Should Vitamin C/Ascorbic Acid infusion be used in the treatment of COVID-19?

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This rapid review summarizes the available evidence on the efficacy and safety of Vitamin C infusion in treating patients with COVID-19. This may change as new evidence emerges.

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 suspected of, or positive for COVID-19.

- Vitamin C is currently not mentioned in the treatment guidelines for COVID.
- Currently, there are 3 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. One meta-analysis showed benefit in decreasing duration of ICU stay and mechanical ventilation but sample size is small. Most showed no benefit on and other key endpoints such as acute kidney injury, duration of hospital stay/ ICU stay/ duration of vasopressor use or duration of mechanical ventilation.
- The use of Vit C infusion is not mentioned in the treatment guidelines for COVID-19 or ARDS.
- 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.

BACKGROUND

Vitamin C is a water-soluble compound that can be administered by oral, enteral, and parenteral routes. It is a known antioxidant and maintains endothelial barriers. It has been shown in animal studies to prevent cytokine surges which lead to alveolar capillary damage, prevent neutrophil accumulation in alveolar spaces, support phagocytosis of bacteria, and support lymphocyte function. Vitamin C is also involved in non-oxidant processes like biosynthesis of collagen, carnitine, tyrosine and peptide hormones as well as of myelin.

The drug is widely used as a nutritional supplement. A Cochrane meta-analysis on oral Vitamin C > 200 mg/day vs. placebo for the treatment and prevention of the common cold was done in 2013. Regular ingestion of vitamin C did not affect incidence of common colds in the ordinary population (n=11306, 29 trials), but had a modest, consistent effect in reducing duration (31 study comparisons, 9745 common cold episodes). In 5 trials with 598 participants exposed to short periods of extreme physical stress (including marathon runners and skiers), vitamin C reduced by half the risk for common colds.[1]

The use of oral Vitamin C is associated mostly with gastrointestinal adverse effects such as such as nausea, vomiting, and diarrhea. Formation of formation of calcium-oxalate stones has been reported with long term use. Intravenous administration is not associated with side effects due to the short-term administration. Patients with G6PD deficiency are at risk for hemolysis. The dose of Vitamin C should be adjusted among patients with renal insufficiency. The complete list of known adverse effects can be found in product labels.

METHODS

See General Methods Section.

Articles were selected based on the following inclusion criteria:

- **Population:** suspected or confirmed COVID-19 patients of any age, with any co-morbidities, any severity
- **Intervention:** Vitamin C infusion any dose, any duration
- **Comparator:** placebo, any active control, no intervention
- **Outcomes:** Mortality, recovery, duration of disease
- **Study designs:** randomized controlled trials (RCTs), non-randomized studies, systemic reviews/meta-analysis, case report

Exclusion Criteria

- Oral Vitamin C alone
- Non-human studies
- Literary articles (e.g. blogs)
- Studies before 2000
- Academic reviews
- Full text publication not available
- Non-English articles

Characteristics of Included Studies

- Summary of Included Studies
  - Number of ongoing clinical trials found: 4
  - Number of included studies in the review: 10
    - Types of studies included and sample size
      - RCT: 2 studies; n=383
      - Retrospective cohort: 1; n= 99
      - Meta-analysis: 6 studies; n= overlapping total of 11,205;, mean of 1867; range of 109 to 6,455
      - Case report: 1
  - Countries where studies were done: most did not specify. Australia, Brazil, Korea, New Zealand, USA
  - Refer to Appendix 2 Table (Characteristics of Included Studies)

There are no completed clinical trials or systematic reviews/meta-analyses studying the efficacy of intravenous vitamin C in COVID-19. Currently, there are 5 trials registered in clinicaltrials.gov studying intravenous (3 trials) or oral (2 trials) vitamin C in COVID-19. See Appendix 2. No other ongoing or planned trials were registered in the other trial registries. [2]

In lieu of the absence of completed trials on COVID-19, we describe below the literature on i.v. Vitamin C used in patients who may be suspected of having the disease. For purposes of rapid review, we have limited this to patients who have viral pneumonia, sepsis with or without ARDS, and critically ill patients due to other disease conditions.

1. There was only 1 published study, a case report, on the use of intravenous Vit C in a virus-induced case of ARDS. The effect of Vitamin C in this case report cannot be accepted as conclusive and may only be coincidental.
   - In 2017, the primary author of the CITRIS-ALI RCT and his team published a case report on the use of intravenous vitamin C as adjunctive therapy for enterovirus/rhinovirus-induced acute respiratory distress syndrome. [3] The patient received standard intensive care management, including antibiotics, mechanical ventilation, bronchoscopy for microbiological sampling, and extracorporeal membrane oxygenation (ECMO). Vitamin C infusion at 200 mg/kg/24hrs was given on the 2nd ECMO day. Patient was eventually discharged on the 12th hospital day.

