Adjunctive Therapy

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

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is associated with a prothrombotic state and an increased incidence of thromboembolic disease. Antithrombotic Therapy in Patients with COVID-19 reviews the existing data and provides recommendations for the care of individuals who were receiving antithrombotic agents before they acquired SARS-CoV-2 and those who need these therapies to prevent or treat thromboembolic events during course of the infection.

Some clinicians advocate for the use of vitamin and mineral supplements to treat respiratory viral infections. Multiple ongoing studies are evaluating the use of vitamin and mineral supplements for both the treatment and prevention of SARS-CoV-2 infection.

The following sections describe the underlying rationale for the use of adjunctive therapies and summarize the existing clinical trial data. Additional adjunctive therapies will be added as new evidence emerges.
## Summary Recommendations

### Laboratory Testing
- In nonhospitalized patients with COVID-19, there are currently no data to support the measurement of coagulation markers (e.g., D-dimers, prothrombin time, platelet count, fibrinogen) (AIII).
- In hospitalized patients with COVID-19, hematologic and coagulation parameters are commonly measured, although there are currently insufficient data to recommend for or against using this data to guide management decisions.

### Chronic Anticoagulant and Antiplatelet Therapy
- Patients who are receiving anticoagulant or antiplatelet therapies for underlying conditions should continue these medications if they receive a diagnosis of COVID-19 (AIII).

### Venous Thromboembolism Prophylaxis and Screening
- For nonhospitalized patients with COVID-19, anticoagulants and antiplatelet therapy should not be initiated for the prevention of venous thromboembolism (VTE) or arterial thrombosis unless the patient has other indications for the therapy or is participating in a clinical trial (AIII).
- Hospitalized nonpregnant adults with COVID-19 should receive prophylactic dose anticoagulation (AIII) (see the recommendations for pregnant individuals below). Anticoagulant or antiplatelet therapy should not be used to prevent arterial thrombosis outside of the usual standard of care for patients without COVID-19 (AIII).
- There are currently insufficient data to recommend either for or against the use of thrombolytics or higher than the prophylactic dose of anticoagulation for VTE prophylaxis in hospitalized COVID-19 patients outside of a clinical trial.
- Hospitalized COVID-19 patients should not routinely be discharged from the hospital while on VTE prophylaxis (AIII). Continuing anticoagulation with a Food and Drug Administration-approved regimen for extended VTE prophylaxis after hospital discharge can be considered in patients who are at low risk for bleeding and high risk for VTE, as per the protocols for patients without COVID-19 (see text for details on defining at-risk patients) (BI).
- There are currently insufficient data to recommend either for or against routine deep vein thrombosis screening in COVID-19 patients without signs or symptoms of VTE, regardless of the status of their coagulation markers.
- For hospitalized COVID-19 patients who experience rapid deterioration of pulmonary, cardiac, or neurological function, or of sudden, localized loss of peripheral perfusion, the possibility of thromboembolic disease should be evaluated (AIII).

### Hospitalized Children With COVID-19
- For hospitalized children with COVID-19, indications for VTE prophylaxis should be the same as those for children without COVID-19 (BIII).

### Treatment
- When diagnostic imaging is not possible, patients with COVID-19 who experience an incident thromboembolic event or who are highly suspected to have thromboembolic disease should be managed with therapeutic doses of anticoagulant therapy (AIII).
- Patients with COVID-19 who require extracorporeal membrane oxygenation or continuous renal replacement therapy or who have thrombosis of catheters or extracorporeal filters should be treated with antithrombotic therapy as per the standard institutional protocols for those without COVID-19 (AIII).

### Special Considerations During Pregnancy and Lactation
- If antithrombotic therapy is prescribed during pregnancy prior to a diagnosis of COVID-19, this therapy should be continued (AIII).
- For pregnant patients hospitalized for severe COVID-19, prophylactic dose anticoagulation is recommended if there are no contraindications to its use (see text) (BIII).
- As for nonpregnant patients, VTE prophylaxis after hospital discharge is not recommended for pregnant patients (AIII). Decisions to continue VTE prophylaxis in the pregnant or postpartum patient after discharge should be individualized, considering concomitant VTE risk factors.
Association Between COVID-19 and Thromboembolism

