

Archived Sections of the Coronavirus Disease 2019 (COVID-19) Treatment Guidelines

Credit NIAID-RML

The *Coronavirus Disease 2019 (COVID-19) Treatment Guidelines*, which was first released on April 21, 2020, provided clinicians with practical recommendations for the treatment of COVID-19. The COVID-19 Treatment Guidelines Panel (the Panel) critically reviewed the rapidly evolving body of research on COVID-19 while developing and revising these recommendations. The Panel published the final version of the Guidelines on February 29, 2024.

During the life of the Guidelines, it became apparent that some of the information that was initially included was no longer relevant. The Panel made the decision to remove that outdated information from the Guidelines. This document contains those deleted sections. To view these sections in their original context, visit the <u>Guidelines Archive</u> on the <u>COVID-19 Treatment Guidelines website</u>.

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Infection Control

Last Updated: October 9, 2020

Health care workers should follow the infection control policies and procedures issued by their health care institutions.

Recommendation

- For health care workers who are performing aerosol-generating procedures on patients with COVID-19, the COVID-19 Treatment Guidelines Panel (the Panel) recommends using an N95 respirator (or equivalent or higher-level respirator) rather than surgical masks, in addition to other personal protective equipment (PPE) (i.e., gloves, gown, and eye protection such as a face shield or safety goggles) (AIII).
 - Aerosol-generating procedures include endotracheal intubation and extubation, sputum induction, bronchoscopy, mini-bronchoalveolar lavage, open suctioning of airways, manual ventilation, unintentional or intentional ventilator disconnections, noninvasive positive pressure ventilation (NIPPV) (e.g., bilevel positive airway pressure [BiPAP], continuous positive airway pressure [CPAP]), cardiopulmonary resuscitation, and, potentially, nebulizer administration and high-flow oxygen delivery. Caution regarding aerosol generation is appropriate in situations such as tracheostomy and proning, where ventilator disconnections are likely to occur.

Rationale

During the severe acute respiratory syndrome (SARS) epidemic, aerosol-generating procedures increased the risk of infection among health care workers.^{1,2} N95 respirators block 95% to 99% of aerosol particles; however, medical staff must be fit-tested for the type used.³ Surgical masks block large particles, droplets, and sprays, but are less effective in blocking small particles (<5 μ m) and aerosols.⁴

Recommendation

- The Panel recommends minimizing the use of aerosol-generating procedures on intensive care unit patients with COVID-19 and carrying out any necessary aerosol-generating procedures in a negative-pressure room, also known as an airborne infection isolation room (AIIR), when available (AIII).
 - The Panel recognizes that aerosol-generating procedures are necessary to perform in some patients, and that such procedures can be carried out with a high degree of safety if infection control guidelines are followed.

Rationale

AIIRs lower the risk of cross-contamination among rooms and lower the risk of infection for staff and patients outside the room when aerosol-generating procedures are performed. AIIRs were effective in preventing virus spread during the SARS epidemic.² If an AIIR is not available, a high-efficiency particulate air (HEPA) filter should be used, especially for patients on high-flow nasal cannula or noninvasive ventilation. HEPA filters reduce virus transmission in simulations.⁵

Recommendations

• For health care workers who are providing usual care for nonventilated patients with COVID-19, the Panel recommends using an N95 respirator (or equivalent or higher-level respirator) or a surgical mask, in addition to other PPE (i.e., gloves, gown, and eye protection such as a face shield

or safety goggles) (AIIa).

• For health care workers who are performing non-aerosol-generating procedures on patients with COVID-19 who are on closed-circuit mechanical ventilation, the Panel recommends using an N95 respirator (or equivalent or higher-level respirator) in addition to other PPE (i.e., gloves, gown, and eye protection such as a face shield or safety goggles) because ventilator circuits may become disrupted unexpectedly (**BIII**).

Rationale

There is evidence from studies of viral diseases, including SARS, that both surgical masks and N95 respirators reduce the risk of transmission.⁶ Moreover, surgical masks are probably not inferior to N95 respirators for preventing the transmission of respiratory viral infections; a recent systematic review and meta-analysis of randomized controlled trials that compared the protective effects of medical masks and N95 respirators demonstrated that the use of medical masks did not increase the incidence of laboratory-confirmed viral respiratory infections (including coronavirus infections) or clinical respiratory illness.⁷

Recommendations

- The Panel recommends that endotracheal intubation in patients with COVID-19 be performed by health care providers with extensive airway management experience, if possible (AIII).
- The Panel recommends that intubation be performed using video laryngoscopy, if possible (CIIa).

Rationale

Practices that maximize the chances of first-pass success and minimize aerosolization should be used when intubating patients with suspected or confirmed COVID-19.^{8,9} Thus, the Panel recommends that the health care worker with the most experience and skill in airway management be the first to attempt intubation. The close facial proximity of direct laryngoscopy can expose health care providers to higher concentrations of viral aerosols. It is also important to avoid having unnecessary staff in the room during intubation procedures.

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Acute Kidney Injury and Renal Replacement Therapy

Last Updated: December 17, 2020

Recommendations

- For critically ill patients with COVID-19 who have acute kidney injury (AKI) and who develop indications for renal replacement therapy (RRT), the COVID-19 Treatment Guidelines Panel (the Panel) recommends continuous renal replacement therapy (CRRT), if available (**BIII**).
- If CRRT is not available or not possible due to limited resources, the Panel recommends prolonged intermittent renal replacement therapy (PIRRT) rather than intermittent hemodialysis (IHD) (BIII).

