

11: Supplements

Last Updated: February 11, 2021

Summary Recommendations
<p>Vitamin C</p> <ul style="list-style-type: none">• There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of vitamin C for the treatment of COVID-19.
<p>Vitamin D</p> <ul style="list-style-type: none">• There are insufficient data for the Panel to recommend either for or against the use of vitamin D for the treatment of COVID-19.
<p>Zinc</p> <ul style="list-style-type: none">• There are insufficient data for the Panel to recommend either for or against the use of zinc for the treatment of COVID-19.• The Panel recommends against using zinc supplementation above the recommended dietary allowance for the prevention of COVID-19, except in a clinical trial (BIII).
<p>Rating of Recommendations: A = Strong; B = Moderate; C = Optional</p> <p>Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion</p>

In addition to the antiviral medications and the immune-based therapies that are discussed elsewhere in the COVID-19 Treatment Guidelines, adjunctive therapies are frequently used in the prevention and/or treatment of COVID-19 or its complications. Some of these agents are being studied in clinical trials.

Some clinicians advocate for the use of vitamin and mineral supplements to treat respiratory viral infections. Ongoing studies are evaluating the use of vitamin and mineral supplements for both the treatment and prevention of severe acute respiratory syndrome coronavirus 2 infection.

The following sections describe the underlying rationale for using adjunctive therapies and summarize the existing clinical trial data. Other adjunctive therapies will be added as new evidence emerges.

Vitamin C

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Vitamin C (ascorbic acid) is a water-soluble vitamin that is thought to have beneficial effects in patients with severe and critical illnesses. It is an antioxidant and free radical scavenger that has anti-inflammatory properties, influences cellular immunity and vascular integrity, and serves as a cofactor in the generation of endogenous catecholamines.^{1,2} Because humans may require more vitamin C in states of oxidative stress, vitamin C supplementation has been evaluated in numerous disease states, including serious infections and sepsis. Because serious COVID-19 may cause sepsis and acute respiratory distress syndrome (ARDS), the potential role of high doses of vitamin C in ameliorating inflammation and vascular injury in patients with COVID-19 is being studied.

Recommendation for Non-Critically Ill Patients With COVID-19

- There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of vitamin C for the treatment of COVID-19 in non-critically ill patients.

Rationale

Because patients who are not critically ill with COVID-19 are less likely to experience oxidative stress or severe inflammation, the role of vitamin C in this setting is unknown.

Recommendation for Critically Ill Patients With COVID-19

- There are insufficient data for the Panel to recommend either for or against the use of vitamin C for the treatment of COVID-19 in critically ill patients.

Rationale

There are no completed controlled trials of vitamin C in patients with COVID-19, and the available observational data are sparse and inconclusive. Studies of vitamin C in sepsis patients and ARDS patients have reported variable efficacy and few safety concerns.

Clinical Data on Vitamin C in Critically Ill Patients Without COVID-19

Intravenous Vitamin C Alone

A small, three-arm pilot study compared two regimens of intravenous (IV) vitamin C to placebo in 24 critically ill patients with sepsis. Over the 4-day study period, patients who received vitamin C 200 mg/kg per day and those who received vitamin C 50 mg/kg per day had lower sequential organ failure assessment (SOFA) scores and levels of proinflammatory markers than patients who received placebo.³

In a randomized controlled trial in critically ill patients with sepsis-induced ARDS (n = 167), patients who received IV vitamin C 200 mg/kg per day for 4 days had SOFA scores and levels of inflammatory markers that were similar to those observed in patients who received placebo. However, 28-day mortality was lower in the treatment group (29.8% vs. 46.3%; $P = 0.03$), coinciding with more days alive and free of the hospital and the intensive care unit.⁴ A post hoc analysis of the study data reported a difference in median SOFA scores between the treatment group and placebo group at 96 hours; however, this difference was not present at baseline or 48 hours.⁵

Intravenous Vitamin C Plus Thiamine With or Without Hydrocortisone

Two small studies that used historic controls reported favorable clinical outcomes (i.e., reduced mortality, reduced risk of progression to organ failure, and improved radiographic findings) in patients with sepsis or severe pneumonia who received a combination of vitamin C, thiamine, and hydrocortisone.^{6,7}

Three recent randomized trials in which patients received vitamin C and thiamine (with or without hydrocortisone) to treat sepsis and septic shock showed that this combination conferred benefits for certain clinical parameters. However, no survival benefit was reported. Two trials observed reductions in organ dysfunction (as measured by a SOFA score at Day 3)^{8,9} or the duration of shock¹⁰ without an effect on clinical outcomes. Two other trials found no differences in any physiologic or outcome measure between the treatment and placebo groups.^{11,12}

See [ClinicalTrials.gov](https://clinicaltrials.gov) for a list of clinical trials that are evaluating the use of vitamin C in patients with COVID-19.

