	4.3
200	90.9	2.7	0.7	4.5	1.1	9.1	2.3	18.2	4.5

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.

1) De Grooth et al. Chest. 2018; 153(6):1368-1377.

- 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
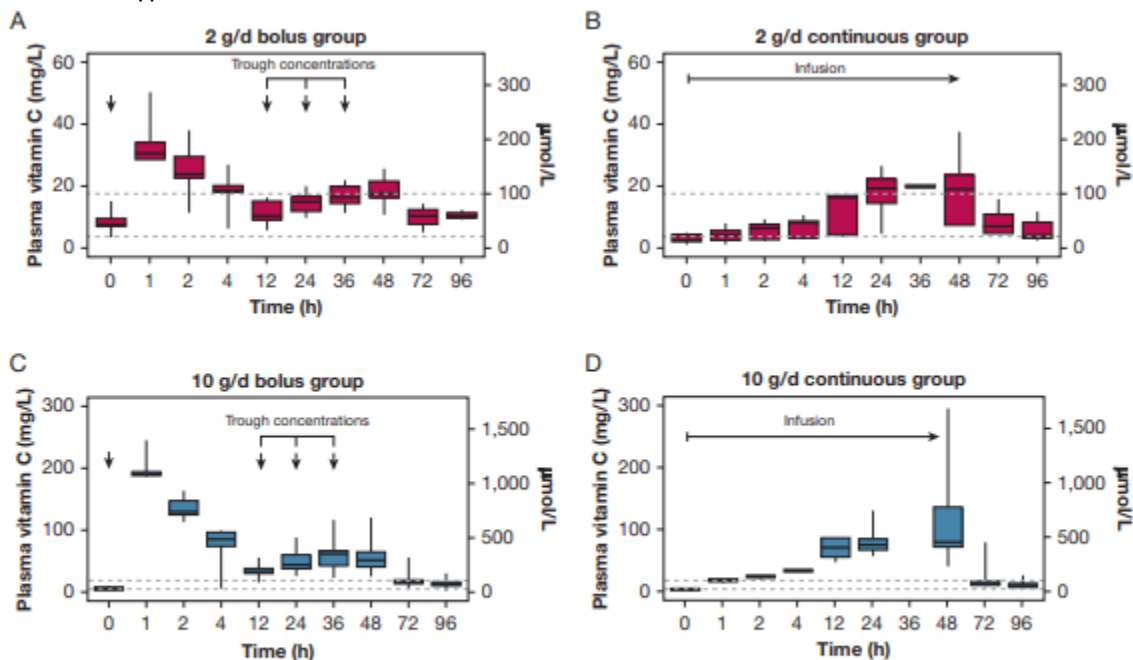