Infection with the novel severe acute respiratory syndrome coronavirus (SARS-CoV-2) and the resulting syndrome, COVID-19, has been associated with inflammation and a prothrombotic state, with increases in fibrin, fibrin degradation products, fibrinogen, and D-dimers.\textsuperscript{1,2} In some studies, elevations in these markers have been associated with worse clinical outcomes.\textsuperscript{3,4} A number of studies have reported varying incidences of venous thromboembolism (VTE) in patients with COVID-19. A meta-analysis of studies in hospitalized patients with COVID-19 found an overall VTE prevalence of 14.1\% (95\% CI, 11.6–16.9).\textsuperscript{5} The VTE prevalence was higher in studies that used ultrasound screening (40.3\%; 95\% CI, 27.0–54.3) than in studies that did not (9.5\%; 95\% CI, 7.5–11.7). In randomized controlled trials conducted prior to the COVID-19 pandemic, the incidence of VTE in non-COVID-19 hospitalized patients who received VTE prophylaxis ranged from 0.3\% to 1\% for symptomatic VTE and from 2.8\% to 5.6\% for VTE overall.\textsuperscript{6-8} The VTE incidence in randomized trials in critically ill non-COVID-19 patients who received prophylactic dose anticoagulants ranged from 5\% to 16\%, and a prospective cohort study of critically ill septic patients reported a VTE incidence of 37\%.\textsuperscript{9-12} VTE guidelines for non-COVID-19 patients have recommended against routine screening ultrasounds in critically ill patients because no study has shown that this strategy reduces the rate of subsequent symptomatic thromboembolic complications.\textsuperscript{13} Although the incidence of thromboembolic events, especially pulmonary emboli, can be high among hospitalized patients with COVID-19, there are no published data demonstrating the clinical utility of routine surveillance for deep vein thrombosis using lower extremity ultrasound.

A meta-analysis performed by the American Society of Hematology Guidelines Panel compared the odds of bleeding and thrombotic outcomes in patients with COVID-19 treated with prophylactic dose anticoagulation versus those treated with intermediate or therapeutic dose anticoagulation.\textsuperscript{14} Overall VTE and mortality were not different between patients treated with prophylactic dose or higher doses of anticoagulation. In critically ill patients, intermediate or therapeutic dose anticoagulation was associated with a lower odds of pulmonary embolism (OR 0.09; 95\% CI, 0.02–0.57) but a higher odds of major bleeding (OR 3.84; 95\% CI, 1.44–10.21). Incidences of symptomatic VTE between 0\% to 0.6\% at 30 to 42 days post hospital discharge have been reported in patients with COVID-19.\textsuperscript{15-17} Epidemiologic studies that control for clinical characteristics, underlying comorbidities, prophylactic anticoagulation, and COVID-19-related therapies are needed.

There are limited prospective data demonstrating the safety and efficacy of using therapeutic doses of anticoagulants in patients with COVID-19 to prevent VTE. A retrospective analysis of 2,773 hospitalized COVID-19 patients from a single center in the United States reported in-hospital mortality in 22.5\% of patients who received therapeutic anticoagulation and 22.8\% of patients who did not receive anticoagulation. The study further reported that in a subset of 395 mechanically ventilated patients,

\begin{itemize}
\item Anticoagulation therapy use during labor and delivery requires specialized care and planning. It should be managed in pregnant patients with COVID-19 in a similar way as in pregnant patients with other conditions that require anticoagulation in pregnancy (AIII).
\item Unfractionated heparin, low molecular weight heparin, and warfarin do not accumulate in breast milk and do not induce an anticoagulant effect in the newborn; therefore, they can be used in breastfeeding individuals with or without COVID-19 who require VTE prophylaxis or treatment (AIII). In contrast, direct-acting oral anticoagulants are not routinely recommended due to lack of safety data (AIII).
\end{itemize}
29.1% who received anticoagulation and 62.7% who did not receive anticoagulation died. The study had important limitations: it lacked details on patient characteristics, indications for anticoagulant initiation, and descriptions of other therapies that the patients received that may have influenced mortality. In addition, the authors did not discuss the potential impact of survival bias on the study results. For these reasons, the data are not sufficient to influence standard of care, and this study further emphasizes the need for prospective trials to define the risks and potential benefits of therapeutic anticoagulation in patients with COVID-19.18

A small, single-center, randomized trial of 20 patients compared therapeutic and prophylactic anticoagulation in mechanically ventilated patients with D-dimers >1,000 µg/L (as measured by the VIDAS D-dimer Exclusion II assay). Only the patients treated with therapeutic anticoagulation showed improvement in \( \text{PaO}_2/\text{FiO}_2 \) ratio. The number of ventilator-free days was higher in the therapeutic anticoagulation group than in the prophylactic anticoagulation group (15 days [IQR 6–16] vs. 0 days [IQR 0–11]; \( P = 0.028 \)). There was no between-group difference in in-hospital or 28-day mortality. Two patients treated with therapeutic anticoagulation had minor bleeding, and two patients in each group experienced thrombosis.19 Additional evidence from large, multicenter trials is needed, and the trial results are expected soon.

