



# Philippine COVID-19 Living Clinical Practice Guidelines

Institute of Clinical Epidemiology, National Institutes of Health, UP Manila

In cooperation with the Philippine Society for Microbiology and Infectious Diseases

Funded by the DOH AHEAD Program through the PCHRD

## EVIDENCE SUMMARY

### Should vitamin C be used in the adjunctive treatment of COVID-19?

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#### RECOMMENDATION

There is insufficient evidence to recommend the use of intravenous Vitamin C as adjunct treatment for patients with COVID-19 infection. (*Low quality of evidence*)

#### Consensus Issues

Since there is insufficient evidence to recommend the use of vitamin C as adjunct treatment for COVID-19 and the quality of evidence is rated low, this means that more randomized controlled trials on vitamin C as adjunct treatment for COVID-19 need to be done.

Intravenous administration was the route used by the included studies in this review. According to the search for pricing, intravenous vitamin C costs Php 430 for 40 ampules of 500mg/2ml but this pricing was from an online selling source; there were no data on pricing of intravenous vitamin C on pharmaceutical websites searched.

#### Key Findings

There were four randomized controlled trials included in this review. Based on these studies, adjunctive treatment with vitamin C among COVID-19 patients did not lead to significant reduction in mortality, need for mechanical ventilation or hospital length of stay. Most of the studies included were found to be at low quality of evidence. There are currently 17 ongoing trials studying the efficacy of vitamin C as an adjunctive treatment for COVID-19.

#### Introduction

Vitamin C (VC), also known as ascorbic acid, is an essential water-soluble vitamin that is required as a cofactor in many enzymatic reactions [1]. It promotes phagocytosis and chemotaxis of leukocytes and development and maturation of T-lymphocytes [2-3]. It also exhibits antioxidant properties through its effect on the NFKB activation that leads to attenuation of inflammation and reduction in reactive oxygen species [4]. Early clinical trials show that VC can alleviate and prevent the common cold [5-6]. However, two observational studies on the effect of VC on COVID-19 showed no mortality benefit and increased hospitalization stay with VC treatment [7-8].

#### Review Methods

We performed a comprehensive systematic search of related literature from Medline and CENTRAL. We also searched for ongoing clinical trials using ClinicalTrial.gov and, Clinicaltrialsregister.eu. Freehand search using Google was also done to check for other sources of information including the Love Platform App. Search was conducted using the following search terms: COVID-19, SARS-CoV-2, vitamin C, ascorbic acid and sodium ascorbate. There was no limit including the date, language and country of publication.



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Eligible articles were evaluated using the following criteria:

Population	COVID-19 patients any age, co-morbidities and severity
Intervention/Exposure	Vitamin C or Sodium Ascorbate or Ascorbic Acid
Comparison	Usual standard of care, placebo, any active control
Outcomes	Mortality, clinical improvement, adverse effects
Methodological filter	randomized controlled trials (RCT), observational clinical studies, systematic review and meta-analysis available

### Results

All of the studies included confirmed COVID-19 patients. A total of four RCTs were included in the study. There were two RCTs on severe COVID-19 [10,12] and one study on patients treated as outpatient [11]. The total daily dose was from 500mg/day to 24g/day given for at least 3 days.

The study of Jamalimoghadamsiahkali et al [9] is a randomized open label clinical trial on the safety and effectiveness of high dose vitamin C in patients with COVID-19. Patients were block-randomized to receive either Vitamin C or no Vitamin C.

The randomized controlled open label trial done by Kumari et al. [10] from March to July 2020 included a total of 150 patients diagnosed with severe COVID-19 based on the national health guidelines of Pakistan. Patients were divided into two groups: 75 patients in the interventional arm receiving 50mg/kg/day of intravenous vitamin C and 75 patients in the placebo arm receiving only the standard therapy for COVID-19.

Another prospective randomized clinical factorial open-label trial was done at multiple hospitals in Ohio and Florida USA [11]. They included 214 adult patients who were diagnosed with COVID-19 by RT-PCR, who received treatment in an outpatient setting.

The randomized controlled trial by Zhang et al. was a multicenter study done in Hubei, China from February 14, 2020 to March 29, 2020 [12]. They included a total of 56 patients 18 to <80 years of age who were diagnosed as SARS-CoV-2 by RT-PCR, pneumonia confirmed by chest imaging with PaO<sub>2</sub>/FiO<sub>2</sub> (P/F) <300mmHg admitted to the ICU.