2. Two randomized clinical trials and 2 meta-analyses studied the effect of vitamin C infusion among septic patients. Of these, 1 RCT and 1 meta-analysis showed significant benefit in mortality but only in the secondary or subset analyses which were underpowered. There was no difference in mortality up to 90 days in the 2nd RCT trial. These are summarized below:
   - The CITRIS-ALI trial [4] 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-induced lung injury present for less than 24 hours. The inclusion criteria included conditions such as presence of systemic inflammatory response, arterial hypoxemia, and ARDS that are found in severe COVID-19 cases. Patients were randomly assigned to receive intravenous infusion of vitamin C 200mg/kg/day divided every 6 hours for 96 hours x 4 doses or placebo D5W infusion. Vitamin C did not improve the primary outcome of organ dysfunction scores or alter markers of

inflammation (CRP) and vascular injury (thrombomodulin). However, statistically significant benefits with regards to 3 of the 46 pre-specified secondary endpoints were observed with Vit C vs. placebo: a) mortality to day 28: 29.8% vs. 46.3%, respectively, p=0.03 and with KM curves statistically significant as well at p=0.01. b) number of ICU-free days to day 28: 10.7 vs. 7.7, respectively, and c) number of hospital free days to day 60: 22.6 vs. 15.5, respectively. The level of significance was not adjusted for the 46 secondary endpoints and potential for Type 1 error is inherent in the multiple comparisons. These findings were considered exploratory. The supposed benefit on mortality (one of many secondary outcomes) in the CITRIS-ALI trial may not be clinically robust and not representative of the true effect of vitamin C. It may not statistically persist in a larger setting. No drug-related adverse events occurred during the trial.

- The VITAMINS trial [5] was a multicenter, open-label, randomized clinical trial conducted in 10 intensive care units in Australia, New Zealand, and Brazil that recruited 216 patients fulfilling the Sepsis-3 definition of septic shock. Patients were randomized to control of hydrocortisone alone, versus hydrocortisone + thiamine + intravenous vitamin C. Treatment with intravenous vitamin C, hydrocortisone, and thiamine, compared with intravenous hydrocortisone alone, did not significantly improve the duration of time alive and free of vasopressor administration over 7 days. There were also no benefits on the secondary endpoints (in-hospital, day 28 and day 90 mortality; number of free days from mechanical ventilation, renal replacement therapy, ICU; and length of hospital stay). Adverse events were reported for 2 patients (2 events, fluid overload and hyperglycemia) in the intervention group and 1 patient (1 event, gastrointestinal bleeding) in the control group. No SAEs or SUSARs reported.
- Lin et al [6] performed a random effects meta-analysis on 6 trials (4 RCTs and 2 retrospective trials) published up to November 2018 focusing on in-hospital or 28-day mortality as the outcome among patients with sepsis (n=109). There was no difference in mortality in the over-all population. Among 40 patients with severe sepsis given high dose vitamin C (66 mg/kg/hour), there was a statistically significant reduction in mortality (OR 0.39, 95% CI 0.16 - 0.94, P < 0.05).
- The meta-analysis by Li in 2018 was excluded because the trials analyzed were already included in other meta-analyses. [7]

3. One retrospective study and several meta-analyses evaluated the use of vitamin C in critically ill patients due to conditions other than or in combination with sepsis. All showed no significant differences observed in mortality vs. control group. Most of included trials are overlapping in these meta-analyses which are summarized below:
    - A 2018 retrospective study on the effect of intravenous Vit C on in-hospital mortality among ICU patients with severe pneumonia was conducted on 53 patients vs. control group of 46 patients. [8] This hospital follows a routine administration of Vit C protocol (vitamin C 1.5 g every 6 h for 4 days + hydrocortisone 50 mg every 6 h for 7 days then tapered over 3 days + i.v. thiamine 200mg every 12 h for 4 days) for severe pneumonia. The treatment group should have received the Vit C protocol within 48 hours of ICU admission. Results in the unmatched cohort showed a tendency towards lower in-hospital mortality in the treatment group. Results in the propensity-matched cohort (n=36 per group) showed a significantly lower mortality in the treatment group. The results were correlated with a significant improvement in radiologic findings starting on 7th day of hospitalization. There were no differences in other secondary outcomes such as event-free days for use of vasopressors and mechanical ventilation, organ function scores, and incidence of AKI. The limitations of this study that preclude its relevance to COVID-19 pneumonia include the following: small sample size, use of corticosteroids, and

unreported etiology of pneumonia (viral vs. bacterial). In addition, the authors did not report if their institution has since then discontinued the routine use of their Vit C protocol.

