JAMA | Preliminary Communication | CARING FOR THE CRITICALLY ILL PATIENT

# 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

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**IMPORTANCE** Experimental data suggest that intravenous vitamin C may attenuate inflammation and vascular injury associated with sepsis and acute respiratory distress syndrome (ARDS).

**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.

**DESIGN, SETTING, AND PARTICIPANTS** The CITRIS-ALI trial was 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.

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

**MAIN OUTCOMES AND MEASURES** The primary outcomes were change in organ failure as assessed by a modified Sequential Organ Failure Assessment score (range, 0-20, with higher scores indicating more dysfunction) from baseline to 96 hours, and plasma biomarkers of inflammation (C-reactive protein levels) and vascular injury (thrombomodulin levels) measured at 0, 48, 96, and 168 hours.

**RESULTS** Among 167 randomized patients (mean [SD] age, 54.8 years [16.7]; 90 men [54%]), 103 (62%) completed the study to day 60. There were no significant differences between the vitamin C and placebo groups in the primary end points of change in mean modified Sequential Organ Failure Assessment score from baseline to 96 hours (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; $P = .86$) or in C-reactive protein levels (54.1 vs 46.1 µg/mL; difference, 7.94 µg/mL; 95% CI, −8.2 to 24.11; $P = .33$) and thrombomodulin levels (14.5 vs 13.8 ng/mL; difference, 0.69 ng/mL; 95% CI, −2.8 to 4.2; $P = .70$) at 168 hours.

**CONCLUSIONS AND RELEVANCE** In this preliminary study of patients with sepsis and ARDS, a 96-hour infusion of vitamin C compared with placebo did not significantly improve organ dysfunction scores or alter markers of inflammation and vascular injury. Further research is needed to evaluate the potential role of vitamin C for other outcomes in sepsis and ARDS.

**TRIAL REGISTRATION** ClinicalTrials.gov Identifier: NCT02106975

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Visual Abstract

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Supplemental content

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Acute respiratory distress syndrome (ARDS) is a common sepsis-associated organ injury and results in significant mortality[1-4]; for instance, the LUNG SAFE study reported 34% to 45% mortality.[5] Despite advances in understanding mechanisms that lead to ARDS,[6] disease-modifying strategies have not improved outcomes.[7-12] Previous research found that vitamin C attenuates systemic inflammation, corrects sepsis-induced coagulopathy, and attenuates vascular injury.[13-15] The CITRIS-ALI randomized trial examined whether high-dose vitamin C would reduce organ failure and biomarkers of inflammation and vascular injury in patients with sepsis and ARDS.

### Key Points

**Question** Can intravenous administration of high-dose vitamin C reduce organ failure scores and biomarkers of inflammation and vascular injury among patients with sepsis and acute respiratory distress syndrome (ARDS)?

**Findings** In this randomized clinical trial that included 167 patients in the intensive care unit, intravenous infusion of high-dose vitamin C vs placebo for 96 hours resulted in no significant differences in the modified Sequential Organ Failure Assessment score at 96 hours, or in levels of C-reactive protein and thrombomodulin at 168 hours.

**Meaning** Among patients with sepsis and ARDS, high-dose vitamin C infusion compared with placebo did not significantly reduce organ failure scores at 96 hours or improve biomarker levels at 168 hours.

## Methods

### Study Oversight

The Food and Drug Administration provided oversight for this trial and issued Investigational New Drug 113856 for its performance. The study protocol, including the complete statistical analysis plan, is available in Supplement 1. The CITRIS-ALI protocol was approved by the institutional review boards at each of 7 participating medical centers. Written informed consent was obtained from patients or patients' legally authorized representatives. Patients were enrolled from September 2014 through November 2017, with last patient follow-up in January 2018.

### Study Patients

After intensive care unit (ICU) admission for sepsis, patients were followed up for development of acute respiratory failure. 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,[16] had suspected or proven infection, and met 2 of 4 systemic inflammatory response criteria.[17] All criteria had to be met within a 24-hour period. 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 criteria); they did not have a patient surrogate or physician committed to full support; they were pregnant or breastfeeding; they were moribund and not expected to survive 24 hours; they required home mechanical ventilation (via tracheostomy 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.

Patients' race or ethnicity was determined by either a researcher or legal next of kin by open-ended questions. No patient was excluded because of race, ethnicity, or sex. Inclusion of race/ethnicity in this study was required by the funding agency.

### Randomization, Masking, and Study Drug Administration

Patients were randomized 1:1 to receive vitamin C or placebo (**Figure 1**), using randomization generated by the VCU Health Investigational Drug Service by means of Research Randomizer at http://www.randomizer.org. 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. Patients were randomized to receive vitamin C or placebo. Vitamin C was intravenously infused in the treatment group at 50 mg/kg actual body weight every 6 hours for 96 hours. Infusion bags (50 mL) containing the calculated vitamin C dosage in dextrose 5% in water or placebo (dextrose 5% in water alone) were prepared at study site investigational pharmacies, light protected with amber covers, and stored refrigerated at 2°C to 8°C for up to 24 hours.