Four RCTs (N=364) were pooled for the overall mortality outcome, which was not significant (OR 0.66; [95%CI 0.34, 1.28]). Two RCTs were pooled for the outcome of mortality among severe cases, which was not significant (OR 0.54; [95%CI 0.25, 1.16]). Three RCTs analyzed the effect of Vitamin C for the outcome of need for invasive mechanical ventilation, but this was not significant (OR 1.15; [95% 0.64, 2.07]).

There were few adverse events noted in two RCTs [11,12], and none in two RCTs [9,10].

There was no clear allocation concealment and blinding in three of the studies [9-11]. All of the studies had adequate follow up of patients. There was serious imprecision for the outcomes of overall mortality, mortality on severe patients, mortality on patients with sequential organ failure assessment (SOFA) score  $\geq 3$  and need for mechanical ventilation due to wide confidence



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intervals. Moreover, there were inconsistent results across four studies for the outcome of hospital length of stay [9-12].

### Recommendations from Other Groups

The World Health Organization (WHO) and IDSA did not mention the use of vitamin C for COVID-19 in their CPG. The US-NIH made no recommendation for or against use of vitamin C for COVID-19 due to insufficient evidence. Ontario CPG does not recommend Vitamin C for COVID-19 outside of approved clinical trials.

### Research Gaps

Currently there are 17 ongoing studies on the efficacy of Vitamin C as an adjunctive treatment for COVID-19 (Appendix 3). Further, more studies are needed to examine the use of either intravenous or oral vitamin C in suppressing cytokine storms in COVID-19.

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### Appendix 1. Characteristics of Included Studies

Author, Year	Patients (n)	Intervention	Comparator	Outcomes	Study Design
Jamalimogh adamsiahkali 2021	COVID-19 confirmed patients by RT-PCR or by clinical symptoms, chest CT/HRCT, low oxygen saturation (n=60)	Vitamin C 1.5g Q6 x 5 days (6g/day)	No Vitamin C	No significant difference in terms of mortality ( $p>0.05$ ), patients on vitamin C had longer length of hospital stay (median 8.5 vs 6.5 days, $p=0.028$ ). Patients on vitamin C had higher SpO <sub>2</sub> on 3rd day of admission (90.5% vs 88%; $p=0.014$ )	Randomized controlled trial, open label
Kumari et al	Severe COVID-19 patients (n=150)	50mg/kg/day intravenous vitamin C	No vitamin C	There were no statistically significant differences between the two groups in terms of mortality and need for mechanical ventilation. Patients on HDIVC group had earlier symptom free status ( $7.1 \pm 1.8$ vs $9.6 \pm 2.1$ days, $p<0.001$ ) and spent fewer days in the hospital ( $8.1 \pm 1.8$ vs $10.7 \pm 2.2$ days, $p<0.0001$ ) compared to patients without vitamin C	Randomized controlled open label
Thomas et al, 2021	COVID-19 confirmed patients treated as outpatient (n=214)	Vitamin C 8,000mg/day Zinc gluconate 50mg Both zinc and vitamin c	Standard of care	The study was discontinued for futility. there was no significant difference among the 4 study groups in terms of days	RCT, open label trial



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Author, Year	Patients (n)	Intervention	Comparator	Outcomes	Study Design
				required to reach a 50% reduction in symptoms. Moreover, there was no significant difference in any of the secondary outcomes.	
Zhang et al 2021	Severe COVID-19 confirmed patients (n=56)	Vitamin C 24g/day IV x 7 days (HDIVC)	No vitamin C	No statistically significant difference between the two groups in terms of invasive mechanical ventilation-free days, 28-day mortality, 28-day mortality for severe (SOFA $\geq 3$ ). Patients on HDIVC had higher P/F ratio compared to the placebo group. The SOFA score increased in the placebo group and decreased in the HDIVC group. The delta P/F from day 1 to 7 was (20 $\pm$ 96.7 in HDIVC and -51.9 $\pm$ 150.7 in the control group. No study related adverse events in the trial.	Randomized, placebo controlled



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## Appendix 2. GRADE Evidence Profile