Rationale

AKI that requires RRT occurs in approximately 22% of patients with COVID-19 who are admitted to the intensive care unit.¹ Evidence pertaining to RRT in patients with COVID-19 is scarce. Until additional evidence is available, the Panel suggests using the same indications for RRT in patients with COVID-19 as those used for other critically ill patients.²

RRT modalities have not been compared in COVID-19 patients; the Panel's recommendations are motivated by the desire to minimize the risk of viral transmission to health care workers. The Panel considers CRRT to be the preferred RRT modality. CRRT is preferable to PIRRT because medication dosing for CRRT is more easily optimized and CRRT does not require nursing staff to enter the patient's room to begin and end dialysis sessions. CRRT and PIRRT are both preferable to IHD because neither requires a dedicated hemodialysis nurse.³ Peritoneal dialysis has also been used during surge situations in patients with COVID-19.

In situations where there may be insufficient CRRT machines or equipment to meet demand, the Panel advocates performing PIRRT instead of CRRT, and then using the machine for another patient after appropriate cleaning.

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Cell-Based Therapy

Last Updated: April 21, 2021

Mesenchymal Stem Cells

Mesenchymal stem cells are investigational products that have been studied extensively for broad clinical applications in regenerative medicine¹ and for their immunomodulatory properties.² It is hypothesized that mesenchymal stem cells could reduce the acute lung injury and inhibit the cellmediated inflammatory response induced by SARS-CoV-2.

Recommendation

• The COVID-19 Treatment Guidelines Panel recommends against the use of mesenchymal stem cells for the treatment of COVID-19, except in a clinical trial (AIIb).

Rationale for Recommendation

No mesenchymal stem cells products are approved by the Food and Drug Administration (FDA) for the treatment of COVID-19. There are limited data to date to assess the role of mesenchymal stem cells for the treatment of COVID-19.

The FDA has recently issued several warnings about patients being vulnerable to stem cell treatments that are illegal and potentially harmful.³ Several umbilical cord blood-derived products are currently licensed by the FDA for indications such as the treatment of cancer (e.g., stem cell transplant) or rare genetic diseases, and as scaffolding for cartilage defects and wound beds. None of these products are approved for the treatment of COVID-19 or any other viral disease.⁴ In the United States, mesenchymal stem cells **should not be used** for the treatment of COVID-19 outside of an FDA-approved clinical trial, expanded access program, or an Emergency Investigational New Drug application (AII).

Rationale for Use in COVID-19

Mesenchymal stem cells are multipotent adult stem cells that are present in most human tissues, including the umbilical cord. Mesenchymal stem cells can self-renew by dividing and can differentiate into multiple types of tissues (including osteoblasts, chondroblasts, adipocytes, hepatocytes, and others), which has led to a robust clinical research agenda in regenerative medicine. It is hypothesized that mesenchymal stem cells could reduce the acute lung injury and inhibit the cell-mediated inflammatory response induced by SARS-CoV-2. Furthermore, because they lack the angiotensin-converting enzyme 2 (ACE2) receptor that SARS-CoV-2 uses for viral entry into cells, mesenchymal stem cells are resistant to infection.^{5,6}

Clinical Data

Data supporting the use of mesenchymal stem cells in patients who have viral infections, including SARS-CoV-2 infection, are limited to case reports and small, open-label studies.

Clinical Data for COVID-19

A pilot study of intravenous mesenchymal stem cell transplantation in China enrolled 10 patients with confirmed COVID-19 categorized according to the National Health Commission of China criteria as critical, severe, or common type. Seven patients (one with critical illness, four with severe illness, and two with common-type illness) received mesenchymal stem cells; three patients with severe illness received placebo. All seven patients who received mesenchymal stem cells recovered. Among the

three severely ill placebo-treated patients, one died, one developed acute respiratory distress syndrome (ARDS), and one remained stable with severe disease.⁷

A small clinical trial evaluated human umbilical cord mesenchymal stem cell (hUC-MSC) infusion in patients with severe COVID-19 who had not responded to standard of care therapies after 7 to 10 days of treatment. The standard of care therapies included supplemental oxygen, umifenovir/oseltamivir, antibiotics if indicated, and glucocorticoids. The study was intended as a randomized controlled trial; however, due to the lack of sufficient hUC-MSCs, it was not possible to randomize the participants as originally planned. Among the 41 patients eligible to participate in the study, 12 received hUC-MSC infusion and 29 received standard of care therapies only. The study arms were well balanced with regard to demographic characteristics, laboratory test results, and disease severity. All 12 participants who received hUC-MSC infusion recovered without requiring mechanical ventilation and were discharged to home. Four patients who received only standard of care therapies progressed to critical illness requiring mechanical ventilation; three of these patients died. These results are not statistically significant, and interpretation of the findings is limited by the study's lack of randomization and small sample size.⁸

A double-blind randomized controlled trial investigated the safety and efficacy of hUC-MSC infusions in patients with COVID-19 ARDS. Twenty-four patients were randomized to receive either two infusions of hUC-MSC (prepared at a single site) or placebo on Day 0 and Day 3. The primary endpoints were occurrence of prespecified infusion-associated adverse events within 6 hours of each hUC-MSC infusion; cardiac arrest or death within 24 hours after an infusion; and the incidence of adverse events. Secondary endpoints included survival at 31 days after hUC-MSC infusion and time to recovery.⁹

There were no differences between the arms in the primary safety analysis; however, more deaths occurred in the placebo arm (7 deaths) than in the hUC-MSC arm (2 deaths) by Day 31. Data for one participant in the hUC-MSC arm who died due to a failed intubation was censored from the analysis. Time to recovery was shorter in the hUC-MSC arm than in the placebo arm (HR 0.29; 95% CI, 0.09–0.95). Interpretation of these results is limited by the small sample size and a change in an eligibility criterion from enrolling only individuals on invasive mechanical ventilation to including those receiving high-flow oxygen or on noninvasive ventilation.