At infusion, ICU nursing infused the hooded study agent through light-protected tubing during 30 minutes. Dose 1 of the study drug was administered within 6 hours of randomization or at earliest available times after clinically indicated procedures (eg, imaging) requiring patients to be out of the ICU. Study drug infusion was stopped when the final dosage was administered (ie, hour 96) or at ICU discharge, discharge from the study hospital, study withdrawal, or death, whichever occurred first.

Vitamin C for injection (Ascor) was supplied by McGuff Pharmaceuticals in amber 50-mL vials containing pH-balanced L-ascorbic acid for injection at 500 mg/mL (Supplement 2).

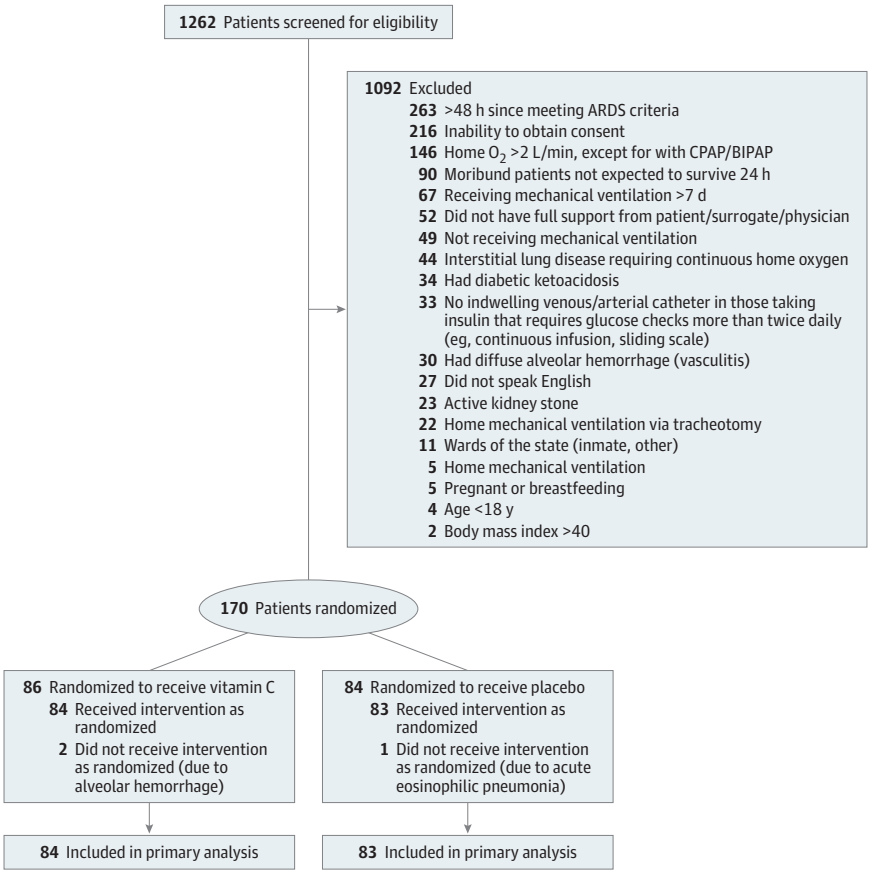
### Ventilator Procedures and Fluid Administration

Mechanical ventilation was performed with ARDS Network tidal volume settings.[18] A conservative fluid administration protocol was used as described in the ARDSNet FACTT Lite trial.[19] FACTT Lite was instituted within the first 4 hours of randomization of patients and was continued until unassisted breathing or study day 7, whichever occurred first.

### Outcomes

The primary outcomes were modified Sequential Organ Failure Assessment (mSOFA) scores at 96 hours and plasma

Figure 1. Flow of Patients Through the CITRIS-ALI Trial in Sepsis and Acute Respiratory Distress Syndrome




Exclusions could occur for 1 or more reasons. None of the patients excluded after randomization received vitamin C. CPAP indicates continuous positive airway pressure; BiPAP, bilevel positive airway pressure.

biomarker levels (C-reactive protein and thrombomodulin) at 168 hours. The selection of the primary outcomes was based on a previously performed phase 1 trial.[15] There were 46 prespecified 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.[20] Ventilator-free days were defined as the number of days a patient was extubated from mechanical ventilation, after ICU admission to day 28. Days requiring reintubation were subtracted from the total days to day 28. If the patient died in the hospital postextubation, a value of zero was assigned. ICU-free days began the moment the patient was transferred out of the ICU to day 28. If the patient was readmitted to the ICU, the days were subtracted from the total ICU-free days. Hospital- and ICU-free days were calculated similarly.

Additional secondary outcomes 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, creatinine level, and biomarkers [angiopoietin 2, procalcitonin, receptor for advanced glycation end products, tissue factor pathway inhibitor, and plasma ascorbate concentrations]).

## Study Measurements and Procedures

For organ system failure, the SOFA score was modified, eliminating bilirubin during the blinded analysis period as a result of many missing values because clinicians determined that bilirubin measurement was not clinically indicated (mSOFA, range from 0 [normal organ function] to 20 [worst organ function]). In previous research, elimination of a SOFA component did not affect its predictive ability.[21-23] mSOFA score was measured at hour 0 and then at hours 48 and 96.[24]

Plasma was obtained for quantification of vitamin C levels at enrollment and then at hours 48, 96, and 168. High-pressure liquid chromatography was used to quantify plasma vitamin C (Supplement 2). Blood was obtained at hours 0, 48, 96, and 168 for biomarker analysis. Tubes were placed on ice and centrifuged (1000*g*) within 30 minutes of collection. Aliquoted plasma was stored at −80°C for batch analysis by Luminex technology (Supplement 2).