**Author(s):** Antonio L. Faltado Jr, MD, Anna Angelica Macalalad-Josue MD  
**Question:** Vitamin C compared to placebo/standard of care for COVID-19  
**Setting:**  
**Bibliography:**

Certainty assessment							N <sub>o</sub> of patients		Effect		Certainty	Importance
N <sub>o</sub> of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin C	placebo/standard of care	Relative (95% CI)	Absolute (95% CI)		
<b>Overall Mortality</b>												
4	randomised trials	serious <sup>a,b</sup>	not serious	not serious	not serious	none	17/180 (9.4%)	25/184 (13.6%)	<b>OR 0.66</b> (0.34 to 1.28)	<b>42 fewer per 1,000</b> (from 85 fewer to 32 more)	⊕⊕⊕○ MODERATE	
<b>Overall Mortality on Severe patients</b>												
2	randomised trials	serious <sup>a,b</sup>	not serious	not serious	serious <sup>c</sup>	none	22/102 (21.6%)	13/104 (12.5%)	<b>OR 0.54</b> (0.25 to 1.16)	<b>53 fewer per 1,000</b> (from 91 fewer to 17 more)	⊕⊕○○ LOW	
<b>Mortality for SOFA &gt;=3</b>												
1	randomised trials	not serious	not serious	not serious	serious <sup>c</sup>	none	5/27 (18.5%)	11/29 (37.9%)	<b>OR 0.37</b> (0.11 to 1.27)	<b>195 fewer per 1,000</b> (from 316 fewer to 58 more)	⊕⊕⊕○ MODERATE	
<b>Hospital Stay</b>												
4	randomised trials	serious <sup>a,b</sup>	serious <sup>a,b,d</sup>	not serious	serious <sup>d</sup>	none	274	276	-	mean <b>0.3 higher</b> (1.06 lower to 1.66 higher)	⊕○○○ VERY LOW	
<b>Need for Invasive Mechanical Ventilation</b>												
3	randomised trials	serious <sup>a,b</sup>	not serious	not serious	serious <sup>c</sup>	none	34/132 (25.8%)	32/105 (30.5%)	<b>OR 1.15</b> (0.64 to 2.07)	<b>30 more per 1,000</b> (from 86 fewer to 171 more)	⊕⊕○○ LOW	
<b>SpO<sub>2</sub> at 3rd Day</b>												
1	randomised trials	serious <sup>a,b</sup>	not serious	not serious	not serious	none	30	30	-	<b>SMD 1.67 SD higher</b> (1.08 higher to 2.26 higher)	⊕⊕⊕○ MODERATE	
<b>Adverse Events</b>												
3	randomised trials	serious <sup>a,b,e</sup>	serious <sup>e</sup>	not serious	not serious	none	The study of Jamal Moghadam Siahkali and reported no adverse events with vitamin C. Thomas et al reported patients who developed diarrhea (7), nausea (6), stomach pains/cramps (5), vomiting (1), Tingling (1) and dizziness/fatness (1)			⊕⊕○○ LOW		

CI: Confidence interval; OR: Odds ratio; SMD: Standardised mean difference

### Explanations

- a. No allocation concealment
- b. In some studies, patients, caregivers and outcome assessors were not blinded
- c. There is wide confidence interval
- d. Studies have inconsistent results
- e. 2 studies reported no adverse events



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### Appendix 3. Characteristics of Ongoing Studies

Clinical Trial Identifier/Title	Study Design	Country	Population	Intervention	Outcome	Estimated Date of Completion
NCT04664010 Efficacy and Safety of High-dose Vitamin C Combined With Traditional Chinese Medicine in the Treatment of Moderate and Severe Coronavirus Pneumonia (COVID-19)	Randomized Controlled Trial, parallel assignment	China	COVID-19	High dose Vitamin C in combination with traditional Chinese Medicine	Primary Outcome: Recovery time Secondary outcome: Relief of Symptoms Conversion time from positive to negative COVID-19	January 31, 2021
NCT04363216 Pharmacologic Ascorbic Acid as an Activator of Lymphocyte Signaling for COVID-19 Treatment	Randomized sequential Assignment	USA	COVID-19	Ascorbic Acid vs routine care	Primary Outcome: Clinical Improvement Secondary Outcome: Patient status upgraded to ICU level, Oxygen supplementation, days with fever, days to discharge, SAEs	May 2021
NCT04710329 High-Dose Vitamin C Treatment in Critically Ill COVID-19 Patients, A Retrospective Cohort Study	Retrospective Cohort Study	Turkey	ARDS Covid-19	Ascorbic Acid	Primary Outcome: Short term mortality Length of ICU stay	Feb 10, 2021