Several randomized controlled trials have been developed to evaluate the risks and benefits of anticoagulation in patients with COVID-19 (visit ClinicalTrials.gov for the current list of trials). Guidelines about coagulopathy and prevention and management of VTE in patients with COVID-19 have been released by multiple organizations, including the Anticoagulation Forum,20 the American College of Chest Physicians,21 the American Society of Hematology,22 the International Society of Thrombosis and Haemostasis (ISTH),23 the Italian Society on Thrombosis and Haemostasis,24 and the Royal College of Physicians.25 In addition, a paper that outlines issues related to thrombotic disease with implications for prevention and therapy has been endorsed by the ISTH, the North American Thrombosis Forum, the European Society of Vascular Medicine, and the International Union of Angiology.26

All guidelines agree that hospitalized patients with COVID-19 should receive prophylactic dose anticoagulation for VTE. Some guidelines note that intermediate dose anticoagulation can be considered for critically ill patients.20,22,25,27 Given the variation in VTE incidence and the unknown risk of bleeding in critically ill patients with COVID-19, the COVID-19 Treatment Guidelines Panel and the American Society of Hematology and the American College of Chest Physician Guidelines Panels recommend treating all hospitalized patients with COVID-19, including critically ill patients, with prophylactic dose anticoagulation.21,28 Participation in clinical trials is suggested to understand the safety and efficacy of different anticoagulant doses in patients with COVID-19.

**Monitoring Coagulation Markers in Patients With COVID-19**

- Nonhospitalized patients with COVID-19 should not routinely be tested for markers of coagulopathy, such as D-dimer level, prothrombin time, fibrinogen level, and platelet count (AIII). Although abnormalities of these markers have been associated with worse outcomes, there is a lack of prospective data demonstrating that they can be used to predict the risk of VTE in those who are asymptomatic or who have mild SARS-CoV-2 infection.
- In hospitalized patients with COVID-19, hematologic and coagulation parameters are commonly measured; however, there are currently insufficient data to recommend either for or against using such data to guide management decisions.
Managing Antithrombotic Therapy in Patients With COVID-19

Selection of Anticoagulant or Antiplatelet Drugs for Patients With COVID-19

- Whenever anticoagulant or antiplatelet therapy is used, potential drug-drug interactions with other concomitant drugs must be considered (AIII). The University of Liverpool has collated a list of drug interactions.
- In hospitalized, critically ill patients, low molecular weight heparin or unfractionated heparin is preferred over oral anticoagulants because of their shorter half-lives, ability to be administered intravenously or subcutaneously, and fewer drug-drug interactions (AIII).

Chronic Anticoagulant or Antiplatelet Therapy

- COVID-19 outpatients receiving warfarin who are in isolation and thus unable to get international normalized ratio monitoring may be candidates for switching to direct oral anticoagulant therapy. Patients with mechanical heart valves, ventricular assist devices, valvular atrial fibrillation, or antiphospholipid antibody syndrome or patients who are lactating should continue treatment with warfarin (AIII).
- Hospitalized patients with COVID-19 who are taking anticoagulant or antiplatelet therapy for underlying medical conditions should continue their treatment unless significant bleeding develops or other contraindications are present (AIII).

Patients with COVID-19 Who Are Managed as Outpatients

- For nonhospitalized patients with COVID-19, anticoagulants and antiplatelet therapy should not be initiated for the prevention of VTE or arterial thrombosis unless the patient has other indications for the therapy or is participating in a clinical trial (AIII).