## Statistical Analysis

Sample size was calculated with means, variances, and correlations for SOFA, C-reactive protein, and thrombomodulin data from another trial.[15] Simulations (1000) were performed at sample sizes of 75 to 100 per group for each of 3 outcome variables and empirical power was calculated according to

Table 1. Baseline and Follow-up Characteristics of All Patients

| Variable | Vitamin C (n = 84) | Placebo (n = 83) |
|---|---|---|
| Demographic data, No. (%) | | |
| Age, median (IQR), y | 54 (39-67) | 57 (44-70) |
| Men | 45 (54) | 45 (54) |
| Women | 39 (46) | 38 (46) |
| Non-Hispanic white | 68 (81) | 60 (72) |
| Non-Hispanic black | 13 (15) | 19 (23) |
| Hispanic/Asian/ Pacific Islander | 3 (4) | 4 (5) |
| Sepsis etiology, No. (%) | | |
| Thorax | 69 (82) | 58 (70) |
| Abdomen | 6 (7) | 13 (16) |
| Urinary tract | 3 (4) | 2 (2) |
| Central nervous system | 1 (1) | 3 (4) |
| Central venous catheter | 0 | 1 (1) |
| Unknown/other | 5 (6) | 6 (7) |
| Admission source, No. (%) | | |
| Emergency department | 39 (46) | 36 (43) |
| Outside hospital transfer | 26 (31) | 28 (34) |
| Inpatient ward transfer | 17 (20) | 18 (22) |
| Operating room | 1 (1) | 1 (1) |
| Direct admission | 1 (1) | 0 |
| Kidney failure, No. (%) | | |
| Acute kidney failure, No. (%) | 21 (25) | 26 (31) |
| Chronic kidney failure/ dialysis, No. (%) | 7 (8) | 8 (10) |
| Respiratory, mean (SD) | | |
| Tidal volume, mL | 423.7 (88.4) | 418.3 (85.5) |
| $Pao_2/Fio_2$ ratio at baseline | 189.3 (95.9) | 214.5 (182.8) |
| PEEP, cm $H_2O$ | 9.9 (4.0) | 9.6 (4.0) |
| Oxygenation index,[a] mean (SD) | 10.7 (7.4) | 10.1 (6.3) |
| Incidence of shock, No. (%) | | |
| At baseline, vasopressor in use | 57 (68) | 60 (72) |
| mSOFA scores,[b] mean (SD) | | |
| At randomization | 9.8 (3.2) | 10.3 (3.1) |
| At 96 h | 8.02 (4.2) | 6.96 (3.5) |
| Corticosteroid use during study, No. (%) | 56 (67) | 54 (65) |
| IV fluids, mL/kg/24 h | | |
| Day 1, mean (SD) | 40 (28.5) | 42.6 (35.5) |
| Day 7, mean (SD) | 32.8 (19.6) | 33.9 (16.8) |
| Day 1, median (IQR) | 35.1 (21.2-50.3) | 33.9 (20.2-55.3) |
| Day 7, median (IQR) | 26.5 (19.7-40.9) | 26.8 (16.7-38.3) |
| Urine output, mL/kg/24 h | | |
| Day 1, mean (SD) | 14.1 (14.5) | 10.5 (11.7) |
| Day 7, mean (SD) | 24.4 (24.9) | 24.6 (22.9) |
| Day 1, median (IQR) | 9.9 (3.9-20) | 6.7 (1.7-15) |
| Day 7, median (IQR) | 18.2 (1.5-36) | 20.9 (6.1-34.4) |

Abbreviations: IQR, interquartile range; PEEP, positive end-expiratory pressure; mSOFA, modified Sequential Organ Failure Assessment; IV, intravenous.

[a] Oxygenation index = mean airway pressure × $Fio_2/Pao_2$.

[b] mSOFA score range, 0 to 20 (values >8 indicate severe illness).

means and sample sizes. In simulations (18 000), a mixed linear model was used to assess the effect of treatment on outcome and to fit a repeated-measures analysis of variance. The model included 1 between-participant factor (group [placebo or vitamin C]), 1 within-participant factor (time [0, 12, 24, 36, 48, 72, and 96 hours, and 7 days]), and the interaction between group and time, testing the hypothesis that differences between treatment groups are the same over time. Group difference at 96 hours for each of the 3 outcomes was calculated with simulations.

Power estimates for the various sample sizes were derived according to the difference at 96 hours in the 3 co-primary end points (SOFA, C-reactive protein, and thrombomodulin). Significance was set at $\alpha = .05$ and a Holm-Bonferroni correction for 3 co-primary end points was conducted. Only if the smallest $P$ value was less than .02, the second smallest less than .03, and the largest less than .05 was simulation considered a success. Simulations and calculations resulted in the empirical power based on various sample sizes (eTable 5 in Supplement 2).

In accordance with these calculations, CITRIS-ALI enrolled 170 patients (85 per group) to allow for 10% dropouts, providing a statistical power of 80%, with an $\alpha < .05$. Testing was 2 sided. Effects are reported with a point estimate and 95% CIs in addition to $P$ values. Distributions of measures were examined to identify outliers.