Figure 2 – A-D, Vitamin C plasma concentrations by dosage regimen (five patients per regimen): (A) 2 g/d bolus group, (B) 2 g/d continuous group, (C) 10 g/d bolus group, and (D) 10 g/d continuous group. Arrows represent infusions (four times bolus or 48-h continuous). The dashed lines represent the lower and upper limit of normal vitamin C plasma concentrations at 3.7 mg/L (21 μmol/L) to 17.6 mg/L (100 μmol/L). Plasma vitamin C was not sampled at 36 h in the continuous groups.
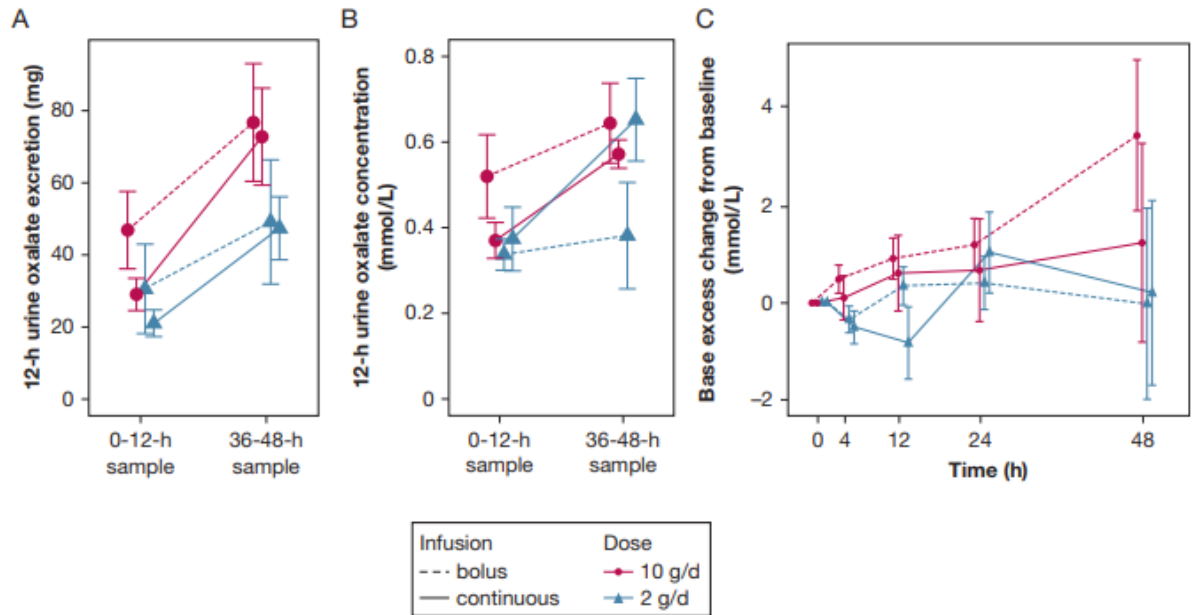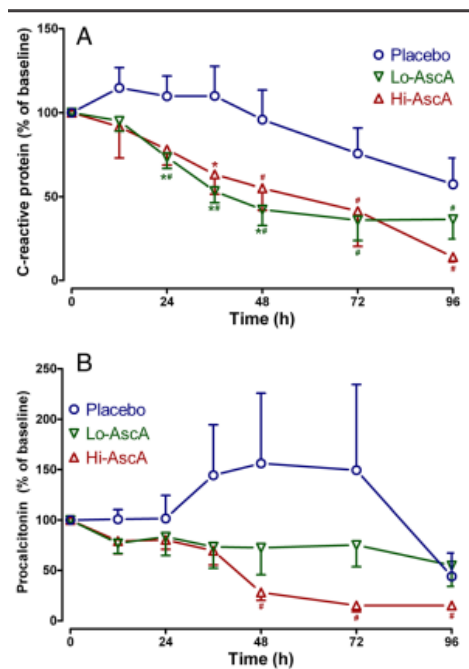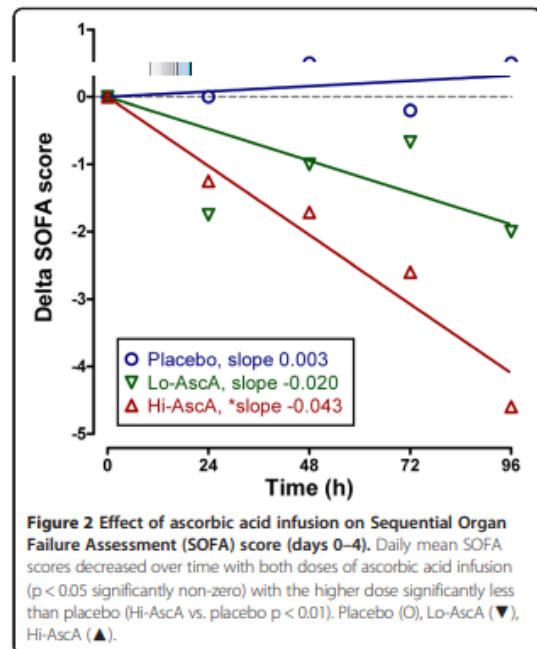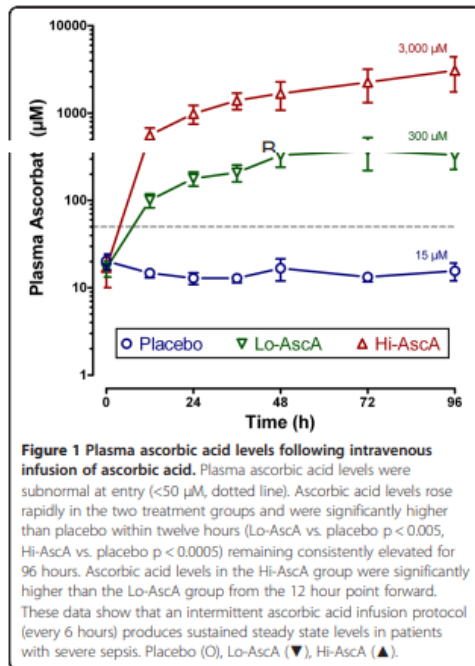
Figure 4 – A-C, Safety end points by intervention group; data points represent mean and SE. A, Urine 12-h oxalate excretion. Twelve-hour oxalate excretion was independently higher in the 10 g/d dose compared with the 2 g/d dose (b = 18.2 mg; 95% CI, 2.65-33.7 mg; P = .023) and in the last (36-48 h) sampling period compared with the first (0-12 h) sampling period (b = 30.2 mg; 95% CI, 14.6-45.7 mg; P = .0004), but not in bolus compared with continuous infusion (b = 9.45 mg; 95% CI, −6.1 to 25.0 mg; P = .224). B, 12-h urine oxalate concentration. C, Change in arterial base excess from baseline. In a linear model, the slope of the change in arterial base excess from 0 to 48 h was associated with the 10 g/d dose (0.047 mmol/h compared with 2 g/d dose, P = .0002), but not with the infusion method.