Clinical Data for Other Viral Infections

In an open-label study of mesenchymal stem cells for the treatment of H7N9 influenza in China, 17 patients received mesenchymal stem cell treatment plus standard of care, and 44 patients received standard of care only. Three patients (17.6%) in the mesenchymal stem cell arm died versus 24 patients (54.5%) in the standard of care arm. The 5-year follow-up was limited to five patients in the mesenchymal stem cell arm. No safety concerns were identified.¹⁰

Clinical Trials

See <u>*ClinicalTrials.gov*</u> for a list of clinical trials evaluating mesenchymal stem cells for the treatment of COVID-19, COVID-19-related ARDS, and COVID-19-associated multisystem inflammatory syndrome in children (MIS-C).

Adverse Effects

Risks associated with mesenchymal stem cell transfusion appear to be uncommon. The potential risks include the potential for mesenchymal stem cells to multiply or change into inappropriate cell types, product contamination, growth of tumors, infections, thrombus formation, and administration site reactions.¹¹

Considerations in Pregnancy

There are insufficient data to assess the risk of using mesenchymal stem cell therapy during pregnancy.

Considerations in Children

There are insufficient data to assess the efficacy and safety of using mesenchymal stem cell therapy in children.

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Chloroquine or Hydroxychloroquine and/or Azithromycin

Last Updated: July 8, 2021

Chloroquine is an antimalarial drug that was developed in 1934. Hydroxychloroquine, an analogue of chloroquine, was developed in 1946. Hydroxychloroquine is used to treat autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis, in addition to malaria.

Both chloroquine and hydroxychloroquine increase the endosomal pH, which inhibits fusion between SARS-CoV-2 and the host cell membrane.¹ Chloroquine inhibits glycosylation of the cellular angiotensin-converting enzyme 2 (ACE2) receptor, which may interfere with the binding of SARS-CoV to the cell receptor.² In vitro studies have suggested that both chloroquine and hydroxychloroquine may block the transport of SARS-CoV-2 from early endosomes to endolysosomes, possibly preventing the release of the viral genome.³ Both chloroquine and hydroxychloroquine also have immunomodulatory effects, which have been hypothesized to be another potential mechanism of action for the treatment of COVID-19. Azithromycin has antiviral and anti-inflammatory properties. When used in combination with hydroxychloroquine, it has been shown to have a synergistic effect on SARS-CoV-2 in vitro and in molecular modeling studies.^{4,5} However, despite demonstrating antiviral activity in some in vitro systems, neither hydroxychloroquine plus azithromycin nor hydroxychloroquine alone reduced upper or lower respiratory tract viral loads or demonstrated clinical efficacy in a rhesus macaque model.⁶

The safety and efficacy of chloroquine or hydroxychloroquine with or without azithromycin and azithromycin alone have been evaluated in randomized clinical trials, observational studies, and/or single-arm studies.

Recommendation

• The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of chloroquine or hydroxychloroquine and/or azithromycin for the treatment of COVID-19 in hospitalized patients (AI) and in nonhospitalized patients (AIIa).

Rationale

Hospitalized Patients

In a large randomized controlled platform trial of hospitalized patients in the United Kingdom (RECOVERY), hydroxychloroquine did not decrease 28-day mortality when compared to the usual standard of care. Patients who were randomized to receive hydroxychloroquine had a longer median hospital stay than those who received the standard of care. In addition, among patients who were not on invasive mechanical ventilation at the time of randomization, those who received hydroxychloroquine were more likely to subsequently require intubation or die during hospitalization than those who received the standard of care.⁷

The results from several additional large randomized controlled trials have been published; these trials have failed to show a benefit for hydroxychloroquine with or without azithromycin or azithromycin alone in hospitalized adults with COVID-19. In the Solidarity trial, an international randomized controlled platform trial that enrolled hospitalized patients with COVID-19, the hydroxychloroquine arm was halted for futility. There was no difference in in-hospital mortality between patients in the hydroxychloroquine arm and those in the control arm.⁸ Similarly, PETAL, a randomized, placebocontrolled, blinded study, was stopped early for futility. In this study, there was no difference in the median scores on the COVID Outcomes Scale between patients who received hydroxychloroquine and those who received placebo.⁹ Data from two additional randomized studies of hospitalized patients

with COVID-19 did not support using hydroxychloroquine plus azithromycin over hydroxychloroquine alone.^{10,11} In RECOVERY, azithromycin alone (without hydroxychloroquine) did not improve survival or other clinical outcomes when compared to the usual standard of care.¹²

In addition to these randomized trials, data from large retrospective observational studies do not consistently show evidence of a benefit for hydroxychloroquine with or without azithromycin in hospitalized patients with COVID-19.¹³⁻¹⁵

Given the lack of a benefit seen in the randomized clinical trials, the Panel **recommends against** using hydroxychloroquine or chloroquine and/or azithromycin to treat COVID-19 in hospitalized patients (AI).