The primary end points were analyzed with a mixed linear model and fit to repeated-measures analysis of variance as described earlier. All-cause mortality to day 28 was estimated with a Kaplan-Meier analysis, and survival curves were compared with the Wilcoxon test because of its greater sensitivity to earlier survival differences. Nonlongitudinal data were analyzed with linear regressions, using a random effect for study site and $P < .05$. Testing was 2 sided. Missing data patterns were examined, revealing monotone missing data, whose pattern provides evidence that assumptions of missing completely at random and missing at random may be violated. Multiple imputation with a pattern-mixture model with control-based pattern imputation was used, with 50 imputed data sets created and analyzed to examine the effect of monotone missing data.

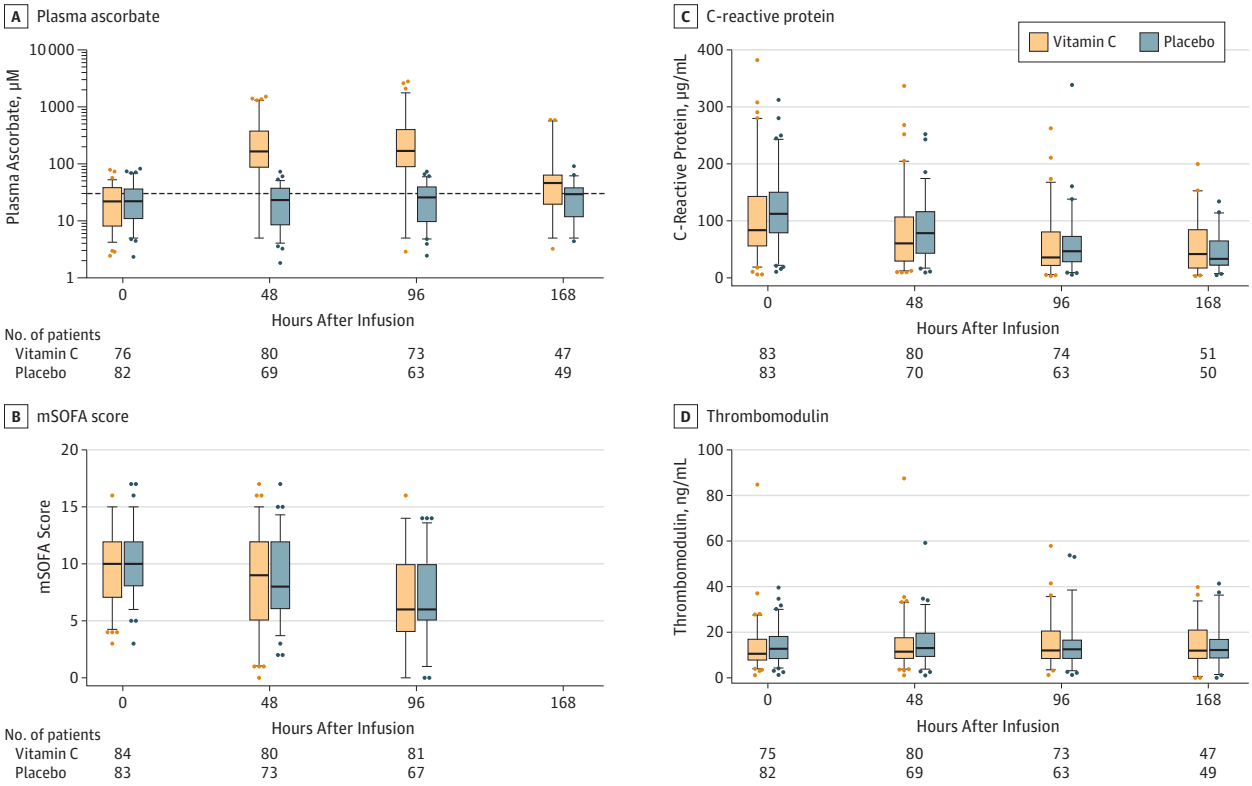
Because of a potential for type I error caused by multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory. Secondary end points and the primary outcomes were analyzed similarly, with exclusion of the multiple imputations. Statistical analysis was performed with SAS version 9.4, Stata version 15.1, and GraphPad Prism version 7.00.

## Results

### Characteristics of the Patients

A total of 1262 eligible patients were identified, of whom 1062 were excluded because of the diagnoses listed in Figure 1. Three patients were excluded after randomization because of a subsequent diagnosis of diffuse alveolar hemorrhage (n = 2) and acute eosinophilic pneumonia (n = 1). None

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 µM [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.

of these patients received vitamin C. One hundred sixty-seven patients were randomized, with 83 assigned to placebo and 84 to vitamin C. Baseline demographic data (eg, sex, race) were similar between the 2 groups (**Table 1**). The presumed etiology of sepsis most commonly resulted from pneumonia (Table 1). Other etiologies included central line sepsis, urosepsis, typhlitis in leukemia patients, cellulitis, and leukopenia in bone marrow transplant patients.

## Primary Outcomes

There was no statistically significant difference in mSOFA scores between placebo and the vitamin C–infused patients from enrollment to 96 hours (**Figure 2**). 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. Two patients were lost to follow-up.