Other Considerations

It is important to note that high circulating concentrations of vitamin C may affect the accuracy of point-of-care glucometers.¹³

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Vitamin D

Last Updated: July 17, 2020

Recommendation

- There are insufficient data to recommend either for or against the use of vitamin D for the prevention or treatment of COVID-19.

General Information

Vitamin D is critical for bone and mineral metabolism. Because the vitamin D receptor is expressed on immune cells such as B cells, T cells, and antigen-presenting cells, and because these cells can synthesize the active vitamin D metabolite, vitamin D also has the potential to modulate innate and adaptive immune responses.¹

Vitamin D deficiency (defined as a serum concentration of 25-hydroxyvitamin D \leq 20 ng/mL) is common in the United States, particularly among persons of Hispanic ethnicity and Black race. These groups are overrepresented among cases of COVID-19 in the United States.² Vitamin D deficiency is also more common in older patients and patients with obesity and hypertension; these factors have been associated with worse outcomes in patients with COVID-19. In observational studies, low vitamin D levels have been associated with an increased risk of community-acquired pneumonia in older adults³ and children.⁴

Vitamin D supplements may increase the levels of T regulatory cells in healthy individuals and patients with autoimmune diseases; vitamin D supplements may also increase T regulatory cell activity.⁵ In a meta-analysis of randomized clinical trials, vitamin D supplementation was shown to protect against acute respiratory tract infection.⁶ However, in two randomized, double-blind, placebo-controlled clinical trials, administering high doses of vitamin D to critically ill patients with vitamin D deficiency (but not COVID-19) did not reduce the length of the hospital stay or the mortality rate when compared to placebo.^{7,8} High levels of vitamin D may cause hypercalcemia and nephrocalcinosis.⁹

Vitamin D and COVID-19

The role of vitamin D supplementation in the prevention or treatment of COVID-19 is not known. The rationale for using vitamin D is based largely on immunomodulatory effects that could potentially protect against COVID-19 infection or decrease the severity of illness. Ongoing observational studies are evaluating the role of vitamin D in preventing and treating COVID-19.

Some investigational trials on the use of vitamin D in people with COVID-19 are being planned or are already accruing participants. These trials will administer vitamin D alone or in combination with other agents to participants with and without vitamin D deficiency. The latest information on these clinical trials can be found on [ClinicalTrials.gov](https://clinicaltrials.gov).

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Zinc Supplementation and COVID-19

Last Updated: February 11, 2021

Recommendations

- There are insufficient data to recommend either for or against the use of zinc for the treatment of COVID-19.
- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** using **zinc** supplementation above the recommended dietary allowance for the prevention of COVID-19, except in a clinical trial (**BIII**).

Rationale

Increased intracellular zinc concentrations efficiently impair replication in a number of RNA viruses.¹ Zinc has been shown to enhance cytotoxicity and induce apoptosis when used in vitro with a zinc ionophore (e.g., chloroquine). Chloroquine has also been shown to enhance intracellular zinc uptake in vitro.² The relationship between zinc and COVID-19, including how zinc deficiency affects the severity of COVID-19 and whether zinc supplements can improve clinical outcomes, is currently under investigation.³ Zinc levels are difficult to measure accurately, as zinc is distributed as a component of various proteins and nucleic acids.⁴

Several clinical trials are currently investigating the use of zinc supplementation alone or in combination with hydroxychloroquine for the prevention and treatment of COVID-19 (see [ClinicalTrials.gov](https://clinicaltrials.gov) for more information about ongoing studies). The recommended dietary allowance for elemental zinc is 11 mg daily for men and 8 mg for nonpregnant women.⁵ The doses used in registered clinical trials for patients with COVID-19 vary between studies, with a maximum dose of zinc sulfate 220 mg (50 mg of elemental zinc) twice daily. However, there are currently insufficient data to recommend either for or against the use of zinc for the treatment of COVID-19.

Long-term zinc supplementation can cause copper deficiency with subsequent reversible hematologic defects (i.e., anemia, leukopenia) and potentially irreversible neurologic manifestations (i.e., myelopathy, paresthesia, ataxia, spasticity).^{6,7} The use of zinc supplementation for durations as short as 10 months has been associated with copper deficiency.⁴ In addition, oral zinc can decrease the absorption of medications that bind with polyvalent cations.⁵ Because zinc has not been shown to have a clinical benefit and may be harmful, the Panel **recommends against** using **zinc** supplementation above the recommended dietary allowance for the prevention of COVID-19, except in a clinical trial (**BIII**).