Nonhospitalized Patients

Several randomized trials have not shown a clinical benefit for hydroxychloroquine in nonhospitalized patients with early, asymptomatic, or mild COVID-19.^{16,17} In an open-label trial, Mitja et al. randomized 307 nonhospitalized people who were recently confirmed to have COVID-19 to receive hydroxychloroquine or no antiviral treatment. Patients in the hydroxychloroquine arm received hydroxychloroquine 800 mg on Day 1 followed by 400 mg daily for an additional 6 days. The authors reported no difference in the mean reduction in SARS-CoV-2 RNA at Day 3 or the time to clinical improvement between the two arms. In another trial, treating patients who had asymptomatic or mild COVID-19 with hydroxychloroquine with or without azithromycin did not result in greater rates of virologic clearance (as measured by a negative polymerase chain reaction [PCR] result on Day 6).¹⁸

An open-label, prospective, randomized trial compared oral azithromycin 500 mg once daily for 3 days plus standard of care to standard of care alone in nonhospitalized, high-risk, older adults who had laboratory-confirmed or suspected COVID-19. No differences were observed between the arms in the primary endpoints of time to first self-reported recovery and hospitalization or death due to COVID-19. These findings remained consistent in an analysis that was restricted to participants with positive SARS-CoV-2 PCR results. The study was ultimately halted due to futility.¹⁹ Similarly, in a preliminary report from ATOMIC-2, adding oral azithromycin 500 mg once daily to standard of care for 14 days did not reduce the risk of hospitalization or death among 292 participants with mild to moderate COVID-19.²⁰

While ongoing clinical trials are still evaluating the use of chloroquine, hydroxychloroquine, and azithromycin in outpatients, the existing data suggest that it is unlikely that clinical benefits will be identified for these agents. The Panel **recommends against** the use of chloroquine or hydroxychloroquine and/or azithromycin for the treatment of COVID-19 in nonhospitalized patients (AIIa).

Adverse Effects

Chloroquine and hydroxychloroquine have similar toxicity profiles, although hydroxychloroquine is better tolerated and has a lower incidence of toxicity than chloroquine. Cardiac adverse events that have been reported in people who received hydroxychloroquine include QTc prolongation, Torsades de Pointes, ventricular arrythmia, and cardiac deaths.²¹

The use of azithromycin has also been associated with QTc prolongation,²² and using it in combination with hydroxychloroquine has been associated with a higher incidence of QTc prolongation and cardiac adverse events in patients with COVID-19.^{23,24}

Drug-Drug Interactions

Chloroquine and hydroxychloroquine are moderate inhibitors of cytochrome P450 2D6, and these drugs are also P-glycoprotein inhibitors. Chloroquine and hydroxychloroquine may decrease the antiviral activity of remdesivir; coadministration of these drugs **is not recommended**.²⁵

Drug Availability

Hydroxychloroquine, chloroquine, and azithromycin **are not approved** by the Food and Drug Administration (FDA) for the treatment of COVID-19. Furthermore, the FDA Emergency Use Authorization for hydroxychloroquine and chloroquine was revoked in June 2020.

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Chloroquine or Hydroxychloroquine and/or Azithromycin: Selected Clinical Data

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The information in this table may include data from preprints or articles that have not been peer reviewed. This section will be updated as new information becomes available. Please see <u>*ClinicalTrials.gov*</u> for more information on clinical trials that are evaluating CQ, HCQ, and/or AZM.

The Panel has reviewed other clinical studies of HCQ with or without AZM, CQ, and AZM for the treatment of COVID-19.¹⁻¹⁹ These studies have limitations that make them less definitive and informative than the studies discussed here. The Panel's summaries and interpretations of some of those studies are available in the <u>archived versions</u> of the COVID-19 Treatment Guidelines.

Study Design	Methods	Results	Limitations and Interpretation
Solidarity Trial: Hydroxy	ychloroquine in Hospitalized Patients	s With COVID-19 ²⁰	
Open-label randomized controlled platform trial with multiple arms; in 1 arm, hospitalized patients received HCQ (n = 11,330)	 Key Inclusion Criteria: Aged ≥18 years Received a diagnosis of COVID-19 Key Exclusion Criteria: Already receiving study drug Expected to be transferred elsewhere within 72 hours Interventions: HCQ plus local SOC. Patients received a loading dose of HCQ 800 mg PO at entry, then HCQ 800 mg PO 6 hours later followed by a daily dose of HCQ 400 mg PO twice daily for 10 days, starting 12 hours after the entry dose. Local SOC alone 	 Number of Participants: ITT analysis: HCQ (n = 947) and HCQ control (n = 906) Enrollment occurred between March 22 and October 4, 2020. Participant Characteristics: 35% of patients enrolled in each arm were aged <50 years; 21% of patients were aged ≥70 years. 21% to 23% of patients had diabetes mellitus, 20% to 21% had heart disease, and 6.5% to 7% had chronic lung disease. At entry, 36% to 38% of patients were not on supplemental oxygen, 53% to 55% were receiving supplemental oxygen only, and 9% were receiving IMV. SOC included corticosteroids for 23% of patients in HCQ arm and 22% of patients in SOC only arm. Outcomes: No significant difference in in-hospital mortality; 104 patients (10.2%) in HCQ arm and 84 patients (8.9%) in SOC arm died by Day 28 (rate ratio 1.19: 95% CL 0.89–1.59: P = 0.23) 	 Key Limitations: Not blinded Disease severity varied widely among patients. Interpretation: HCQ does not decrease in- hospital mortality in hospitalized patients with COVID-19 when compared to SOC. HCQ does not decrease the need for mechanical ventilation when compared to SOC. There was no evidence of harm in the HCQ arm.

