Adjunctive Therapy

Last Updated: July 17, 2020

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.

Antithrombotic Therapy in Patients with COVID-19

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Summary Recommendations

Laboratory Testing:

- In non-hospitalized 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 **(BIII)**.

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 non-hospitalized patients with COVID-19, anticoagulants and antiplatelet therapy should not be initiated for prevention of venous thromboembolism (VTE) or arterial thrombosis unless there are other indications **(AIII)**.
- Hospitalized adults with COVID-19 should receive VTE prophylaxis per the standard of care for other hospitalized adults **(AIII)**. A diagnosis of COVID-19 should not influence a pediatrician's recommendations about VTE prophylaxis in hospitalized children **(BIII)**. 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)**.
- Reported incidence of VTE in hospitalized patients with COVID-19 varies. There are currently insufficient data to recommend for or against the use of thrombolytics or increasing anticoagulant doses for VTE prophylaxis in hospitalized COVID-19 patients outside the setting of a clinical trial **(BIII)**.
- Hospitalized patients with COVID-19 should not routinely be discharged on VTE prophylaxis **(AIII)**. Using Food and Drug Administration-approved regimens, extended VTE prophylaxis can be considered in patients who are at low risk for bleeding and high risk for VTE as per protocols for patients without COVID-19 (see text for details on defining at-risk patients) **(BI)**.
- There are currently insufficient data to recommend 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 **(BIII)**.
- For hospitalized COVID-19 patients, the possibility of thromboembolic disease should be evaluated in the event of rapid deterioration of pulmonary, cardiac, or neurological function, or of sudden, localized loss of peripheral perfusion **(AIII)**.

Treatment:

- Patients with COVID-19 who experience an incident thromboembolic event or who are highly suspected to have thromboembolic disease at a time when imaging is not possible should be managed with therapeutic doses of anticoagulant therapy as per the standard of care for patients without COVID-19 **(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 per the standard institutional protocols for those without COVID-19 **(AIII)**.

Special Considerations During Pregnancy and Lactation:

- Management of anticoagulation therapy during labor and delivery requires specialized care and planning and should be managed similarly in pregnant patients with COVID-19 as 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)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

Association Between COVID-19 and Thromboembolism

Infection with the novel coronavirus SARS-CoV-2 and the resulting syndrome coronavirus disease (COVID-19) has been associated with inflammation and a prothrombotic state, with increases in fibrin, fibrin degradation products, fibrinogen, and D-dimers.[1,2] In fact, these markers have been associated with worse clinical outcomes.[3,4] Although the true incidence of these complications among those with different severities of disease is not completely defined, there have been reports of increased incidence of thromboembolic disease associated with COVID-19 in patients in the intensive care unit (ICU).[5,6] In a French prospective multicenter cohort of 150 ICU patients, 16.7% had pulmonary embolism despite prophylactic anticoagulation. Patients with COVID-19 and acute respiratory distress syndrome (ARDS) had increased incidence of pulmonary embolism compared to patients without COVID-19-associated ARDS.[6] A Dutch study of 184 ICU patients reported a cumulative incidence of venous thromboembolism (VTE) of 27% (95% confidence interval, 17% to 32%), despite prophylaxis.[7] A study that used routine ultrasounds reported VTE incidence of 69%[5] in those admitted to the ICU. However, other centers have reported lower event rates. An Italian study found a VTE rate of 22.2%.[8] Among 393 patients from New York, only 13 patients (3.3%) experienced VTE; 10 of those patients (7.7%) were mechanically ventilated, and three (1.1%) were not mechanically ventilated.[9] Epidemiologic studies that control for clinical characteristics, underlying comorbidities, prophylactic anticoagulation, and COVID-19-related therapies are needed.

Notably, all of the studies described above relied on clinical findings that were suggestive of thromboembolic events to trigger a diagnosis of thromboembolism. Although the incidence of thromboembolic events, especially pulmonary emboli, can be quite high, there are, as of yet, no published data investigating the utility of routine surveillance for deep vein thrombosis via lower extremity ultrasound. However, for clinicians who routinely perform ultrasound examinations in critically ill patients, adding deep veins to the daily examination could be a useful adjunct to care.