- 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.

2) **Fowler, et al. J of Translational Med. 2014; 12:32**
   - Phase I safety trial of IV ascorbic acid in patients with severe sepsis (randomized, double-blineded 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
     - o Measured C-reactive protein and procalcitonin as systemic markers of inflammation and thrombomodulin as a marker of vascular injury

Figure 1 Plasma ascorbic acid levels following intravenous infusion of ascorbic acid. Plasma ascorbic acid levels were subnormal at entry (<50 μM, dotted line). Ascorbic acid levels rose rapidly in the two treatment groups and were significantly higher than placebo within twelve hours (Lo-AscA vs. placebo p < 0.005, Hi-AscA vs. placebo p < 0.0005) remaining consistently elevated for 96 hours. Ascorbic acid levels in the Hi-AscA group were significantly higher than the Lo-AscA group from the 12 hour point forward. These data show that an intermittent ascorbic acid infusion protocol (every 6 hours) produces sustained steady state levels in patients with severe sepsis. Placebo (O), Lo-AscA (▼), Hi-AscA (▲).

Figure 2 Effect of ascorbic acid infusion on Sequential Organ Failure Assessment (SOFA) score (days 0–4). Daily mean SOFA scores decreased over time with both doses of ascorbic acid infusion (p < 0.05 significantly non-zero) with the higher dose significantly less than placebo (Hi-AscA vs. placebo p < 0.01). Placebo (O), Lo-AscA (▼), Hi-AscA (▲).

Figure 3 Serum C-reactive protein (CRP) and procalcitonin levels in septic placebo controls and ascorbic acid infused patients. (A) Both the Lo-AscA and the Hi-AscA dosages produced rapid reductions in serum CRP levels, becoming significantly lower than placebo (*p < 0.05 vs placebo) as early as 24 hours. Ascorbic acid infusion reduced CRP levels in both groups throughout the 4 study days (#p < 0.05 vs 0 hr). CRP levels in placebo patients slowly fell over the course of the 4 day study period. (B) Patients in the Lo-AscA and Hi-AscA groups exhibited reduced serum PCT levels beginning at 12 hours. Patients in the Hi-VitC group exhibited further significant reduction in serum PCT between 36 to 48 hours (#p < 0.05 vs 0 hr). Placebo patients exhibited a trend towards increased PCT levels which declined starting at 72 hours post onset of sepsis. Placebo (O), Lo-AscA (▼), Hi-AscA (▲).

- o 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)
- o 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

3) **Zabet et al. J of Research in Pharmacy Practice. 2016; 188(24):116.**
   - 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 4: Primary and secondary outcomes of the study in ascorbic and placebo groups

Characteristics	Ascorbic acid group (n=14)	Control group (n=14)	P
Mean dose of norepinephrine (mcg/min) during the study period (72 h)	7.44±3.65	13.79±6.48	0.004
Mean dose of norepinephrine (mcg/min) during first 24 h (mcg/min)	6.51±3.53	12.58±5.99	0.003
Total dose of norepinephrine during the first 24 h (mcg)	156.42±84.81	302.14±143.85	0.003
Duration of norepinephrine administration (h)	49.64±25.67	71.57±1.60	0.007
Length of ICU stay (days)	21.45±10.23	20.57±13.04	0.85
28-day mortality	2 (14.28)	9 (64.28)	0.009

Data presented as mean±SD or n (%). SD=Standard deviation, ICU=Intensive Care Unit