Study Design	Methods	Results	Limitations and Interpretation
Solidarity Trial: Hydroxy	chloroquine in Hospitalized Patients	With COVID-19 ²⁰ , continued	
	 Primary Endpoint: In-hospital mortality (i.e., death during the original hospitalization; follow-up ended at discharge from the hospital) 	 Subgroup analyses based on age or respiratory support at entry reported no significant difference in mortality between the arms. No difference between the arms in the secondary outcome of initiation of ventilation, and no difference in the composite outcome of in-hospital mortality or initiation of ventilation The number of deaths due to any cardiac cause during the 14 days after enrollment (the dosing period) was lower in these 2 arms than in the other study arms (the RDV, LPV/RTV, and IFN arms and their respective control arms). 	
PETAL Trial: Hydroxychl	oroquine in Hospitalized Patients Wi	th COVID-19 ²¹	
Randomized, placebo-	Key Inclusion Criteria:	Number of Participants:	Key Limitations:
controlled, blinded trial in hospitalized adults (n = 479)	 Laboratory-confirmed SARS- CoV-2 infection Symptoms of respiratory illness for <10 days Key Exclusion Criteria: More than 1 dose of HCQ or CQ during the previous 10 days Prolonged QTc interval (>500 ms) Interventions: HCQ 400 mg PO twice daily for 2 doses, then HCQ 200 mg PO twice daily for 8 doses Matching placebo Primary Endpoint: Clinical status 14 days after rendomization as measured by a 	 Enrollment occurred between April 2 and June 19, 2020. HCQ (n = 242) and placebo (n = 237) Planned sample size was 510 participants, but study enrollment was halted early due to futility. Participant Characteristics: Median age was 58 and 57 years in HCQ and placebo arms, respectively; 33% of patients were aged ≥65 years and 24% of patients were Black/African American. 33% to 36% of patients had diabetes mellitus, 6% to 12% had heart disease, and 7% to 9% had chronic lung disease. At randomization, 5.4% of patients in HCQ arm and 8% in placebo arm were receiving IMV or ECMO. In both arms, 11% to 12% of patients were receiving noninvasive ventilation or HFNC oxygen, 46% to 48% were receiving low-flow oxygen, and 35% were receiving no respiratory support. 	 It is unclear how the primary outcome of this study (a median COVID Outcomes Scale score) translates to clinical practice. Interpretation: HCQ does not improve patient scores on the COVID Outcomes Scale in hospitalized patients with laboratory-confirmed SARS-CoV-2 infection when compared to placebo. HCQ did not improve survival or time to discharge in these patients when compared to placebo.

Study Design	Methods	Results	Limitations and Interpretation
PETAL Trial: Hydroxych	oroquine in Hospitalized Patients	With COVID-19 ²¹ , continued	·
		 Outcomes: Median COVID Outcomes Scale score was 6 in HCQ arm (IQR 4–7) and 6 in placebo arm (IQR 4–7; aOR 1.02; 95% CI, 0.73–1.42). No difference between the arms in the secondary outcome of all-cause, all-location death at Day 14 and Day 28 No difference between the arms in the number of any of the following systematically collected safety events: cardiac arrest treated with CPR, symptomatic hypoglycemia, ventricular arrhythmia, or seizure Among patients who had QTc assessed, 5.9% in HCQ arm and 3.3% in placebo arm had a recorded QTc interval >500 ms during the first 5 days of docing 	
RECOVERY Trial ²²			
Open-label, randomized	Key Inclusion Criteria:	Number of Participants:	Key Limitations:
controlled platform trial	Clinically suspected or	• HCQ (n = 1,561) and SOC (n = 3,155)	Not blinded
with multiple arms; in 1 arm, hospitalized patients received HCQ	laboratory-confirmed SARS- CoV-2 infection	• Study enrollment ended early after investigators and trial- steering committee concluded that the data showed no benefit for HCQ.	• Information on occurrence of new major cardiac arrythmia was not collected throughout the trial.
(11 = 11, 197)	Patients with prolonged QTc	Participant Characteristics:	Interpretation:
	 Patients with proforged Grc intervals were excluded from HCQ arm. Interventions: HCQ 800 mg at entry and at 6 hours, then HCQ 400 mg every 12 hours for 9 days or until discharge Usual SOC Primary Endpoint: All-cause mortality at Day 28 after randomization 	 Mean age was 65 years in both arms; 41% of patients were aged ≥70 years. 90% of patients had laboratory-confirmed SARS-CoV-2 infection. 57% of patients had ≥1 major comorbidity: 27% had diabetes mellitus, 26% had heart disease, and 22% had chronic lung disease. At randomization, 17% of patients were receiving IMV or ECMO, 60% were receiving oxygen only (with or without noninvasive ventilation), and 24% were receiving neither. Use of AZM or another macrolide during the follow-up period was similar in both arms, as was use of dexamethasone. 	 HCQ does not decrease 28-day all-cause mortality when compared to the usual SOC in hospitalized patients with clinically suspected or laboratory-confirmed SARS-CoV-2 infection. Patients who received HCQ had a longer median length of hospital stay, and those who were not on IMV at the time of randomization were more likely to require intubation or die during hospitalization if they received HCQ.

Study Design	Methods	Results	Limitations and Interpretation
RECOVERY Trial ²² , conti	nued		
		 Outcomes: No significant difference in 28-day mortality between the 2 arms; 421 patients (26.8%) in HCQ arm and 790 patients (27.0%) in SOC arm had died by Day 28 (rate ratio 1.09; 95% Cl, 0.97–1.23; P = 0.15). A similar 28-day mortality for HCQ patients was reported during the post hoc exploratory analysis that was restricted to the 4,266 participants (90.5%) who had a positive SARS-CoV-2 test result. Patients in HCQ arm were less likely to survive hospitalization and had a longer median time to discharge than patients in SOC arm. Patients who received HCQ and who were not on IMV at baseline had an increased risk of requiring intubation and an increased risk of death. At the beginning of the study, the researchers did not record whether a patient developed a major cardiac arrhythmia after study enrollment; however, these data were later collected for 735 patients (47.1%) in HCQ arm and 1,421 patients (45.0%) in SOC arm. No differences between the arms in the frequency of supraventricular tachycardia, ventricular tachycardia or fibrillation, or instances of AV block that required intervention; 1 case of Torsades de Pointes was reported in HCQ arm 	
Hydroxychloroquine and	d Hydroxychloroquine Plus Azithrom	ycin for Mild or Moderate COVID-19 ²³	
Open-label, 3-arm RCT	Key Inclusion Criteria:	Number of Participants:	Key Limitations:
in hospitalized adults (n = 667)	 Aged ≥18 years Clinically suspected or 	• mITT analysis included patients with laboratory- confirmed SARS-CoV-2 infection (n = 504).	Not blindedFollow-up period was restricted to 15 days.
	 Indoratory-confirmed SARS- CoV-2 infection Mild or moderate COVID-19 Duration of symptoms ≤14 days 	 Participant Characteristics: Mean age was 50 years. 58% of patients were men. 	 Interpretation: Neither HCQ alone nor HCQ plus AZM improved clinical outcomes at Day 15 after randomization among hospitalized patients