There remains very little prospective data demonstrating the benefits of monitoring coagulation markers or the safety and efficacy of using therapeutic doses of anticoagulants in those with COVID-19 in the absence of other indications. A retrospective analysis of 2,773 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, 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.[10]

A number of 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). Interim guidance on recognizing and managing coagulopathy in patients with COVID-19 has been released by the International Society of Thrombosis and Haemostasis (ISTH).[11] The American Society of Hematology has developed guidance statements about coagulopathy and venous thromboembolism. An additional 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.[12]

Monitoring Coagulation Markers in Patients with COVID-19:

- Non-hospitalized patients with COVID-19 should not routinely be tested for measures 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 for risk stratification in those who are asymptomatic or those with mild SARS-CoV-2 infection.
- Hematologic and coagulation parameters are commonly measured in hospitalized patients with COVID-19. Nevertheless, there are currently insufficient data to recommend for or against using such data to guide management decisions **(BIII)**.

Managing Coagulopathy in Patients with COVID-19

Selection of Anticoagulant or Antiplatelet Drugs for Patients with COVID-19:[13]

- Any time anticoagulant or antiplatelet therapy is being used, consideration must be given to potential drug-drug interactions with other concomitant drugs **(AIII)**. The University of Liverpool has collated a list of drug interactions.
- Low molecular weight heparin or unfractionated heparin may be preferred in hospitalized, critically ill patients because of their shorter half-lives, ability to be administered intravenously or subcutaneously, and fewer drug-drug interactions compared with oral anticoagulants **(AIII)**.
- Outpatients receiving warfarin who are unable to get international normalized ratio monitoring during isolation may be candidates for 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 therapy **(AIII)**.

Chronic Anticoagulant or Antiplatelet Therapy:

- 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 non-hospitalized patients with COVID-19, anticoagulant or antiplatelet therapy should not be initiated for VTE prophylaxis or at therapeutic doses **(AIII)**.

Hospitalized Patients with COVID-19:

- For adults who are admitted to a hospital with COVID-19, VTE prophylaxis, unless contraindicated (e.g., a patient has active hemorrhage or severe thrombocytopenia), should be prescribed using the recommendations for patients who have been admitted to a hospital for other indications **(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.[4]
- A recent meta-analysis of COVID-19 infection in children did not discuss venous thromboembolism.[14] Given insufficient data, COVID-19 infection should not change VTE prophylaxis recommendations for hospitalized children **(BIII)**.
- Anticoagulant or antiplatelet therapy should not be used to prevent arterial thrombosis outside of the standard of care for those without COVID-19 **(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.

- Patients with COVID-19 who experience an incident thromboembolic event or who are highly suspected to have thromboembolic disease at a time when imaging is not possible 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 admitted to a hospital **(BIII)**. While there is evidence that multi-organ failure is more likely in patients with sepsis if they develop coagulopathy,[15] there are 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)**.

Patients with COVID-19 Who Are Discharged from the Hospital:

- Routine post-discharge VTE prophylaxis **is not recommended** for patients with COVID-19 **(AIII)**. However, the benefits of post-discharge prophylaxis for certain high-risk patients without COVID-19 led to the Food and Drug Administration approval of two regimens: rivaroxaban 10 mg daily for 31 to 39 days, and betrixaban 160 mg on Day 1, followed by betrixaban 80 mg once daily for 35 to 42 days.[16,17] Inclusion criteria for the trials that studied these regimens included:
  - Modified IMPROVE-VTE score ≥4; *or*
  - Modified IMPROVE-VTE score ≥2 and D-dimer level >2 times the upper limit of normal;[16] *or*
  - Age ≥75 years; *or*
  - Age >60 years and D-dimer level >2 times the upper limit of normal; *or*
  - Age 40 to 60 years, D-dimer level >2 times the upper limit of normal, and previous VTE event or cancer.[17]
- Any decision to use post-discharge VTE prophylaxis should consider the individual patient's risk factors, including reduced mobility, bleeding risks, and feasibility.