## Secondary Outcomes

Forty-three of the 46 prespecified secondary outcomes were not significantly different between the vitamin C group and the placebo group (**Table 2**). In exploratory analyses that did not adjust for multiple comparisons, 3 secondary outcomes were significantly different between groups. At day 28, mortality was 46.3% (38/82) in the placebo group vs 29.8% (25/84) in the vitamin C group ($\chi^2 = 4.84$; $P = .03$; between-group difference, 16.58% [95% CI, 2% to 31.1%]) (**Figure 3**). The Kaplan-Meier survival curves for the 2 groups were significantly different by the Wilcoxon test ($\chi^2_1 = 6.5$; $P = .01$).

The number of ventilator-free days was 13.1 in the vitamin C group vs 10.6 in the placebo group (mean difference, 2.47;

Table 2. Secondary Outcomes in a Trial of Vitamin C Infusion in Patients With Sepsis and Severe Acute Respiratory Failure

| | | Vitamin C | | | Placebo | | | Difference, Coefficient (95% CI) | *P* Value |
|---|---|---|---|---|---|---|---|---|---|
| Variable | Hour | No. | Median or % | IQR | No. | Median or % | IQR | | |
| Angiopoietin-2, median (IQR), ng/mL[a] | 0 | 83 | 8.8 | 14.9 | 83 | 11.6 | 17.5 | −5.1 (−10.9 to 0.6) | .08 |
| | 48 | 80 | 6.9 | 11.5 | 70 | 9.7 | 16.9 | −2.4 (−9.0 to 4.2) | .48 |
| | 96 | 74 | 5.7 | 9.5 | 63 | 5.2 | 7.3 | 3.8 (−2.5 to 10.0) | .24 |
| | 168 | 53 | 5.3 | 6.4 | 51 | 3.9 | 5.5 | 2.9 (−2.0 to 7.9) | .24 |
| Procalcitonin, median (IQR), ng/mL[b] | 0 | 83 | 2.4 | 8.5 | 83 | 3.7 | 19.7 | −14.3 (−30.0 to 1.5) | .07 |
| | 48 | 80 | 1.1 | 5.2 | 70 | 1.7 | 5.5 | −1.3 (−7.4 to 4.8) | .68 |
| | 96 | 74 | 0.7 | 2.5 | 63 | 0.7 | 2.2 | −1.0 (−3.6 to 1.6) | .44 |
| | 168 | 53 | 0.5 | 1.6 | 51 | 0.5 | 1.3 | −1.5 (−4.6 to 1.7) | .36 |
| RAGE, median (IQR), ng/mL[c] | 0 | 83 | 4.0 | 5.2 | 83 | 5.0 | 6.2 | −0.9 (−2.5 to 0.7) | .26 |
| | 48 | 80 | 2.8 | 4.2 | 70 | 3.3 | 4.0 | 0.3 (−0.9 to 1.4) | .67 |
| | 96 | 74 | 2.1 | 4.0 | 63 | 2.0 | 3.4 | 0.8 (−0.3 to 1.8) | .15 |
| | 168 | 53 | 1.7 | 2.9 | 51 | 1.5 | 3.2 | 0.3 (−0.6 to 1.1) | .55 |
| TFPI, median (IQR), ng/mL[d] | 0 | 83 | 36.7 | 52.4 | 83 | 36.3 | 33.7 | 3.4 (−6.2 to 13.0) | .48 |
| | 48 | 80 | 31.3 | 34.5 | 70 | 34.3 | 33.4 | −0.5 (−10.8 to 9.8) | .92 |
| | 96 | 74 | 36.2 | 39.0 | 63 | 36.7 | 30.6 | −2.0 (−11.2 to 7.2) | .66 |
| | 168 | 53 | 30.5 | 51.0 | 51 | 30.2 | 31.7 | 1.6 (−11.1 to 14.2) | .81 |
| Vasopressor use, % | 0 | 84 | 64.3 | | 83 | 71.1 | | −6.8 | .35 |
| | 48 | 82 | 54.9 | | 72 | 50.0 | | 4.9 | .55 |