Hospitalized Patients With COVID-19

- For hospitalized patients with COVID-19, prophylactic dose anticoagulation should be prescribed unless contraindicated (e.g., a patient has active hemorrhage or severe thrombocytopenia) (AIII). Although data supporting this recommendation are limited, a retrospective study showed reduced mortality in patients who received prophylactic anticoagulation, particularly if the patient had a sepsis-induced coagulopathy score ≥4. For those without COVID-19, anticoagulant or antiplatelet therapy should not be used to prevent arterial thrombosis outside of the standard of care (AIII). Anticoagulation is routinely used to prevent arterial thromboembolism in patients with heart arrhythmias. Although there are reports of strokes and myocardial infarction in patients with COVID-19, the incidence of these events is unknown.
- When imaging is not possible, patients with COVID-19 who experience an incident thromboembolic event or who are highly suspected to have thromboembolic disease should be managed with therapeutic doses of anticoagulant therapy as per the standard of care for patients without COVID-19 (AIII).
- There are currently insufficient data to recommend either for or against using therapeutic doses of antithrombotic or thrombolytic agents for COVID-19 in patients who are hospitalized. Although there is evidence that multi-organ failure is more likely in patients with sepsis if they develop coagulopathy, there is no convincing evidence to show that any specific antithrombotic treatment will influence outcomes in those with or without COVID-19. Participation in randomized trials is encouraged (if trials are available).
- Patients with COVID-19 who require extracorporeal membrane oxygenation or continuous renal replacement therapy or who have thrombosis of catheters or extracorporeal filters should be
treated as per the standard institutional protocols for those without COVID-19 (AIII).

**Hospitalized Children With COVID-19**

- A recent meta-analysis of publications on COVID-19 in children did not discuss VTE.\(^{30}\)
- Indications for VTE prophylaxis in hospitalized children with COVID-19 should be the same as those for hospitalized children without COVID-19 (BIII).

**Patients With COVID-19 Who Are Discharged from the Hospital**

- After hospital discharge, VTE prophylaxis is **not recommended** for patients with COVID-19 (AIII). For certain high-VTE risk patients without COVID-19, post-discharge prophylaxis has been shown to be beneficial. The Food and Drug Administration approved the use of rivaroxaban 10 mg daily for 31 to 39 days in these patients.\(^{31,32}\)
- Inclusion criteria for the trials that studied post discharge VTE prophylaxis included:
  - Modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) VTE risk score ≥4; or
  - Modified IMPROVE VTE risk score ≥2 and D-dimer level >2 times the upper limit of normal.\(^{31}\)
- Any decision to use post-discharge VTE prophylaxis for patients with COVID-19 should consider the individual patient’s risk factors for VTE, including reduced mobility, bleeding risks, and feasibility. Participation in clinical trials is encouraged.

**Special Considerations During Pregnancy and Lactation**

Because pregnancy is a hypercoagulable state, the risk of thromboembolism is greater in pregnant individuals than in nonpregnant individuals.\(^{33}\)
- It is not yet known whether COVID-19 increases this risk. In several cohort studies of pregnant women with COVID-19 in the United States and Europe, VTE was not reported as a complication even among women with severe disease, although the receipt of prophylactic or therapeutic anticoagulation varied across the studies.\(^{34-36}\)
- The American College of Obstetricians and Gynecologists (ACOG) advises that although there are no data for or against thromboprophylaxis in the setting of COVID-19 in pregnancy, VTE prophylaxis can reasonably be considered for pregnant women hospitalized with COVID-19, particularly for those who have severe disease.\(^{37}\)
- If there are no contraindications to use, the Society of Maternal Fetal Medicine recommends prophylactic heparin or low molecular weight heparin in critically ill or mechanically ventilated pregnant patients.\(^{38}\)
- Several professional societies, including the American Society of Hematology and ACOG, have guidelines that specifically address the management of VTE in the context of pregnancy.\(^{39,40}\)
- If delivery is threatened, or if there are other risks for bleeding, the risk of bleeding may outweigh the potential benefit of VTE prophylaxis in pregnancy.
- There are no data on the use of scoring systems to predict VTE risk in pregnant individuals.
- Additionally, during pregnancy, the D-dimer level may not be a reliable predictor of VTE because there is a physiologic increase of D-dimer levels throughout gestation.\(^{41-43}\)
- In general, the preferred anticoagulants during pregnancy are heparin compounds. Because of its reliability and ease of administration, low-molecular weight heparin is recommended rather than unfractionated heparin for the prevention and treatment of VTE in pregnancy.\(^{40}\)
- Direct-acting anticoagulants are not routinely used during pregnancy due to the lack of safety data in pregnant individuals.\(^{39}\)
- The use of warfarin to prevent or treat VTE should be avoided in pregnant individuals, regardless of their COVID-19 status, and especially during the first trimester due to the concern for teratogenicity.
Specific recommendations for pregnant or lactating individuals with COVID-19 include:

- If antithrombotic therapy is prescribed during pregnancy prior to a diagnosis of COVID-19, this therapy should be continued (AIII).