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Clinical Trial Identifier/Title	Study Design	Country	Population	Intervention	Outcome	Estimated Date of Completion
NCT04584437  The Treatment and Prevention of Covid-19 Pandemic Using Infrared and /or Vitamin C.	Single group assignment	Canada	All patients seeking prevention and treatment of COVID-19	Infrared Energy	Treatment and prevention of COVID-19	May 10, 2021
NCT04530539  The Effect of Melatonin and Vitamin C on COVID-19	Randomized parallel assignment	USA	COVID-19 patients	Ascorbic Acid Melatonin Vs Placebo	Primary Outcome: Symptom severity  Secondary Outcome: Symptom progression	Dec. 1, 2021
NCT04323514  Use of Ascorbic Acid in Patients With COVID 19	Single group assignment, open label	Italy	COVID-19 patients	Vitamin C	Primary Outcome: In-hospital Mortality Secondary Outcomes: PCR levels, lactate clearance, hospital stay, symptoms, positive swab, tomography imaging	Mar 13, 2021
NCT04558424  Randomized, Double - Blind, Placebo Controlled, Trial to Evaluate the Effect of Zinc and Ascorbic Acid Supplementation in COVID-19 Positive Hospitalized	Randomized, Double - Blind, Placebo Controlled, Trial	Bangladesh	COVID-19	Vitamin C and Zinc	Primary outcome: Symptoms reduction time frame  Secondary Outcome: Symptom resolution	Sept 1, 2021





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Clinical Trial Identifier/Title	Study Design	Country	Population	Intervention	Outcome	Estimated Date of Completion
Patients in BSMMU						
NCT04468139 The Study of Quadruple Therapy Zinc, Quercetin, Bromelain and Vitamin C on the Clinical Outcomes of Patients Infected With COVID-19	Single group assignment	Saudi Arabia	COVID-19	Quercetin Bromelain Zinc Vitamin C	Primary Outcome: Hospital Stay after treatment	July 2020
NCT04395768 Therapies to Prevent Progression of COVID-19, Including Hydroxychloroquine, Azithromycin, Zinc, Vitamin D, Vitamin B12 With or Without Vitamin C, a Multi-centre, International, Randomized Trial: The International ALLIANCE Study	Randomized parallel assignment	Australia	COVID 19	Vitamin C in combination with, Hydroxychloroquine, Azithromycin, Zinc, Vitamin B12 and Vitamin D3 vs control	Symptoms, length of hospital stay, invasive mechanical ventilation	Sept 30, 2021
NCT04357782 Administration of Intravenous with hypoxemia	Non-Randomized, single group assignment, open label	USA	COVID-19 with hypoxemia	L-Ascorbic acid	Primary Outcome: Incidence of Adverse events, serious adverse reactions  Secondary Outcome:	Oct 13, 2020



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Clinical Trial Identifier/Title	Study Design	Country	Population	Intervention	Outcome	Estimated Date of Completion
Vitamin C in Novel Coronavirus Infection and Decreased Oxygenation (AVoCaDO): A Phase I/II Safety, Tolerability, and Efficacy Clinical Trial					Ventilator-free days, ICU-free days, hospital-free days, all-cause mortality, change in S/F ratio, CRP, LDH, D-dimer, lymphocyte count, NLR, serum ferritin	
NCT04342728 Coronavirus Disease 2019- Using Ascorbic Acid and Zinc Supplementation (COVIDAtoZ) Research Study A Randomized, Open Label Single Center Study	Randomized, single group assignment	USA	COVID-19	Ascorbic acid vs Zinc vs Ascorbic acid + Zinc vs standard of care	Primary Outcome: Symptom reduction  Secondary Outcome: Symptom resolution; fever, cough, SOB, fatigue, muscle/body aches, headache, new loss of taste, new loss of smell, congestion, nausea, vomiting, diarrhea, hospitalization, severity of symptoms, adjunctive medications, side effects	April 30, 2021
NCT04682574 Efficacy of Mega Dose Vitamin C in Critically Ill COVID-19 Patients	Randomized parallel assignment	Pakistan	Critically Ill COVID-19 patients	Vitamin C vs placebo	Primary Outcome: Partial pressure of Oxygen in arterial blood to fraction of inspired Oxygen (P/F ratio) [ Time Frame: 2 to 7 day Secondary Outcome: Duration of hospital stay	Jan 10, 2021
NCT04344184 SAFEty Study of	Randomized, parallel assignment	USA	COVID-19 with hypoxemia	Intravenous vitamin C vs	Primary Outcome: Change in COVID disease status	May 2021



