EVMS Emergency Medicine Journal Club
Therapy Worksheet

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Citation: Fowler AA et al, Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients With Sepsis and Severe Acute Respiratory Failure: The CITRIS-ALI Randomized Clinical Trial JAMA. 2019 Oct 1;322(13):1261-1270.

Background: Despite advances in the evidence-based management of sepsis such as early identification. antibiotics, protective ventilator management, glycemic control and early hemodynamic support, mortality rates in patients with sepsis and septic shock remain high. Ascorbic acid was identified in the 1920's and since then proponents have advocated for its use as an adjunct in the management of clinical entities from the common cold to cancer management. In 2017, Marik et al, published a retrospective before-after study of (N=94) that demonstrated a major mortality benefit (ARR 31.9%), and no harms associated with the use of what has come to be known as the "Marik cocktail" which includes Vitamin C, hydrocortisone and thiamine. Since then three publications (Litwak, Mitchell,) with enrollments ranging from 94-167 patients have reported negative primary outcome measures. The VICTAS trial, a multicentered RCT intended to enroll up to 2000 patients and interim data from that investigation is pending publication.

Objective: ***"****To determine the effect of intravenous vitamin C infusion on organ failure scores and biological markers of inflammation and vascular injury in patients with sepsis and ARDS."*

Methodology

Design: "a randomized, double-blind, placebo-controlled, multicenter trial conducted in 7 medical intensive care units in the United States, enrolling patients (N = 167) with sepsis and ARDS present for less than 24 hours. The study was conducted from September 2014 to November 2017, and final follow-up was January 2018.

Inclusion criteria: They were included in CITRIS-ALI if they were undergoing mechanical ventilation through an endotracheal tube, had a PaO_2 to FiO_2 ratio less than 300 mm Hg, had bilateral opacities by chest radiography within 1 week of known clinical insult, had new or worsening respiratory symptoms without evidence of left atrial hypertension, had suspected or proven infection, and met 2 of 4 systemic inflammatory response criteria. All criteria had to be met within a 24-hour period.

Exclusion criteria: Patients were excluded if they had a known allergy to vitamin C; there was no ability to obtain informed consent; they were younger than 18 years, non-English speaking, or a ward of the state; more than 48 hours had elapsed since they met ARDS criteria (ie, informed consent was required to occur within 48 hours of the patients' meeting ARDS crite- ria); they did not have a patient surrogate or physician com- mitted to full support; they were pregnant or breastfeeding; they were moribund and not expected to survive 24 hours; they required home mechanical ventilation (via tracheos- tomy or noninvasively); they were receiving home oxygen greater than 2 L/min; or they had interstitial lung disease, diffuse alveolar hemorrhage, diabetic ketoacidosis, or an active kidney stone.

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Interventions: "Patients were randomly assigned to receive intravenous infusion of vitamin C (50mg/kg in dextrose 5%in water, n = 84) or placebo (dextrose 5%in water only, n = 83) every 6 hours for 96 hours."

Outcomes: Primary - modified Sequential Organ Failure Assessment (mSOFA) scores at 96 hours and plasma biomarker levels (C-reactive protein and thrombomodulin) at 168 hours. **Secondary** - There were 46 pre- specified secondary outcomes, including all-cause mortality at day 28, ventilator-free days to day 28, ICU-free days to day 28, and hospital-free days at day 60. At study hours 0, 48, 96, and 168 were oxygenation index (FiO_2 × mean airway pressure/PO_2) (if ventilated), VE-40 (minute ventilation, L/min) (vent RR [respiratory rate] × tidal volume/weight) × ($PaCO_2$/40) (if intubated), and SOFA score components (ie, PaO_2 to FiO_2 ratio, SpO_2 to FiO_2 ratio, platelet counts, total bilirubin, vasopressor use, Glasgow Coma Scale score, creati- nine level, and biomarkers [angiopoietin 2, procalcitonin, receptor for advanced glycation end products, tissue factor pathway inhibitor, and plasma ascorbate concentrations]).