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

4) **Marik, et al. Chest. 2017.; 151(6):1229.**
   - A retrospective observational study, before and after implementing a protocol with hdrocortisone (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)

TABLE 2] Outcome and Treatment Variables

Variable	Treated (n = 47)	Control (n = 47)
Hospital mortality, No. (%)	4 (8.5)	19 (40.4)[a]
ICU LOS, median and IQR, d	4 (3-5)	4 (4-10)
Duration of vasopressors, mean ± SD, h	18.3 ± 9.8	54.9 ± 28.4 [a]
RRT for AKI, No. (%)	3 of 31 (10%)	11 of 30 (33%)[b]
ΔSOFA, 72 h	4.8 ± 2.4	0.9 ± 2.7[a]
Procalcitonin clearance, median % and IQR, 72 h	86.4 (80.1-90.8)	33.9 (−62.4 to 64.3)[a]

AKI = acute kidney injury; LOS = length of stay; RRT = renal replacement therapy; ΔSOFA = change in Sepsis-Related Organ Failure Assessment score. See Table 1 legend for expansion of other abbreviations.
[a]$P < .001.$
[b]$P = .02.$

Figure 3 – Time course of the SOFA score over the 4-day treatment period in the treatment group and in the control group survivors and nonsurvivors. *P < .001 for comparison of treatment group vs control group (see text). SOFA = Sepsis-Related Organ Failure Assessment.
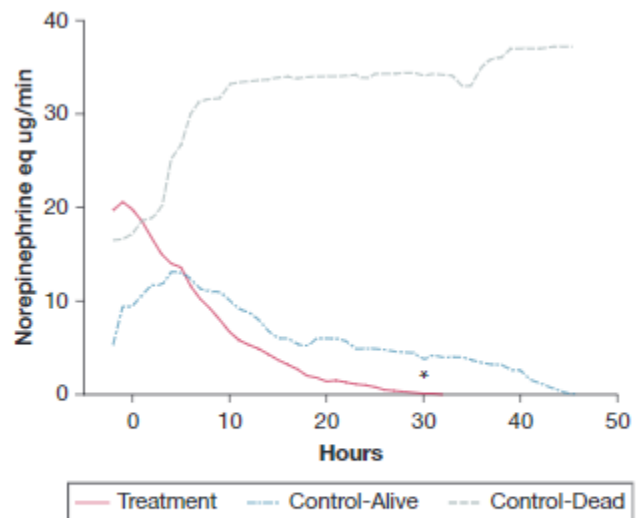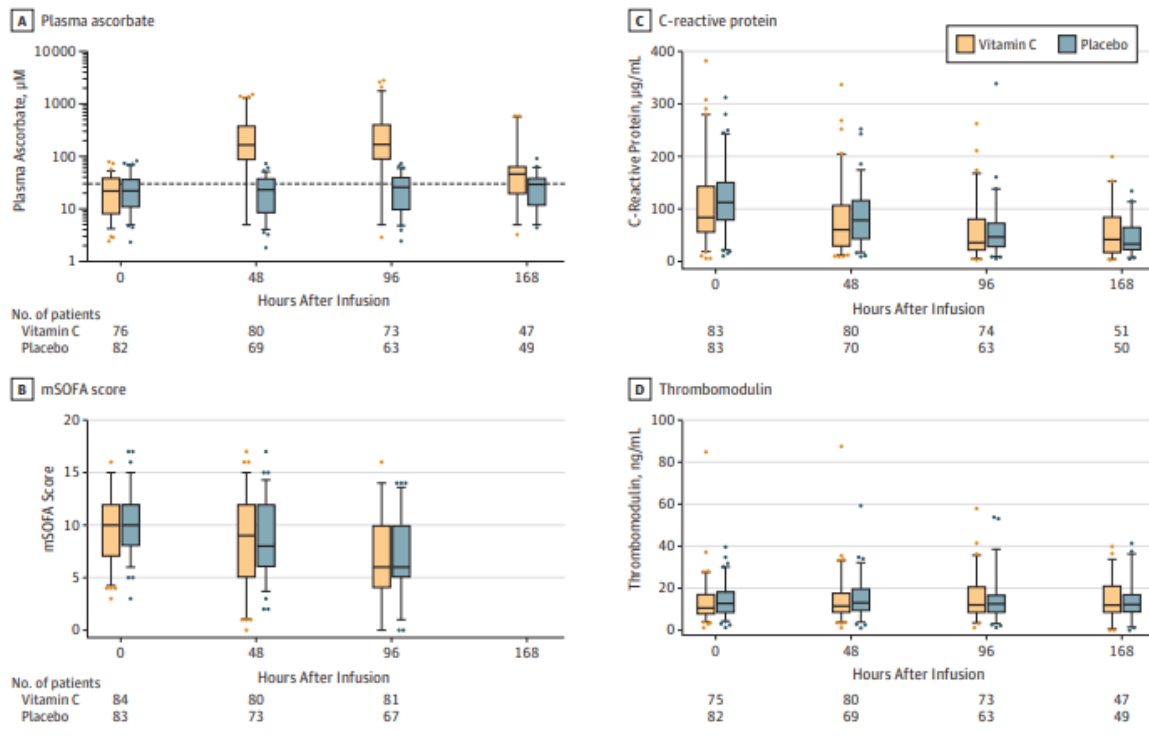