Special Considerations for Pregnancy and Lactation

Several professional societies, including the American Society of Hematology and the American College of Obstetricians and Gynecologists, have guidelines that specifically address management of VTE in the context of pregnancy.[18,19] There is a lack of data on the use of these scoring systems to predict VTE risk in pregnant people. Additionally, the D-dimer level may not be a reliable predictor of VTE in pregnancy, because there is a physiologic increase of D-dimer levels throughout gestation.[20-22]

In general, the preferred anticoagulants during pregnancy are heparin compounds.[2] Because of its reliability and ease of administration, low-molecular weight heparin is recommended rather than unfractionated heparin for prevention and treatment of VTE in pregnancy.[19]

Direct-acting anticoagulants are not routinely used during pregnancy due to the lack of safety data in pregnant people.[18] The use of warfarin for the prevention or treatment of VTE should be avoided in pregnant people, regardless of their COVID-19 status; this is especially true during the first trimester, due to the concern for teratogenicity.

Specific recommendations for pregnant women with COVID-19 include:

- If antithrombotic therapy is prescribed during pregnancy for another indication, this therapy should be continued if the patient receives a diagnosis of COVID-19 **(AIII)**.
- For pregnant patients admitted to the hospital with COVID-19, recommendations for VTE prophylaxis are the same as those for hospitalized nonpregnant patients **(AIII)**.
- Management of anticoagulation therapy during labor and delivery requires specialized care and planning and should be managed similarly in pregnant patients with COVID-19 as other conditions that require anticoagulation in pregnancy **(AIII)**.

Thrombolytic Therapy in Pregnancy:

Due to the potential risk of maternal hemorrhage, during pregnancy, thrombolytic therapy should be reserved for acute pulmonary embolism with life-threatening hemodynamic instability regardless of whether a patient has COVID-19 **(AIII)**.[18]

Lactation:

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)**.[19] In contrast, direct-acting oral anticoagulants are not routinely recommended due to the lack of safety data **(AIII)**.[18]

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Vitamin C

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Rationale for Using Vitamin C in Patients With COVID-19

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, there is no compelling reason to use vitamin C in this setting.

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 shown variable efficacy and limited safety concerns (as described below).

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

In a small, three-arm, pilot study of two regimens of intravenous (IV) vitamin C versus placebo in 24 critically ill patients with sepsis, there were reductions over the 4-day study period in sequential organ failure assessment (SOFA) scores and levels of proinflammatory markers in patients who received vitamin C 200 mg/kg per day and those who received vitamin C 50 mg/kg per day, compared with patients who received placebo.[3]

In a randomized, controlled trial in critically ill patients with sepsis-induced ARDS (n = 167), administration of IV vitamin C 200 mg/kg per day for 4 days did not change SOFA scores or levels of inflammatory markers. 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 (ICU).[4]

Two historically controlled studies found that the combination of vitamin C, thiamine, and hydrocortisone had beneficial effects in patients with sepsis or severe pneumonia.[5,6] In response, a randomized controlled trial in critically ill patients with septic shock compared the combination

of vitamin C (6 g per day), thiamine (400 mg per day), and hydrocortisone (200 mg per day) to hydrocortisone alone. The study reported that the combination therapy had no effect on the duration of shock. It also had no effect on the mortality rate in the ICU, at 28 days, or at 90 days (90-day mortality was 28.6% in the vitamin C group vs. 24.5% in the placebo group, $P = 0.51$). Only one of the 10 secondary outcomes differed between the two groups; the change in SOFA score from baseline to Day 3 favored the treatment group (median score change of -2 vs. -1, $P = 0.02$).[7]

Other Considerations

- It is worth noting that high circulating concentrations of vitamin C may affect the accuracy of point-of-care glucometers.[8]
- Additional large, randomized clinical trials in severely ill patients with sepsis have completed enrollment. These studies may provide additional data on the safety and efficacy of vitamin C that support its potential use in treating patients with COVID-19.[9,10]
- Several trials of oral and IV vitamin C supplementation in people with COVID-19 are ongoing. Please check *ClinicalTrials.gov* for the latest information.

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Vitamin D

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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 C8OVID-19. In observational studies, low vitamin D levels have been associated with an increased risk of community-acquired pneumonia in older adults[3] 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*.

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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.[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]

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.[5] 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).[6,7] Zinc supplementation for a duration as short as 10 months has been associated with copper deficiency.[8] In addition, oral zinc can decrease the absorption of medications that bind with polyvalent cations.[5] 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 FiO_2, maximum FiO_2, admission to the intensive care unit (ICU), duration of ICU stay, death or transfer to hospice, need for intubation, and discharge destination.[9]

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 FiO_2.
- 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.

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