	Comments
A. Are the results of the study valid? Answer questions below	
1. Were patients randomized?	Yes. 1:1 randomization using computer generated proprietary Research Randomizer
2. Was randomization concealed (Blinded)	Yes.
3. Were patients analyzed in the groups to which they were randomized?	Yes. NO explicit ITT statement though only 2 lost to f/u
4. Were patients in the treatment and control groups similar with respect to known prognostic factors?	Most reported baseline characteristics were the same. There was a difference in Thorax vs Abdomen as primary source of infection, with more thorax in Vit. C group (69% vs. 58%) and more abd in placebo group (16% vs.7%).
C. Did experimental and control groups retain a similar prognosis after the study started (answer the questions below)?	
1. Were patients aware of group allocation?	No.
2. Were clinicians aware of group allocation?	No.Blinding was maintained by the investigational pharmacy at each institution. Investigators were blinded from onset of enrollment to completed analysis of primary and secondary outcomes. Nursing infused the hooded study agent through light-protected tubing

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3. Were outcome assessors aware of group allocation?	No. As above
4. Was follow-up complete?	Yes. Only 2 lost to follow up.
D. What were the results?	
1. How large was the treatment effect? (difference between treatment and control group).	Primary outcomes: not significant. Secondary outcomes: In exploratory analyses that did not adjust for multiple comparisons, 3 or 46 secondary outcomes were significantly different between groups.
2. How precise was the estimated treatment effect at a 95% confidence interval?	Primary: The mean mSOFA score from baseline to 96 hours decreased from 9.8 to 6.8 in the vitamin C group (3 points) and from 10.3 to 6.8 in the placebo group (3.5 points) (difference, –0.10; 95% CI, –1.23 to 1.03; *P* = .86). There were no significant differences between the vitamin C group and placebo group in the C-reactive protein levels (54.1 vs 46.1 μg/mL; difference, 7.94; 95% CI, –8.23 to 24.1; *P* = .33) or thrombomodulin levels (14.5 vs 13.8 ng/mL; difference, 0.69; 95% CI, –2.8 to 4.2; *P* = .70) assessed at 168 hours. Secondary: Mortality was 46.3% (38/82) in the placebo group vs 29.8% (25/84) in the vitamin C group Absolute risk reduction(ARR) 16.58% [95% CI, 2% to 31.1%]) P = .03 The number of ICU-free days to day 28 was 10.7% in the vitamin C group vs 7.7% in the placebo group (ARR) 3.2%; [95%CI, 0.3 to 5.9]; P = .03 The number of hospital-free days in the vitamin C group vs the placebo group was 22.6% vs 15.5%, (ARR) 6.69% [95%CI,0.3 to13.8;] P = .04)
D. How can I apply the results to patient care	

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IV. Were the study patients similar to my patients?	The majority of their patients (75%) were caucasion which is non-representative of ours.
1. Were all clinically important outcomes considered?	Many of what I consider patient-centered clinically important outcomes were **secondary outcomes** and were actually found to be statistically significant in favor of Vitamin C. These include Mortality at day 28, The number of ICU-free days to day 28 and the number of hospital-free days.
2. Are the likely treatment benefits worth the potential harms and costs?	Possibly. I would be willing to pocket the expense of some vitamin C if it meant my loved one had less of a chance of dying. Plus, the decrease in ICU days more than pays for it.

Limitations:
1. CITRIS-ALI as proposed, was based on a previously performed phase 1 safety trial of vitamin C administered to patients in the very early stages of severe sepsis, not ARDS.

2. CITRIS-ALI enrollment required fully developed ARDS with endotracheal intubation, which could have delayed vitamin C administration in the treatment group and possibly limited the ability to detect an effect on mSOFA scores and biomarkers.

3. mSofa scores have limited external validity

4. CITRIS-ALI may have been underpowered to accurately detect a difference in mSOFA scores and biomarker levels. The authors make no mention whether the study was sufficiently powered to accurately detect differences in 46 secondary outcomes. Also secondary analysis did not adjust for multiple comparisons so statistical differences that were reported may be due to chance

5. Differences in baseline characteristics as well as unmeasured interventions in this heterogeneous population may have influenced mortality.

6. The dosage of vitamin C used in this trial (50 mg/kg every 6 hours for 96 hours) may be insufficient for optimal care of sepsis- associated ARDS. Higher vitamin C dosages or longer administration times may have produced different results.

7. Death and ICU graduation rates between the 2 groups were dissimilar, thus rendering the results susceptible to internal selection bias. The mortality data from this trial were intended for use in the design of future trials.

Clinical Bottom Line: In ICU patient with sepsis and ARDS, the primary outcomes of organ failure and systemic inflammation were not found to be significant but favorable differences in several secondary outcomes raise questions as to whether Vit. C makes a clinically significant difference in patient outcomes in ARDS and sepsis and awaits future large prospective trial results such as VICTAS