



ASIA PACIFIC CENTER FOR
EVIDENCE BASED HEALTHCARE

Should vitamin C/ ascorbic acid be used in the treatment of COVID-19?

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KEY FINDINGS

There is no direct evidence available as of this point for efficacy of intravenous vitamin C as an adjunctive treatment in preventing mortality or shortening disease course among adults with COVID-19.

- Vitamin C infusion is currently not mentioned in the treatment guidelines for COVID-19 or ARDS.
- Currently, there are 6 ongoing trials registered in clinicaltrials.gov studying intravenous vitamin C in COVID-19. No other ongoing or planned trials were registered in the other trial registries.
- Most of the available data are from studies on disease populations which may be considered as COVID-19 suspects:
 - Conflicting results on mortality from indirect evidence among patients with sepsis with or without ARDS with significant reduction in mortality found in only a small subset of patients (n=40) with severe sepsis given high dose Vitamin C infusion.
 - Strong evidence supporting no mortality benefit from 5 meta-analyses on critically ill patients due to conditions other than or in combination with sepsis who were given Vit C infusion alone or in combinations with other medications. In a small subset population of 69 patients with severe sepsis who received moderate dose (3-10 gm iv/day), the absolute mortality reduction was significant at 8.5% compared to control.[11] One meta-analysis showed a significant benefit in decreasing duration of ICU stay by 7.7% (n=839) and duration of mechanical ventilation by 18.2 % (n=185).[9] Most showed no benefit on other key endpoints such as acute kidney injury, duration of hospital stay/ ICU stay/ or duration of vasopressor use.
- The risks or adverse events with short term use of Vitamin C infusion in the general population is negligible or minimal. It should be avoided in patients with G6PD insufficiency. The dose should be carefully adjusted for patients with renal insufficiency.

Declaration of Conflict of Interest

No conflict of interest

Disclaimer: The aim of these rapid reviews is to retrieve, appraise, summarize and update the available evidence on COVID-related health technology. The reviews have not been externally peer-reviewed; they should not replace individual clinical judgement and the sources cited should be checked. The views expressed represent the views of the authors and not necessarily those of their host institutions. The views are not a substitute for professional medical advice.

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REFERENCES

1. Hemilä H, Chalker E. Vitamin C for preventing and treating the common cold. Cochrane Database of Systematic Reviews 2013, Issue 1. Art. No.: CD000980. DOI: 10.1002/14651858.CD000980.pub4
2. https://clinicaltrials.gov/ct2/results?cond=covid-19&term=&type=&rslt=&age_v=&qndr=&intr=Vitamin+C&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfd_s=&rfd_e=&lupd_s=&lupd_e=&sort=
3. Fowler, AA III et al. 2017. Intravenous vitamin C as adjunctive therapy for enterovirus/rhinovirus induced acute respiratory distress syndrome. *World J Crit Care Med* 2017 February 4; 6(1): 85-90
4. Fowler, AA III et al. 2019. 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*. 322(13):1261-1270. doi:10.1001/jama.2019.11825
5. Fuji, T et al. 2020. Effect of Vitamin C, Hydrocortisone, and Thiamine vs Hydrocortisone Alone on Time Alive and Free of Vasopressor Support Among Patients With Septic Shock: The VITAMINS Randomized Clinical Trial. *JAMA*. 2020 Jan 17. doi: 10.1001/jama.2019.22176.
6. Lin J, Li H, Wen Y, Zhang M. Adjuvant administration of vitamin C improves mortality of patients with sepsis and septic shock: A systems review and meta-analysis. *Open J Intern Med* 2018;8:146–59.
7. Li J. Evidence is stronger than you think: a meta-analysis of vitamin C use in patients with sepsis. *Crit Care*. 2018;22(1):258.
8. Kim WY, et al. Combined vitamin C, hydrocortisone, and thiamine therapy for patients with severe pneumonia who were admitted to the intensive care unit: Propensity score-based analysis of a before-after cohort study. *J Crit Care*. 2018 Oct;47:211-218. doi:10.1016/j.jcrc.2018.07.004. Epub 2018 Jul 5. PubMed PMID: 30029205.
9. Hemilä, H and E Chalker. 2019. Vitamin C Can Shorten the Length of Stay in the ICU: A Meta-Analysis. *Nutrients*. 11: 708; doi:10.3390/nu11040708
10. Putzu, A., Daems, A.-M., Lopez-Delgado, J. C., Giordano, V. F., & Landoni, G. 2019. The Effect of Vitamin C on Clinical Outcome in Critically Ill Patients. *Critical Care Medicine*, 1. doi:10.1097/ccm.0000000000003700
11. Wang Y, Lin H, Lin BW, Lin JD. Effects of different ascorbic acid doses on the mortality of critically ill patients: a meta-analysis. *Annals of intensive care*. 2019;9(1):58.
12. Zhang, M and DF Jativa. 2018. Vitamin C supplementation in the critically ill: A systematic review and meta-analysis. *SAGE Open Medicine*. 6: 1–12
13. Langlois PL, Manzanares W, Adhikari NKJ, Lamontagne F, Stoppe C, Hill A, et al. Vitamin C supplementation in the critically ill: A systematic review and meta-analysis. *JPEN Parenter Enteral Nutr*. 2019.
14. [Jin, Ying-Hui et al for the Zhongnan Hospital of Wuhan University Novel Coronavirus; Research Team, Evidence-Based Medicine Chapter of China International Exchange; Promotive Association for, Medical; Health, Care. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus \(2019-nCoV\) infected pneumonia. *Military Medical Research* \(2020\) 7:4 <https://doi.org/10.1186/s40779-020-0233-6>](https://doi.org/10.1186/s40779-020-0233-6)
15. [Alhazzani, Waleed; Møller, Morten Hylander; et al Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 \(COVID-19\). \(2020\) *Intensive Care Med* <https://doi.org/10.1007/s00134-020-06022-5>](https://doi.org/10.1007/s00134-020-06022-5)
16. [Griffiths MJD, et al. Guidelines on the management of acute respiratory distress syndrome. *BMJ Open Res* 2019;6:e000420. doi:10.1136/bmjresp-2019-000420](https://doi.org/10.1136/bmjresp-2019-000420)
17. <https://www.tga.gov.au/alert/no-evidence-support-intravenous-high-dose-vitamin-c-management-covid-19>