- A Cochrane meta-analysis [9] on i.v. and oral vitamin C and length of stay in the ICU based on a search that extended to January 2019 included 17 studies (n=1967). Thirteen of these studies involved cardiac patients, 2 involved septic patients, and the rest, lung contusion and burns. No analysis on mortality was done. Benefits on surrogate endpoints such as length of ICU stay and duration of ventilation were found. Length of ICU stay was significantly lower by 7.7% among those given intravenous Vitamin C (6 trials on i.v. Vit C; n=839). Among patients on mechanical ventilation > 24 hours (2 trials on i.v. Vit C with n=65, 1 on oral Vit C with n= 185), the duration of ventilation was significantly shorter by 18.2 %. This was largely driven by the trial on oral Vit. C. There was no effect on patients who were on ventilation ≤ 24 hours on 3 trials (2 oral n=238; 1 iv n=40).
- Meta-analysis by Putz et al [10] was done on randomized trials of vitamin C and mixed ICU patients using online search up to October 2018. Both oral and intravenous Vitamin C were used in 44 randomized trials involving 6,455 patients. Among ICU patients (16 trials, n=2,857), vitamin C administration was not associated with a difference in mortality in any of the disease conditions analyzed (sepsis, acute pancreatitis, burns, and other mixed conditions) as well as no difference in acute kidney injury, ICU or hospital length of stay compared with control. Among patients who underwent cardiac surgery (28 trials, n=3598) there was also no difference in mortality, AKI, stroke, and ventricular arrhythmias. There were significant reductions in supraventricular arrhythmias (mainly with atrial fibrillation) and length of ICU stay.
- A meta-analysis by Wang et al in 2019 [11] using trials identified after search of databases up to 2018. They analyzed the impact of different doses of Vitamin C infusion in 12 randomized trials comparing Vit C (n=624) with placebo or other antioxidants (n=586) for patients with sepsis, burns, critical injury, and postoperative conditions. Four trials, including 1 on patients with sepsis, were new or have not been included in the other meta-analyses described in this report. There was no impact on mortality among patients who given low (< 3g/day) and high (≥ 10 g/day). A significant absolute mortality reduction of 8.5% was found among those who received moderate dose (3-10 gm/day) which included small number of patients with sepsis (69 / 405 patients in the treatment arm vs. 69/395 patients in the placebo arm). For all dosing groups, there were no differences found in the duration of vasopressor and ventilatory support, occurrence of AKI , and hospital/ICU stay.
- A small meta-analysis in 2018 by Zhang and Jativa [12] was conducted on studies up to September 2017 dealing with intravenous vitamin C in critically ill patients (trauma, burns, post-surgery). Five studies (4 RCTs and 1 retrospective review) involving 142 patients were included, with follow-up ranging from 6 to 28 days. Three of the trials were also included in the 2019 Cochrane meta-analysis. However, in contrast to the Cochrane study, mortality was the primary outcome analyzed, of which the results were not significantly different. Intravenous vitamin C use was associated with a statistically significant decrease in need for pressor support and decrease in duration of mechanical ventilation.
- Langlois et al [13] performed a meta-analysis on 11 RCTs identified after a database search of up to December 2017 with mortality as the primary outcome. Four of these were conducted using Vit C infusion and the rest were administered via oral or enteral routes. All 4 infusion trials (n=1024) were previously included in other meta-analyses. There were no differences in mortality rates in the overall population (9 trials, n=1322)

and in the different subset analyses infusion trials which were conducted on patients with sepsis (n=54), mixed conditions (n=200), or surgical/trauma cases (n=770); combination therapy; monotherapy; high vs low dose; and high vs. low methodological quality. In addition, there were also no effects seen in other endpoints such as other infections, ICU/hospital stay, and duration of ventilation.

Effectiveness Outcomes

There are currently no completed clinical trials on Vitamin C in COVID-19 with effectiveness outcomes on recovery from the illness, duration of illness, reduction of mortality, reduction in hospitalization.

Safety Outcomes

There are currently no completed clinical trials on Vitamin C in COVID-19 with safety outcomes such as drug-related adverse events.