Study Design	Methods	Results	Limitations and Interpretation
Hydroxychloroquine and	Hydroxychloroquine Plus Azithromyc	in for Mild or Moderate COVID-19 ²³ , continued	
	 Key Exclusion Criteria: Need for >4 L of supplemental oxygen or ≥40% FiO₂ by face mask History of ventricular tachycardia QT interval ≥480 ms 	 At baseline, 58.2% of patients were Ordinal Level 3; 41.8% were Ordinal Level 4. Median time from symptom onset to randomization was 7 days. 23.3% to 23.9% of patients received oseltamivir. 	with mild or moderate COVID-19.
	Interventions:	Outcomes:	
	 HCQ 400 mg twice daily for 7 days plus SOC HCQ 400 mg twice daily plus AZM 500 mg daily for 7 days plus SOC SOC alone Primary Endpoint: Clinical status at Day 15, as measured by a 7-point ordinal scale among the patients with confirmed SARS-CoV-2 infection 	 No significant difference in the odds of worse clinical status at Day 15 between patients in HCQ arm (OR 1.21; 95% Cl, 0.69–2.11; P = 1.00) and patients in HCQ plus AZM arm (OR 0.99; 95% Cl, 0.57–1.73; P = 1.00) No significant differences in secondary outcomes of the 3 arms, including progression to mechanical ventilation during the first 15 days and mean number of days "alive and free of respiratory support" A greater proportion of patients in HCQ plus AZM arm (39.3%) and HCQ arm (33.7%) experienced AEs than those in SOC arm (22.6%). 	
	 Ordinal Scale Definitions: 1. Not hospitalized, no limitations 2. Not hospitalized, with limitations 3. Hospitalized, not on oxygen 4. Hospitalized, on oxygen 5. Hospitalized, oxygen administered by HFNC or noninvasive ventilation 6. Hospitalized, on mechanical ventilation 7. Death 	• QT prolongation was more common in patients who received HCQ plus AZM or HCQ alone than in patients who received SOC alone, but fewer patients in SOC arm had serial electrocardiographic studies performed during the follow-up period.	

Study Design	Methods	Results	Limitations and Interpretation
Hydroxychloroquine in N	onhospitalized Adults With Early CO	VID-19 ²⁴	
Randomized, placebo-	Key Inclusion Criteria:	Number of Participants:	Key Limitations:
controlled trial in nonhospitalized adults	 Symptoms that were compatible with COVID-19 and lasted ≤4 	• Contributed to primary endpoint data: HCQ (n = 212) and placebo (n = 211)	 This study enrolled a highly heterogeneous population.
(11 = 491)	days	Participant Characteristics:	• Only 227 of 423 participants (53.7%)
	Either laboratory-confirmed SARS-CoV-2 infection or high- risk exposure within the previous	• 241 patients were exposed to people with COVID-19 through their position as health care workers (57%), 106	were confirmed PCR-positive for SARS-CoV-2.
	14 days	were exposed through household contacts (25%), and 76 had other types of exposure (18%).	Changing the primary endpoint without a new power calculation
	Key Exclusion Criteria:	Median age was 40 years.	makes it difficult to assess whether
	• Aged <18 years	• 56% of patients were women.	differences in outcomes between the
	Hospitalized	Only 3% of patients were Black.	study arms.
	Receipt of certain medications	 Very few patients had comorbidities: 11% had 	 This study used surveys for
	Interventions:	hypertension, 4% had diabetes, and 68% had no chronic medical conditions.	screening, symptom assessment, and adherence reporting.
	mg in 6–8 hours, then HCQ 600 mg once daily for 4 days	 56% of patients were enrolled on Day 1 of symptom onset. 	 Visual analogue scales are not commonly used, and their ability
	• Placebo	• 341 participants (81%) had either a positive PCR result or	to assess acute viral respiratory infections in clinical trials has not
	Primary Endpoints:	a high-risk exposure to a PCR-positive contact.	been validated.
	• Planned primary endpoint was	Outcomes:	Interpretation:
	ordinal outcome by Day 14 in 4 categories: not hospitalized, hospitalized, ICU stay, or death.	• Compared to the placebo recipients, HCQ recipients had a nonsignificant 12% difference in improvement in symptoms between baseline and Day 14 (-2.60 vs2.33	• The study has some limitations, and it did not find evidence that
	Because event rates were lower	points; $P = 0.117$).	symptom severity in patients with
	than expected, a new primary endpoint was defined: change in overall symptom severity over 14	• Ongoing symptoms were reported by 24% of those in HCQ arm and 30% of those in the placebo arm at Day 14 $(P = 0.21)$.	mild COVID-19.
	days, measured by a 10-point, self-reported, visual analogue scale	• No difference in the incidence of hospitalization between the arms (4 patients in the HCQ arm vs. 10 patients in placebo arm); 2 of 10 placebo participants were hospitalized for reasons that were unrelated to COVID-19	
		• A higher percentage of patients in HCQ arm experienced AEs than patients in placebo arm (43% vs. 22%; <i>P</i> < 0.001).	