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Clinical Trial Identifier/Title	Study Design	Country	Population	Intervention	Outcome	Estimated Date of Completion
Early Infusion of Vitamin C for Treatment of Novel Coronavirus Acute Lung Injury (SAFE EVICT CORONA-ALI)				Standard of care	Secondary Outcome: Renal safety biomarkers, AKI-free days, number of deaths, plasma ferritin levels, D-dimer, LDH, IL-6, proportion of patients alive and free of respiratory failure, proportion of patients alive and free of invasive mechanical ventilation.	
NCT04570254 Open Clinical Trial of the Use of Antioxidants and Pentoxifylline as Adjuvant Therapy to Standard Therapy in Patients With and Without Septic Shock Secondary to COVID-19 Severe Pneumonia	Non Randomized, Parallel Assignment	Mexico	Severe Covid 19	Vitamins C, E, melatonin, N-acetylcysteine, Pentoxifylline	Primary Outcome: Death from Any Cause, Orotracheal intubation, Use of Mechanical Ventilation, ICU admission  Secondary outcome: Lipoperoxidation levels before and after treatment, total antioxidant capacity, oxidant and antioxidant stress, effect of antioxidant therapy at the level on organ failure	Oct. 15, 2020
NCT04401150 Lessening Organ Dysfunction With VITamin C - COVID-19	multicentre concealed-allocation parallel-group blinded randomized controlled trial	Canada	Confirmed COVID-19	Vitamin C vs placebo	Primary Outcome: Death or persistent organ dysfunction	November 2021
NCT04357782 Administration of Intravenous	Non Randomized Single Group Assignment	USA	COVID-19 patients with decreased oxygenation	Intravenous Vitamin C for mild hypoxemia,	Primary Outcome: Incidence of adverse events, serious adverse events, adverse reactions	Oct 13, 2020



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Clinical Trial Identifier/Title	Study Design	Country	Population	Intervention	Outcome	Estimated Date of Completion
Vitamin C in Novel Coronavirus Infection and Decreased Oxygenation (AVoCaDO): A Phase I/II Safety, Tolerability, and Efficacy Clinical Trial				vs Intravenous Vitamin C for severe hypoxemia	Secondary outcome: Ventilator free days, ICU free days, hospital free days, all cause mortality, change in SF ratio, CRP, LDH, D-dimer, lymphocyte count, NLR, serum ferritin	
NCT04395768 Therapies to Prevent Progression of COVID-19, Including Hydroxychloroquine, Azithromycin, Zinc, Vitamin D, Vitamin B12 With or Without Vitamin C, a Multi-centre, International, Randomized Trial: The International ALLIANCE Study	Multi-centre, International, Randomized Trial	Australia	Active COVID-19 infection	azithromycin, hydroxychloroquine, zinc, Vitamin D3/B12 and IV vitamin C vs azithromycin, zinc and hydroxychloroquine, Vitamin D3/B12.	Primary Outcome: Change in severity of symptoms, length of hospital stay, invasive mechanical ventilation.  Secondary Outcome: Mortality, mechanical ventilation, oxygen requirement, ICU admission, days in hospital, days in ICU, renal replacement therapy, extracorporeal support	Sept 30, 2021
NCT04530539 The Effect of Melatonin and Vitamin C on COVID-19	Randomized, double-blind placebo controlled trial	USA	Symptomatic confirmed COVID-19 patients	Vitamin C vs Melatonin vs placebo	Primary Outcome: Symptom severity  Secondary Outcome: Symptom Progression	Sept 1, 2021