Recommendations from Other Guidelines

- There are no guidelines mentioning the use of vitamin C in the management of COVID-19 [14,15] or ARDS.[16]
- The TGA (Therapeutic Goods Administration) of the Australian Government Department of Health had issued guidance stating, “there is no robust scientific evidence to support the usage of this vitamin in the management of COVID-19”.[17]

CONCLUSION

There is no direct evidence available as of this point for efficacy of intravenous vitamin C in preventing mortality or shortening disease course among adults with COVID-19 illness. Three trials on intravenous Vit C and 1 trial on prophylactic oral intake are currently ongoing

Indirect evidence from use of intravenous vitamin C in sepsis showed conflicting benefits on mortality. The studies are small and further studies may be attempted to elucidate the effects of vitamin C, especially on hard outcomes like mortality and length of disease course. The supposed benefit on mortality (one of many secondary outcomes) in the CITRIS-ALI trial [5] may not be clinically robust and not representative of the true effect of vitamin C. It may not statistically persist in a larger setting. The reduction in length of ICU stay may be statistically significant but modest (7.7%) in 1 meta-analysis. This may or may not translate to a clinically significant effect (e.g. 1 day shortened in a 13-day ICU stay). The same meta-analysis showed modest, statistically-significant benefits demonstrated in other outcomes such as decreased need for vasopressors, reduced duration of mechanical ventilation), but may not be clinically robust.

The findings from the retrospective study and 5 meta-analyses on critically-ill patients with conditions other than or in combination with sepsis cannot directly be applied to COVID-19 or other viral illness, especially moderate to severe ones, since the pathophysiology of the diseases are different, and interaction with other factors like comorbidities may further modify the effect of

the intervention. Indirect evidence from all these articles showed no effect on mortality. All other meta-analyses that evaluated the use Vitamin C infusion given alone or in combination with other agents when compared to placebo or other treatments did not show benefit with other clinical outcomes (AKI, arrhythmias) and surrogate outcomes (hospital/ICU LOS, duration of vasopressor use , duration of ventilation).

The trials have reported no or minimal adverse events, and the decision to use intravenous vitamin C should also take this into account.

In summary, there is currently no direct evidence showing benefit on mortality and other softer endpoints with the administration of intravenous Vit C to patients with COVID -19. There may be a benefit on mortality, length of ICU stay and duration of mechanical ventilation among patients with sepsis and ARDs who may be considered COVID-19 suspects but larger studies are needed. The use of Vit C in other critical conditions did not lead to a benefit in mortality and other key clinical endpoints.

Declaration of Conflict of Interest

No conflict of interest

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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=&gndr=&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=&rfpd_s=&rfpd_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 Stayin 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
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
16. Griffiths MJD, et al. Guidelines on the management of acute respiratory distress syndrome. BMJ Open Resp Res 2019;6:e000420. doi: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 included studies

Author	Journal/Year	Study design	Country	Disease condition	Population size	Intervention Group(s)	Comparison Group(s)	Primary outcomes	Key Secondary Outcomes	Key findings	Reported AEs	Limitations
Fowler et al (CITRIS-ALI)	JAMA. 2019	RCT	USA	Sepsis ARDS	170	Vit C 200mg/kg/day divided over 4 doses. Administered every 6 hours for 96 hours	5% Dextrose	change in organ failure (mSOFA score) CRP level Thrombomodulin	all cause death day 28 ventilator free, ICU free days at day 28 Hospital free day - 60 days Glasgow Coma Scale	Primary endpoints not met + benefit on some Secondary endpoints: mortality to day 28: 29.8% vs. 46.3%, respectively, p=0.03 and with KM curves statistically significant as well at p=0.01. b) number of ICU-free days to day 28: 10.7 vs. 7.7, respectively, and c) number of hospital free days to day 28: 22.6 vs. 15.5, respectively.	none	underpowered for the analyis of 46 secondary endpoints no adjustment of statistical signficance for the secondary outcomes benefit in mortality is not consistent with failure to meet mSOFA endpoint. Dose of vit C was correlated with plasma vit c measurements
VITAMINS trial investigators.	Crit Care Resusc. 2019	RCT	AU, NZ, Brazil	Septic shock	216	Vit C + hydrocortisone + Vit B	Hydrocortisone	duration of time alive Freedom from vasopressor	mortality in hosp day 28 and day 90 at day 28 number of free days from ventilation, RRT, ICU LOS hospital	no difference in all primary and secondary outcomes	fluid overload, hyperglycemia	open label ; underpowered to detect mortality and secondary clinical outcomes
HemilÃ¤ H, Chalker E.	Nutrients. 2019	MA	17 studies	Sepsis Burns post-cardiac surgery	1,967	Iv Vit c	placebo	ICU stay, duration of ventillation		Shorter LOS ICU by 7.7%, shorter ventillation time in patients > 24 hours by 18.2%		Mixed disease condition
Kim et al	J Crit Care. 2018	Retrospective, single-center propensity matched cohort	Korea	ICU Severe pneumonia	99	Vit C + hydrocortisone + Vit B vs. SOC		in-hospital mortality	AKI; LOS hospital; event - free days for vasopressor, intubation; AKI	NO difference in mortality in over-all cohort. Significant benefit in mortality in the propensity matched cohort correlated with significant improvement in CXR findings	equal incidence of AKI	small sample size, microbial etiology not reported,