Study Design	Methods	Results	Limitations and Interpretation
Hydroxychloroquine in	Nonhospitalized Adults With Mild CO	VID-19 ²⁵	
Open-label RCT in	Key Inclusion Criteria:	Number of Participants:	Key Limitations:
Hydroxychloroquine in Open-label RCT in nonhospitalized adults (n = 353)	 Nonhospitalized Adults With Mild CO Key Inclusion Criteria: Laboratory-confirmed SARS-CoV-2 infection <5 days of mild COVID-19 symptoms Key Exclusion Criteria: Moderate to severe COVID-19 Severe liver or renal disease History of cardiac arrhythmia QT prolongation Interventions: HCQ 800 mg on Day 1, then HCQ 400 mg once daily for 6 days No antiviral treatment (control arm) Primary Endpoint: Reduction in SARS-CoV-2 viral load, assessed using NP swabs on Days 3 and 7 Secondary Endpoints: Disease progression up to Day 28 Time to complete resolution of symptoms 	 VID-19²⁵ Number of Participants: ITT analysis: HCQ (n = 136) and control (n = 157) 60 patients were excluded from the ITT analysis due to negative baseline RT-PCR, missing RT-PCR at follow-up visits, or consent withdrawal. Participant Characteristics: Mean age was 41.6 years. 67% of patients were woman. Majority of patients were health care workers (87%). 53% of patients reported chronic health conditions. Median time from symptom onset to enrollment was 3 days (IQR 2–4 days). Most common COVID-19 symptoms were fever, cough, and sudden olfactory loss. Outcomes: No significant difference in viral load reduction between control arm and HCQ arm at Day 3 (-1.41 vs1.41 log₁₀ copies/mL; difference of 0.01; 95% Cl, -0.28 to 0.29), or at Day 7 (-3.37 vs3.44 log10 copies/mL; difference of -0.07; 95% Cl, -0.24 to 0.29). No difference in the risk of hospitalization between control arm and HCQ arm (7.1% vs. 5.9%; risk ratio 0.75; 95% Cl, 0.32–1.77) No difference in the median time from randomization to the resolution of COVID-19 symptoms between the 2 arms (12.0 days in control arm vs. 10.0 days in HCQ arm; <i>P</i> = 0.38) A higher percentage of participants in the HCQ arm than in the control arm experienced AEs during the 28-day follow-up of the participants in the HCQ arm than in the control arm experienced AEs during the 28-day follow-up of the participants in the HCQ arm than in the control arm experienced AEs during the 28-day follow-up of the participant in the participant of participants in the HCQ arm than in the control arm experienced AEs during the 28-day follow-up of the participants in the HCQ arm than in the control arm experienced AEs during the 28-day follow-up of the participants in the HCQ arm than in the control arm of participants in the HCQ arm than in the control arm of participants in the HCQ arm than in the control arm	 Key Limitations: Open-label, non-placebo-controlled trial Study design allowed for the possibility of dropouts in control arm and over-reporting of AEs in HCQ arm. The intervention changed during the study; the authors initially planned to include HCQ plus DRV/COBI. The majority of the participants were relatively young health care workers. Interpretation: Early administration of HCQ to patients with mild COVID-19 did not result in improvement in virologic clearance, a lower risk of disease progression, or a reduced time to symptom improvement.
	 Disease progression up to Day 28 Time to complete resolution of symptoms 	 No difference in the risk of hospitalization between control arm and HCQ arm (7.1% vs. 5.9%; risk ratio 0.75; 95% CI, 0.32–1.77) No difference in the median time from randomization to the resolution of COVID-19 symptoms between the 2 arms (12.0 days in control arm vs. 10.0 days in HCQ arm; <i>P</i> = 0.38) A higher percentage of participants in the HCQ arm than in the control arm experienced AEs during the 28-day follow-up period (72% vs. 9%). Most common AEs were GI disorders and "nervous system disorders." SAEs were reported in 12 patients in control arm and 8 patients in HCQ arm. SAEs that occurred among patients in 	