- For pregnant patients hospitalized for severe COVID-19, prophylactic dose anticoagulation is recommended if there are no contraindications to its use (BIII).

- As for nonpregnant patients, VTE prophylaxis after hospital discharge is not recommended for pregnant patients (AIII). Decisions to continue VTE prophylaxis in the pregnant or postpartum patient should be individualized, considering concomitant VTE risk factors.

- Anticoagulation therapy use during labor and delivery requires specialized care and planning. It should be managed in pregnant patients with COVID-19 in a similar way as in pregnant patients with other conditions that require anticoagulation in pregnancy (AIII).

- Unfractionated heparin, low molecular weight heparin, and warfarin do not accumulate in breast milk and do not induce an anticoagulant effect in the newborn; therefore, they can be used in breastfeeding women with or without COVID-19 who require VTE prophylaxis or treatment (AIII). In contrast, direct-acting oral anticoagulants are not routinely recommended due to lack of safety data (AIII).39

References


10. PROTECT Investigators for the Canadian Critical Care Trials Group and the Australian and New Zealand...


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 shock\(^10\) 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.\(^13\)

**References**


**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 ≤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).

**References**


Zinc Supplementation and COVID-19

Last Updated: July 17, 2020

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. 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. 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. Zinc levels are difficult to measure accurately, as zinc is distributed as a component of various proteins and nucleic acids.

Zinc supplementation alone or in combination with hydroxychloroquine for prevention and treatment of COVID-19 is currently being evaluated in clinical trials. The optimal dose of zinc for the treatment of COVID-19 is not established. The recommended dietary allowance for elemental zinc is 11 mg daily for men and 8 mg for nonpregnant women. The doses used in registered clinical trials for COVID-19 vary between studies, with a maximum dose of zinc sulfate 220 mg (50 mg of elemental zinc) twice daily.

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). Zinc supplementation for a duration as short as 10 months has been associated with copper deficiency. In addition, oral zinc can decrease the absorption of medications that bind with polyvalent cations. Because zinc has not been shown to have 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

Retrospective Study of Hydroxychloroquine and Azithromycin With or Without Zinc

This study has not been peer-reviewed.

A retrospective observational study compared zinc supplementation to no zinc supplementation in hospitalized patients with COVID-19 who received hydroxychloroquine and azithromycin from March 2 to April 5, 2020. On March 25, the institution’s standard of care was updated to include supplementation with zinc sulfate 220 mg orally twice daily. Patients who received any other investigational therapies were excluded. Only patients who were discharged from the hospital, transferred to hospice, or died were included in the analysis. Outcome measures included duration of hospital stay, duration of mechanical ventilation, maximum oxygen flow rate, average oxygen flow rate, average FiO₂, maximum FiO₂, admission to the intensive care unit (ICU), duration of ICU stay, death or transfer to hospice, need for intubation, and discharge destination.
Results

- A total of 932 patients were included in this analysis; 411 patients received zinc, and 521 did not.
- The two groups had similar demographic characteristics.
- Patients who received zinc had higher absolute lymphocyte count and lower troponin and procalcitonin levels at baseline than those who did not receive zinc.
- In univariate analysis, no differences were observed between the two groups in duration of hospital stay, duration of mechanical ventilation, maximum oxygen flow rate, average oxygen flow rate, or average FiO₂.
- In bivariate logistic regression analysis, zinc supplementation was associated with a decreased mortality rate or rate of transfer to hospice; however, the association with a decreased mortality rate was no longer significant when analysis was limited to patients who were treated in the ICU.

Limitations

- This is a retrospective review; patients were not randomized to receive zinc therapy or to receive no zinc. The statistical methods used do not account for confounding variables or patient differences between those who were treated with zinc sulfate and those who were not, with one exception: the authors attempted to account for the change in the institution’s treatment standards by using a logistic regression analysis for patients admitted after March 25.
- The preprint did not include specific details on the timing of zinc initiation, and the patients’ clinical statuses at the start of therapy were not reported.
- The preprint also did not specify how many patients did or did not receive zinc before and after the institution’s treatment standards changed to include zinc sulfate on March 25. The authors used a logistic regression analysis to account for this, as discussed above.
- Only patients who died or who were transferred to hospice or discharged are included in the analyses. The exclusion of those who were still hospitalized as of April 5 makes it difficult to compare the clinical outcomes for those who received or did not receive zinc sulfate.

Given the nature of the study design and its limitations, the authors do not recommend using this study to guide clinical practice.

References