Lin J, et al	Open J Int Med , 2018	MA	no	sepsis/ septic shock	4 RCTs 2 retrospective n=109	Vit c low, medium or high dose (oral and iv)	placebo	in-hospital mortality 28-day mortality		overall : not associated with a reduction in mortality as compared placebo (OR 0.46, 95% CI 0.17 - 1.24, P > 0.05) 40 patients with severe sepsis given high dose vitamin C (66 mg/kg/hour): statistically significant reduction in mortality (OR 0.39, 95% CI 0.16 - 0.94, P < 0.05).		significant heterogeneity (P = 0.04 < 0.05, I 2 = 58%). Small sample size
Putzu, et al	Crit Care Med 2019	MA	Italy, india, spain, USA, canada, Egypt, Greece, Germany, Japan, Iran , Switzerland, KSA,	Critically ill - sepsis, burns, acute pancreatitis, mixed ICU	16 ICU RCT n=2857 28 cardiac surgery RCT=3598		placebo or no treatment	Mortality, AKI , stroke, arrhythmias		in BOTH groups NO difference in mortality ICU group: risk ratio, 0.90; 95% CI, 0.74–1.10; p = 0.31), cardiac surgery: RR, 1.00; 95% CI, 0.48–2.08; p = 1.00 No differences in AKI, Stroke, ventricular arrhythmia		heterogenous patient population, clinical settings, and vit c treatment
Langlois PL et al	JPEN Nutr 2019	MA	not specified	Critically ill - sepsis, burns, mixed ICU	11 RCTs (9 with mortality) n=1322	iv or oral Vit C	placebo	in-hospital mortality 28-day mortality		No difference in mortality in overall population and all subgroups (high vs low dose, combined vs. monotherapy, septic vs. non-septic, oral vs. parenteral; high vs low quality		Mixed disease conditions, small sample size
Wang Y, Lin H, Lin BW, Lin JD.	Ann In Care 2019	MA	not specified	sepsis, burn, post-op, critical injury	12 (RCT, observational) n=1210	IV Vit C low, medium, high dose	placebo	Mortality	duration of vasopressor and ventilatory support, occurrence of AKI , and hospital/ICU stay.	mortality reduction of 8.5% was found among those who received moderate dose (3-10 gm/day) ; no differences found in low and high dose benefit in duration of vasopressor and MV use;		Mortality study not sufficiently powered

										no benefit in AKI, LOS ICU or hospital		
Fowler et al	WJCCM 2017	Case report	USA	Severe virus-induced pneumonia	1	200 mg/kg/24hr	NA	Recovery		Discharged from ICU on day 12		Case report

Appendix 2. Characteristics of ongoing 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	• 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	• Sepsis • ICU • COVID-19 • Pandemic • Coronavirus	• 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	• Drug: Hydroxychloroquine400 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 3. Literature search

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	(("ascorbic acid"[MeSH Terms] OR ("ascorbic"[All Fields] AND "acid"[All Fields]) OR "ascorbic acid"[All Fields] OR "vitamin c"[All Fields]) AND ("virus diseases"[MeSH Terms] OR ("virus"[All Fields] AND "diseases"[All Fields]) OR "virus diseases"[All Fields] OR ("viral"[All Fields] AND "disease"[All Fields]) OR "viral disease"[All Fields])) AND ("2010/04/06"[PDat] : "2020/04/02"[PDat])	4/2/2020	8	0
Medline	MeSH Terms: ascorbic acid; coronavirus		1	0
Medline	((("Ascorbic Acid"[Mesh]) OR ("ascorbic acid") OR (ascorbate) OR ("vitamin C"))) AND (("Respiratory Insufficiency"[Mesh]) OR ("Respiratory Distress Syndrome, Adult"[Mesh]) OR ("Intubation"[Mesh]) OR ("Ventilator Weaning"[Mesh] OR "Ventilators, Mechanical"[Mesh]) OR ("Lung Injury"[Mesh]) OR ("Intensive Care Units"[Mesh]) OR ("Pneumonia, Viral"[Mesh]))		134	4
	Trials identified from individual review of manuscripts		7	7
Trial Registries				
ClinicalTrials.gov			5	0
Chinese Clinical Trial Registry			0	0