| | 96 | 80 | 30.0 | | 65 | 27.7 | | 2.3 | .76 |
| | 168 | 72 | 22.2 | | 59 | 10.2 | | 10 | .07 |
| Oxygenation index,[e] median (IQR) | 0 | 76 | 0.082 | 0.090 | 80 | 0.089 | .077 | 0.129 (−0.096 to 0.353) | .26 |
| | 48 | 53 | 0.058 | 0.062 | 57 | 0.056 | .054 | 0.004 (−0.016 to 0.023) | .71 |
| | 96 | 42 | 0.079 | 0.084 | 33 | 0.045 | .040 | 0.016 (−0.017 to 0.049) | .33 |
| | 168 | 28 | 0.052 | 0.051 | 16 | 0.074 | .066 | −0.003 (−0.050 to 0.044) | .90 |
| VE-40[f] to median (IQR) | 0 | 78 | 0.126 | 0.044 | 81 | 0.115 | .058 | 0.013 (−0.002 to 0.028) | .09 |
| | 48 | 59 | 0.109 | 0.049 | 60 | 0.110 | .061 | 0.001 (−0.017 to 0.019) | .94 |
| | 96 | 46 | 0.129 | 0.060 | 39 | 0.105 | .047 | 0.036 (−0.015 to 0.086) | .16 |
| | 168 | 29 | 0.114 | 0.043 | 17 | 0.118 | .057 | −0.020 (−0.055 to 0.015) | .26 |
| Net fluid balance to median (IQR), mL | 0 | 83 | 1604 | 2927 | 79 | 1901 | 3034 | −3759 (−1123 to 373) | .32 |
| | 48 | 81 | 768 | 2471 | 73 | 473 | 1797 | 545 (−255 to 1345) | .18 |
| | 96 | 76 | 134 | 2168 | 66 | −659 | 2560 | 792 (208 to 1376) | .01 |
| | 168 | 57 | 190 | 2076 | 54 | −380 | 2213 | 496 (−206 to 1198) | .16 |
| All-cause mortality to day 28, % | | | 84 | 29.8 | 38 | 82 | 46.3 | −0.17 | .03 |
| Ventilator-free days to day 28, median (IQR), d | | 84 | 17 | 24 | 82 | 8 | 22 | 2.5 (−0.9 to 5.9) | .15 |
| ICU-free days to day 28, median (IQR), d | | 83 | 11 | 21 | 82 | 0 | 18 | 3.2 (0.3 to 6.0) | .03 |
| Hospital-free days, to day 60, median (IQR), d | | 82 | 22 | 46 | 80 | 0 | 39 | 7.0 (0.3 to 13.8) | .04 |
| Bilirubin, total, median (IQR), mg/dL | 0 | 77 | 0.7 | 2.8 | 79 | 1.2 | 1.7 | 0 (−1.3 to 1.2) | .96 |
| | 48 | 72 | 0.8 | 2.0 | 68 | 0.8 | 2.3 | 0.1 (−1.3 to 1.5) | .87 |
| | 96 | 62 | 0.8 | 2.5 | 64 | 0.8 | 1.7 | 0.6 (−1.1 to 2.2) | .50 |
| | 168 | 45 | 0.6 | 1.0 | 42 | 0.8 | 1.0 | 0.6 (−1.6 to 2.7) | .60 |
| Creatinine, median (IQR), mg/dL | 0 | 84 | 1.4 | 1.3 | 83 | 1.7 | 1.8 | −0.1 (−0.6 to 0.3) | .49 |
| | 48 | 82 | 1.6 | 1.4 | 73 | 1.2 | 1.0 | 0.2 (−0.3 to 0.6) | .41 |
| | 96 | 78 | 1.1 | 1.1 | 65 | 1.1 | .9 | 0.1 (−0.2 to 0.5) | .47 |
| | 168 | 64 | 1.0 | 1.2 | 55 | 1.2 | 1.6 | 0.1 (−0.5 to 0.6) | .82 |
| Platelets, median (IQR), $\times 10^3/\mu L$ | 0 | 83 | 147 | 174 | 83 | 160 | 137 | −5.1 (−45.0 to 34.8) | .80 |
| | 48 | 82 | 137 | 166 | 73 | 116 | 153 | 23.8 (−15.9 to 63.4) | .24 |
| | 96 | 77 | 144 | 183 | 63 | 146 | 175 | 15.2 (−29.5 to 59.9) | .50 |
| | 168 | 64 | 183 | 209 | 55 | 219 | 149 | −2.4 (−59.9 to 55.0) | .93 |