Figure 2 – Time course of vasopressor dose (in norepinephrine equivalents) in the treatment group and in the control group survivors and nonsurvivors. *P < .001 for comparison of treatment group vs control group (see text).

- 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

Figure 2. Plasma Ascorbate Concentrations, Modified Sequential Organ Failure Assessment Score, and Plasma Biomarkers

Median values are shown by the horizontal line inside the box, interquartile range (IQR) by the top and bottom of the boxes, 95% CI by the whiskers, and values were outside the 5th and 95th percentiles by circles. Box plots have been offset to avoid superimposition.

A, Plasma ascorbate levels at enrollment were marginally deficient (dotted line, <28 µM) in both groups. After initiation of treatment, plasma ascorbate levels were significantly greater in vitamin C patients compared with placebo patients (median at baseline, 22 vs 22 µM [IQR, 8-39 vs 11-37], $P = .68$). At 48 hours, median was 166 µM [IQR, 88-376] for vitamin C vs 23 µM for placebo [9-37], $P < .001$). At 96 hours, median was 169 µM [IQR, 87-412] for vitamin C vs 26 µM for placebo [9-41], $P < .001$). At 168 hours, median was 46 µM [IQR, 19-66] for
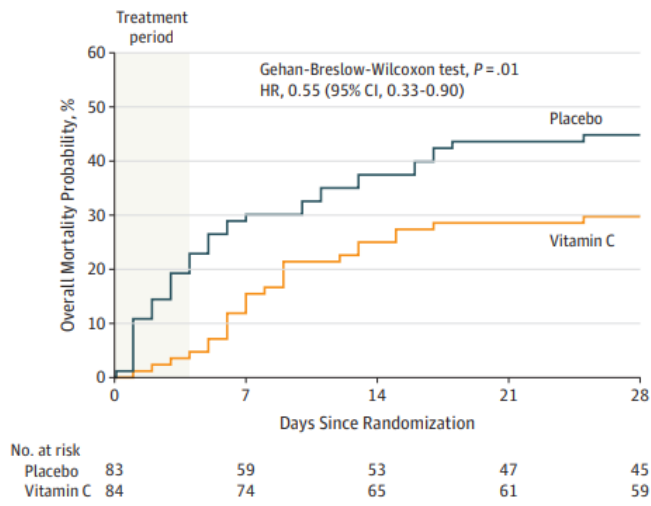
vitamin C vs 29 µM for placebo [12-39], $P < .002$). After cessation of vitamin C infusion, plasma levels in the vitamin C cohort decreased below 100 µM but remained significantly higher than plasma ascorbate levels in placebo patients.

B, There was no difference in the initial modified Sequential Organ Failure Assessment (mSOFA) scores of the 2 groups at baseline (vitamin C vs placebo, median, 10 [IQR, 7-12] vs 10 [8-12]). During the next 96 hours, mSOFA scores decreased but were not different between the 2 groups.

C and D, Plasma levels of C-reactive protein and thrombomodulin were measured at baseline and at 48, 96, and 168 hours. At no time were the levels of these significantly different between the 2 groups.

- 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).

Figure 3. All-Cause Mortality From Randomization (Day 0) to Day 28 Among Patients With Sepsis-Associated Acute Respiratory Distress Syndrome

Vitamin C–infused patients exhibited a significant reduction in 28-day all-cause mortality, although the *P* value was not adjusted for multiple comparisons. The median observation time was 28 days (interquartile range, 15-28 days) for the vitamin C group and 28 days (interquartile range, 5-28 days) for the placebo group.

- 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