Clinical Data

Randomized Clinical Trial of Zinc Plus Hydroxychloroquine Versus Hydroxychloroquine Alone in Hospitalized Patients With COVID-19

In a randomized clinical trial conducted at three academic medical centers in Egypt, 191 patients with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection were randomized to receive either zinc 220 mg twice daily plus hydroxychloroquine or hydroxychloroquine alone for a 5-day course. The primary endpoints were recovery within 28 days, the need for mechanical ventilation, and death. The two groups were matched for age and gender.⁸

Results

- There were no significant differences between the two arms in the percentages of patients who recovered within 28 days (79.2% in the hydroxychloroquine plus zinc arm vs. 77.9% in the

hydroxychloroquine only arm; $P = 0.969$), the need for mechanical ventilation ($P = 0.537$), or overall mortality ($P = 0.986$).

- The only risk factors for mortality were age and the need for mechanical ventilation.

Limitations

- This study had a relatively small sample size.

Interpretation

A moderately sized randomized clinical trial failed to find a clinical benefit for the combination of zinc and hydroxychloroquine.

Observational Study of Zinc Supplementation in Hospitalized Patients

A retrospective study enrolled 242 patients with polymerase chain reaction-confirmed SARS-CoV-2 infection who were admitted to Hoboken University Medical Center. One hundred and ninety-six patients (81.0%) received a total daily dose of zinc sulfate 440 mg (100 mg of elemental zinc); of those, 191 patients (97%) also received hydroxychloroquine. Among the 46 patients who did not receive zinc, 32 patients (70%) received hydroxychloroquine. The primary outcome was days from hospital admission to in-hospital mortality, and the primary analysis explored the causal association between zinc therapy and survival.⁹

Results

- There were no significant differences in baseline characteristics between the groups. In the zinc group, 73 patients (37.2%) died compared with 21 patients (45.7%) in the control group. In the primary analysis, which used inverse probability weighting (IPW), the effect estimate of zinc therapy was an additional 0.84 days of survival (95% CI, -1.51 days to 3.20 days; $P = 0.48$).
- In a multivariate Cox regression analysis with IPW, the use of zinc sulfate was not significantly associated with a change in the risk of in-hospital mortality (aHR 0.66; 95% CI, 0.41–1.07; $P = 0.09$).
- Older age, male sex, and severe or critical COVID-19 were significantly associated with an increased risk of in-hospital mortality.

Limitations

- This is a retrospective study; patients were not randomized to receive zinc supplementation or to receive no zinc.

Interpretation

This single-center, retrospective study failed to find a mortality benefit in patients who received zinc supplementation.

Multicenter Retrospective Cohort Study That Compared Hospitalized Patients Who Received Zinc Plus Hydroxychloroquine to Those Who Did Not

This study has not been peer reviewed.

This multicenter retrospective cohort study of hospitalized adults with SARS-CoV-2 infection who were admitted to four New York City hospitals between March 10 and May 20, 2020, compared patients who received zinc plus hydroxychloroquine to those who received treatment that did not include this combination.¹⁰

Results

- The records of 3,473 patients were reviewed.
- The median patient age was 64 years; 1,947 patients (56%) were male, and 522 patients (15%) were mechanically ventilated.
- Patients who received an interleukin-6 inhibitor or remdesivir were excluded from the analysis.
- A total of 1,006 patients (29%) received zinc plus hydroxychloroquine, and 2,467 patients (71%) received hydroxychloroquine without zinc.
- During the study, 545 patients (16%) died. In univariate analyses, mortality rates were significantly lower among patients who received zinc plus hydroxychloroquine than among those who did not (12% vs. 17%; $P < 0.001$). Similarly, hospital discharge rates were significantly higher among patients who received zinc plus hydroxychloroquine than among those who did not (72% vs. 67%; $P < 0.001$).
- In a Cox regression analysis that adjusted for confounders, treatment with zinc plus hydroxychloroquine was associated with a significantly reduced risk of in-hospital death (aHR 0.76; 95% CI, 0.60–0.96; $P = 0.023$). Treatment with zinc alone ($n = 1,097$) did not affect mortality (aHR 1.14; 95% CI, 0.89–1.44; $P = 0.296$), and treatment with hydroxychloroquine alone ($n = 2,299$) appeared to be harmful (aHR 1.60; 95% CI, 1.22–2.11; $P = 0.001$).
- There were no significant interactions between zinc plus hydroxychloroquine and other COVID-19-specific medications.

Limitations

- This is a retrospective review; patients were not randomized to receive zinc plus hydroxychloroquine or to receive other treatments.
- The authors do not have data on whether patients were taking zinc and/or hydroxychloroquine prior to study admission.
- The groups were not balanced; recipients of zinc plus hydroxychloroquine were more likely to be male, Black, or to have a higher body mass index and diabetes. Patients who received zinc plus hydroxychloroquine were also treated with corticosteroids and azithromycin more often and treated with lopinavir/ritonavir less often than those who did not receive this drug combination.

Interpretation

In this preprint, the use of zinc plus hydroxychloroquine was associated with decreased rates of in-hospital mortality, but neither zinc alone nor hydroxychloroquine alone reduced mortality. Treatment with hydroxychloroquine alone appeared to be harmful.

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