(continued)

Table 2. Secondary Outcomes in a Trial of Vitamin C Infusion in Patients With Sepsis and Severe Acute Respiratory Failure (continued)

| | | Vitamin C | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Variable | Hour | No. | Median or % | IQR | No. | Median or % | IQR | Difference, Coefficient (95% CI) | *P* Value |
| Glasgow Coma Scale score, median (IQR) | 0 | 84 | 8 | 4 | 83 | 7 | 5 | 0.7 (−0.3 to 1.6) | .15 |
| | 48 | 80 | 9 | 5 | 72 | 9 | 4 | 0.6 (−0.5 to 1.7) | .30 |
| | 96 | 75 | 10 | 5 | 66 | 10 | 3 | −0.4 (−1.7 to 0.8) | .49 |
| | 168 | 56 | 10 | 6 | 53 | 12 | 6 | −1.5 (−3.0 to −0.1) | .04 |
| SOFA component, cardiovascular, median (IQR) | 0 | 84 | 3.0 | 4.0 | 83 | 3.0 | 3.0 | −0.2 (−0.8 to 0.3) | .35 |
| | 48 | 80 | 3.0 | 4.0 | 73 | 3.0 | 4.0 | 0.1 (−0.5 to 0.6) | .82 |
| | 96 | 71 | 0 | 3.0 | 61 | 0 | 3.0 | 0.2 (−0.3 to 0.8) | .41 |
| | 168 | 51 | 0 | 3.0 | 48 | 0 | 1.0 | 0.8 (0.2 to 1.3) | .01 |
| SOFA component, hematologic, median (IQR) | 0 | 82 | 1.0 | 1.0 | 74 | 1.0 | 1.0 | 0.1 (−0.1 to 0.3) | .40 |
| | 48 | 75 | 1.0 | 1.0 | 65 | 0 | 1.0 | 0 (−0.2 to 0.2) | .91 |
| | 96 | 56 | 0 | 1.0 | 49 | 0 | 1.0 | 0.1 (−0.2 to 0.4) | .43 |
| | 168 | 84 | 0 | 2.0 | 83 | 0 | 2.0 | 0.2 (−0.1 to 0.5) | .19 |
| SOFA component, liver, median (IQR) | 0 | 82 | 0 | 2.0 | 74 | 0 | 2.0 | −0.2 (−0.5 to 0.2) | .39 |
| | 48 | 72 | 0 | 1.0 | 64 | 0 | 2.0 | −0.1 (−0.5 to 0.3) | .70 |
| | 96 | 53 | 0 | 0 | 49 | 0 | 1.0 | 0 (−0.5 to 0.4) | .87 |
| | 168 | 84 | 3.0 | 1.0 | 83 | 3.0 | 2.0 | 0 (−0.4 to 0.5) | .95 |
| SOFA component, neurologic, median (IQR) | 0 | 82 | 3.0 | 1.0 | 75 | 3.0 | 1.0 | −0.2 (−0.5 to 0.1) | .21 |
| | 48 | 72 | 2.5 | 1.0 | 66 | 2.0 | 1.0 | −0.2 (−0.6 to 0.2) | .32 |
| | 96 | 54 | 2.0 | 1.0 | 51 | 2.0 | 3.0 | 0.1 (−0.3 to 0.5) | .71 |
| | 168 | 82 | 1.0 | 1.0 | 74 | 1.0 | 1.0 | 0.4 (−0.1 to 0.9) | .08 |
| SOFA component, kidney, median (IQR) | 0 | 84 | 1.0 | 2.0 | 83 | 1.0 | 2.0 | −0.1 (−0.5 to 0.2) | .45 |
| | 48 | 82 | 1.0 | 2.0 | 72 | 1.0 | 1.0 | 0.1 (−0.2 to 0.4) | .52 |
| | 96 | 72 | 0 | 1.5 | 64 | 0 | 1.0 | 0.1 (−0.2 to 0.5) | .43 |
| | 168 | 56 | 1.0 | 2.0 | 50 | 1.0 | 2.0 | −0.1 (−0.5 to 0.4) | .80 |
| SOFA component, respiratory, median (IQR) | 0 | 80 | 3.0 | 1.0 | 82 | 3.0 | 1.0 | 0.1 (−0.2 to 0.4) | .41 |
| | 48 | 64 | 2.0 | 1.5 | 66 | 2.0 | 2.0 | 0.1 (−0.3 to 0.5) | .48 |
| | 96 | 53 | 2.0 | 2.0 | 50 | 2.0 | 2.0 | 0.3 (−0.1 to 0.7) | .16 |
| | 168 | 35 | 2.0 | 2.0 | 27 | 2.0 | 2.0 | 0.1 (−0.6 to 0.8) | .78 |

Abbreviations: ICU, intensive care unit; IQR, interquartile range; RAGE, receptor for advanced glycation end products; TFPI, tissue factor pathway inhibitor; VE-4O, minute ventilation 4O L/min; SOFA, Sequential Organ Failure Assessment.

SI conversion factors: To convert creatinine to µmol/L, multiply values by 88.4.

[a] Angiopoietin (range of normal, 1.1-4.4 ng/mL).

[b] Procalcitonin (range of normal, <0.05 ng/mL).

[c] Receptor for advanced glycation end products (range of normal, 0.4-4.3 ng/mL).

[d] Tissue factor pathway inhibitor (range of normal, 13.0-44.9 ng/mL).

[e] $Fio_2$ × mean airway pressure/$Po_2$ × 100.

[f] VE-4O vent RR (respiratory rate) × tidal volume/weight × ($Paco_2$/4O). SOFA score range, 0 to 24, with higher values indicating greater severity of organ failure. Individual SOFA components range from 0 to 4, with higher component values indicating greater severity on score values. *P* values calculated by linear regression for continuous variables and logistic regression for binary variables.

95% CI, −0.90 to 5.85; *P* = .15) (eFigure 1 in Supplement 2). The number of ICU-free days to day 28 was 10.7 in the vitamin C group vs 7.7 in the placebo group (mean difference, 3.2; 95% CI, 0.3 to 5.9; *P* = .03) (eFigure 1 in Supplement 2). Transfer out of the ICU by hour 168 or less occurred in 25% of patients in the vitamin C group (21/84) vs 12.5% in the placebo group (10/83) ($\chi^2$ = 4.63; *P* = .03; difference, 12.95% [95% CI, 1.16% to 24.73%; *P* = .31]). The number of hospital-free days in the vitamin C group vs the placebo group was 22.6 vs 15.5, respectively (mean difference, 6.69; 95% CI, 0.3 to 13.8; *P* = .04) (eFigure 1 in Supplement 2).