Appendix 1. Characteristics of clinical trials

Title	Design	N	Conditions	Interventions	Primary outcome measures	Locations
Use of Ascorbic Acid in Patients With COVID 19	Open label prospective	500	Hospitalized Patients With Covid-19 Pneumonia	10 gr of vitamin C intravenously in addition to conventional therapy.	In-hospital (72 hr) mortality	A.R.N.A.S. Civico - Di Cristina - Benfratelli, Palermo, Italy
Vitamin C Infusion for the Treatment of Severe 2019-nCoV Infected Pneumonia	RCT	140	<ul style="list-style-type: none"> • Pneumonia, Viral • Pneumonia, Ventilator-Associated 	Drug: VC Vs. Sterile Water for Injection	Ventilation-free days [Time Frame: day 28 after enrollment] 2ndary outcome: 28-day mortality	Zhongnan Hospital of Wuhan University, Wuhan, Hubei, China
Lessening Organ Dysfunction With VITamin C (LOVIT trial)	Multicenter concealed-allocation parallel-group blinded randomized controlled trial	800	<ul style="list-style-type: none"> • Sepsis • ICU • COVID-19 • Pandemic • Coronavirus 	<ul style="list-style-type: none"> • Drug: Vitamin C • Other: Control 	Death or persistent organ dysfunction at day 28	Research Center of the CHUS, Sherbrooke, Quebec, Canada
Hydroxychloroquine for COVID-19 PEP (not yet recruiting)	RCT	2000	Post-exposure prophylaxis	<ul style="list-style-type: none"> • Drug: Hydroxychloroquine 400 mg orally daily for 3 days, then 200 mg orally daily for an additional 11 days • Placebo: acid 500 mg orally daily for 3 days, then 250 mg orally daily for 11 days 	PCR-confirmed SARS-CoV-2 infection through 14 days after enrollment	US (NY, Washington)
Prophylaxis Using Hydroxychloroquine Plus Vitamins-Zinc During COVID-19 Pandemia	Observational	80	Healthcare professionals	Plaquenil 200Mg Tablet + Vitamin combination of Vitamins A, C, D and Zinc	Freedom from COVID-19 infection	Istinye University Medical School, Istanbul, Turkey