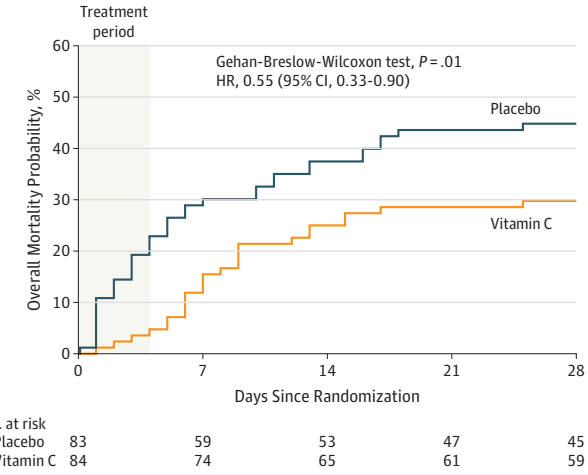
## Adverse Events

Patients were followed up for adverse events. No unexpected study-related adverse events occurred during the trial.

## Vitamin C Pharmacokinetic Findings

Plasma vitamin C levels in all patients were subnormal at enrollment (<28 µmol/L), with no significant difference between groups (median for vitamin C-infused patients vs placebo, 22 vs 22 µmol/L [interquartile range {IQR}, 8-39 vs 11-37]; *P* = .49). (To convert vitamin C to mg/dL, divide values by 56.78.) Plasma vitamin C levels sampled at trough periods before infusion had increased significantly in vitamin C-infused patients by hours 48 (median, 166 µmol/L; IQR, 88-376) and 96 (median, 169 µmol/L; IQR, 87-412) compared with placebo patients by hours 48 (median, 23 µmol/L; IQR, 9-37) and 96 (median, 26 µmol/L; IQR, 9-41) (Figure 3). At hour 168, plasma vitamin C level in placebo patients remained low (median, 29 µmol/L; IQR, 12-39). After cessation of vitamin C infusion at 96 hours, vitamin C

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.

levels declined but remained significantly elevated at hour 168 (median, 46 µmol/L; IQR, 19-66) compared with placebo (Figure 3).

## Discussion

In this preliminary study of patients with sepsis and severe ARDS, a 96-hour infusion of vitamin C compared with placebo did not improve organ dysfunction (as measured by the mSOFA score at 96 hours) or levels of biomarkers indicating inflammation (C-reactive protein) or vascular injury (thrombomodulin) by 168 hours. The inability of vitamin C to affect C-reactive protein and thrombomodulin levels in this trial possibly resulted from the advanced stages of sepsis that were present before the development of ARDS. Delayed quantification of these biomarkers in CITRIS-ALI compared with early vitamin C infusion in severe sepsis may explain results discordant with those of previous studies of vitamin C in severe sepsis.[15] Preclinical research in early sepsis revealed that vitamin C prevented sepsis-induced cytokine surges that activate and sequester neutrophils in lung, thus damaging alveolar capillaries.[13,14] Vitamin C increased alveolar fluid clearance by preventing activated neutrophil accumulation in alveolar spaces, limiting alveolar epithelial water-channel damage, and promoting their increased expression.[14] In addition, vitamin C prevented neutrophil extracellular trap formation, a biological event in activated neutrophils that promotes vascular injury.[25]

Among the 46 secondary outcomes that were examined in this trial, 43 showed no significant differences between the vitamin C group and the placebo group, although vitamin C compared with placebo was associated with a significant reduction in 28-day all-cause mortality, and with significantly increased ICU-free days to day 28 and hospital-free days to day 60. However, these findings were based on analyses that did not account for multiple comparisons and therefore must be considered exploratory. It is possible that these observations represent the effects of vitamin C on underlying sepsis-induced biological abnormalities that are not reflected in the biomarker analysis, a hypothesis supported by 3 findings: early deaths in the placebo group, the proportion of patients in the vitamin C–infused cohort who left the ICU before 168 hours, and the survival curve parallel to that of placebo after cessation of vitamin C infusion. However, these observations and hypotheses would require further evaluation.

Patients with sepsis have a high mortality and accounted for $23.7 billion in US hospital costs in 2013.[26] Patients with sepsis and acute respiratory distress syndrome have worse clinical outcomes than those without sepsis and ARDS, with higher 30- and 60-day mortality and with fewer ventilator- and ICU-free days.[27] A report from US hospitals revealed declining ARDS mortality, likely because of both improved supportive care and regimented approaches to mechanical ventilation.[4] However, in the LUNG SAFE study, which included more than 3000 patients with ARDS in 50 countries, all-cause mortality remained high, varying from 34% to 46%, depending on ARDS severity.[5] Given these facts, a new approach in the form of a disease-modifying therapy is needed. The exploratory findings from the CITRIS-ALI trial suggest that further research may be warranted to determine whether vitamin C has a role in the care of patients with sepsis and ARDS.

### Limitations

This study has several limitations. First, 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.[15] 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. Second, CITRIS-ALI may have been underpowered to detect a difference in mSOFA scores and biomarker levels. Third, differences in baseline characteristics of this necessarily heterogeneous population may have influenced mortality. Fourth, 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. Fifth, given the absence of previous clinical data, this proof-of-concept trial was designed to measure the effect of ascorbic acid on organ failure and laboratory measures of inflammation in patients with severe sepsis rather than mortality. Sixth, 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.

## Conclusions

In this preliminary study of patients with sepsis and ARDS, a 96-hour infusion of vitamin C compared with placebo did not significantly improve organ dysfunction scores or alter markers of inflammation and vascular injury. Further research would be needed to evaluate the potential role of vitamin C for other outcomes in sepsis and ARDS.


### ARTICLE INFORMATION

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