Appendix 2. Characteristics of ongoing clinical trials

URL and Clinical trial ID	Title	Design	Estimated size	Primary outcome measures	Status	Study Results	Conditions	Interventions	Locations	Estimated primary completion date
https://ClinicalTrials.gov/show/NCT04363216	Pharmacologic Ascorbic Acid as an Activator of Lymphocyte Signaling for COVID-19 Treatment	randomized 2:1 single-center open label	66	Clinical Improvement [Time Frame: 72 hours]	Not yet recruiting	No Results Available	COVID-19, adults, hospitalized on supplemental O2 but not on ventilator	ascorbic acid 2-hour infusion daily (for 6 days), escalating dose (0.3g/kg, 0.6g/kg, 0.9g/kg) vs. routine care	USA	May 2021
https://ClinicalTrials.gov/show/NCT04357782	Administration of Intravenous Vitamin C in Novel Coronavirus Infection (COVID-19) and Decreased Oxygenation	prospective single arm , phase I/II	20	Incidence of adverse events, Serious adverse reactions, adverse reactions [Time Frame: Days 1-4	Recruiting	No Results Available	COVID-19 Hypoxia, hospitalized, adult	50 mg/kg L-ascorbic acid infusion given every 6 hours for 4 days (16 total doses)	USA	June 1, 2020
https://ClinicalTrials.gov/show/NCT04344184	Early Infusion of Vitamin C for Treatment of Novel COVID-19 Acute Lung Injury (EVICT-CORONA-AL)	randomized, quadruple masked	200	Number of ventilator-free days [Time Frame: Up to 28 days	Not yet recruiting	No Results Available	COVID-19 Lung Injury, Acute; hospitalized, with hypoxemia ; adults	100 mg/kg intravenous vitamin C infusion every 8 hours for up to 72 hours vs. Placebo	USA	May 2021
https://ClinicalTrials.gov/show/NCT04323514	Use of Ascorbic Acid in Patients With COVID 19	randomized single-center open label	500	In-hospital mortality [Time Frame: 72 hours	Recruiting	No Results Available	Hospitalized Patients With Covid-19 Pneumonia; children adults	10 gr of vitamin C intravenously + conventional Tx	Italy	March 2021
https://ClinicalTrials.gov/show/NCT04264533	Vitamin C Infusion for the Treatment of Severe 2019-nCoV Infected Pneumonia	randomized, 3-masking	140	Ventilation-free days [Time Frame:day 28 after enrollment]	Recruiting	No Results Available	COVID 19 Serious Acute Respiratory infection, mechanical ventilation, adults	12g Vitamin C+sterile water for injection; total volume: 50ml. 12ml/h; infusion pump ; q12h vs. placebo	China	September 30, 2020
https://ClinicalTrials.gov/show/NCT03680274	Lessening Organ Dysfunction With VITamin C (LOVIT trial)	randomized, 4-masked	800	Mortality or patients with persistent organ dysfunction at 28 days	Recruiting	No Results Available	Sepsis Vitamin C Intensive Care Unit COVID-19 on iv vasopressors, adults	vitamin C administered in bolus doses of 50 mg/kg mixed in a 50-mL solution of either dextrose 5% in water (D5W) or normal saline (0.9% NaCl), during 30 to 60 minutes, every 6 hours for 96 hours (i.e. 200 mg/kg/day and 16 doses in total) vs. placebo	Canada	December 2021

https://ClinicalTrials.gov/show/NCT04328961	Hydroxychloroquine for COVID-19 PEP	randomized double blind	2000	PCR) confirmed SARS-CoV-2 infection [Time Frame: Day 1 through Day 14 after enrolment and Day 28	Recruiting	No Results Available	Adults exposed to COVID	Ascorbic acid 500 mg orally daily for 3 days, then 250 mg x 11 days vs. Hydrochloroquine 400 mg orally daily for 3 days, then 200 mg orally daily for an additional 11 days	USA	September 30, 2020
https://ClinicalTrials.gov/show/NCT04334967	Hydroxychloroquine in Patients With Newly Diagnosed COVID-19 Compared to Standard of Care	Randomized 1: 1	1250	Total Hospitalization , Mechanical ventilation, [Time Frame: 14 days	Enrolling by invitation	No Results Available	COVID 19 not hospitalized	200 mg oral hydroxychloroquine. Day 1: 400 mg doses twice (800 mg total). Days 2-5: 200 mg dose twice (400 mg total daily) vs. 500 mg oral Vitamin C. Day 1: 1000 mg dose twice; Days 2-5: 500 mg dose twice	USA	September 2021
https://ClinicalTrials.gov/show/NCT04354428	Treatment for SARS-CoV-2 in High-Risk Adult Outpatients	RCT 3-arm, double blind	630	Lower respiratory tract infection (LRTI) rates, hospitalization or mortality [Time Frame: 28 days]; viral shedding day 1-14	Recruiting	No Results Available	COVID -19 adults	oral Vit C vs. HC + Folic acid vs. HC + azithromycin	USA	July 2020
https://ClinicalTrials.gov/show/NCT04347889	Preventing COVID-19 in Healthcare Workers With HCQ: A RCT	Randomized, open label	1212	Seroconversion rate [Time Frame: 3 months]	Not yet recruiting	No Results Available	Covid-19 healthcare worker at risk	Oral Vitamin C 1,000 mg daily for 3 mos vs. Oral loading dose of Hydroxychloroquine 800 mg followed by once weekly oral 400 mg x 3 mos.	USA	December 2020
https://ClinicalTrials.gov/show/NCT04342728	Coronavirus 2019 (COVID-19)- Using Ascorbic Acid and Zinc Supplementation	randomized open label 4-arm	520	Symptom Reduction [Time Frame: 28 days]	Enrolling by invitation	No Results Available	COVID Corona Virus Infection outpatient adults	8000 mg of oral ascorbic acid divided into 2-3 doses/day with food vs. Zinc vs. Zinc + Vit C vs. Standard of Care	USA	September 30, 2020