Study Design	Methods	Results	Limitations and Interpretation
Observational Study on I	Hydroxychloroquine With or Without	Azithromycin ²⁶	
Retrospective,	Key Inclusion Criteria:	Number of Participants:	Key Limitations:
multicenter, observational study in	 Laboratory-confirmed SARS- CoV-2 infection 	• HCQ plus AZM (n = 735), HCQ alone (n = 271), AZM alone (n = 211), and neither drug (n = 221)	 This study has the inherent limitations of an observational study,
hospitalized adults with	Interventions:	Participant Characteristics:	including residual confounding from
COVID-19 from the New	• HCQ plus AZM	• Patients in the treatment arms had more severe disease	unrecognized and/or unavailable for
York Department of	• HCQ alone	at baseline than those who received neither drug.	analysis.
$\Pi = 1,430$	• AZM alone	Outcomes:	Interpretation:
	Neither drug	 In adjusted analyses, patients who received 1 of the 2 treatment regimens did not show a decreased in 	• Despite the limitations discussed
	Primary Endpoint:	hospital mortality rate when compared with those who	above, these findings suggest that
	 In-hospital mortality 	received neither drug.	associated with an increased risk of
	Secondary Endpoint:	• Patients who received HCQ plus AZM had a greater risk	in-hospital death, the combination of
	 Cardiac arrest and arrhythmia or QT prolongation on an ECG 	(OR 2.13; 95% Cl, 1.12–4.05).	HCQ and AZM may be associated with an increased risk of cardiac arrest.
Observational Study of H	lydroxychloroquine Versus No Hydro	xychloroquine in New York City ²⁷	
Observational study in	Key Inclusion Criteria:	Number of Participants:	Key Limitations:
hospitalized adults with COVID-19 at a large	 Laboratory-confirmed SARS- CoV-2 infection 	• Received HCQ (n = 811) and did not receive HCQ (n = 565)	• This study has the inherent limitations of an observational study,
1,376)	Key Exclusion Criteria:	Participant Characteristics:	Including residual contounding from
	 Intubation, death, or transfer to another facility within 24 hours 	 HCQ recipients were more severely ill at baseline than those who did not receive HCQ. 	unrecognized and/or unavailable for analysis.
	of arriving at the emergency department	Outcomes:	Interpretation:
	Interventions:	Using propensity scores to adjust for major predictors of received and inverse probability uniobting	• The use of HCQ for treatment of
	 HCQ 600 mg twice daily on Day 1, then HCQ 400 mg once daily for 4 days 	the study demonstrated that HCQ use was not associated with intubation or death (HR 1.04; 95% CI, 0.82–1.32).	COVID-19 was not associated with harm or benefit in a large observational study.
	• No HCQ	No association between concomitant use of AZM and	
	Primary Endpoint:	the composite endpoint of intubation or death (HR 1.03; 95% CL 0.81–1.31)	
	• Time from study baseline (24 hours after patients arrived at the ED) to intubation or death		

Key: AE = adverse event; AV = atrioventricular; AZM = azithromycin; CPR = cardiopulmonary resuscitation; CQ = chloroquine; DRV/COBI = darunavir/cobicistat; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; ED = emergency department, FiO₂ = fraction of inspired oxygen; GI = gastrointestinal; HCQ = hydroxychloroquine; HFNC = high-flow nasal cannula; ICU = intensive care unit; IFN = interferon; IMV = invasive mechanical ventilation; ITT = intention-to-treat; LPV/ RTV = lopinavir/ritonavir; mITT = modified intention-to-treat; NP = nasopharyngeal; the Panel = the COVID-19 Treatment Guidelines Panel; PCR = polymerase chain reaction; PO = orally; RCT = randomized controlled trial; RDV = remdesivir; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SOC = standard of care

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Colchicine

Last Updated: May 31, 2022

Colchicine is an anti-inflammatory drug that is used to treat a variety of conditions, including gout, recurrent pericarditis, and familial Mediterranean fever.¹ Recently, the drug has been shown to potentially reduce the risk of cardiovascular events in those with coronary artery disease.² Colchicine has several potential mechanisms of action, including reducing the chemotaxis of neutrophils, inhibiting inflammasome signaling, and decreasing the production of cytokines, such as interleukin-1 beta.³ When colchicine is administered early in the course of COVID-19, these mechanisms could potentially mitigate or prevent inflammation-associated manifestations of the disease. These anti-inflammatory properties coupled with the drug's limited immunosuppressive potential, favorable safety profile, and widespread availability have prompted investigation of colchicine for the treatment of COVID-19.

Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **colchicine** for the treatment of nonhospitalized patients with COVID-19, except in a clinical trial **(BIIa)**.
- The Panel **recommends against** the use of **colchicine** for the treatment of hospitalized patients with COVID-19 (AI).

Rationale: Nonhospitalized Patients

COLCORONA, a large, placebo-controlled, randomized trial that evaluated colchicine in outpatients with COVID-19, did not reach its primary efficacy endpoint of reducing hospitalizations and death.⁴ However, in the subset of patients whose diagnosis was confirmed by a positive SARS-CoV-2 polymerase chain reaction (PCR) result from a nasopharyngeal swab, a slight reduction in hospitalizations was observed among those who received colchicine.

PRINCIPLE, an open-label, adaptive-platform, randomized trial that evaluated colchicine versus usual care, was stopped for futility when no significant difference was found between the colchicine and usual care recipients for the outcome of time to first self-reported recovery from COVID-19.⁵

The PRINCIPLE trial showed no benefit for colchicine, and the larger COLCORONA trial failed to reach its primary endpoint, found only a very modest effect of colchicine in the subgroup of patients with positive SARS-CoV-2 PCR results, and reported more gastrointestinal adverse events for those receiving colchicine. Therefore, the Panel **recommends against** the use of **colchicine** for the treatment of COVID-19 in nonhospitalized patients, except in a clinical trial (**BIIa**).

Rationale: Hospitalized Patients

In the RECOVERY trial, a large, randomized trial in hospitalized patients with COVID-19, colchicine demonstrated no benefit with regard to 28-day mortality or any secondary outcomes.⁶ Based on the results from this large trial, the Panel **recommends against** the use of **colchicine** for the treatment of COVID-19 in hospitalized patients (AI).

Clinical Data for COVID-19

COLCORONA Trial: Nonhospitalized Patients

The COLCORONA trial was a double-blind, placebo-controlled, randomized trial in outpatients who received a diagnosis of COVID-19 within 24 hours of enrollment.⁴ Participants were aged \geq 70 years

or aged \geq 40 years with at least 1 of the following criteria: body mass index \geq 30, diabetes mellitus, uncontrolled hypertension, known respiratory disease, heart failure or coronary disease, fever \geq 38.4°C within the past 48 hours, dyspnea at presentation, bicytopenia, pancytopenia, or the combination of high neutrophil count and low lymphocyte count. Participants were randomized 1:1 to receive placebo or colchicine 0.5 mg twice daily for 3 days, then once daily for 27 days. The primary endpoint was a composite of death or hospitalization by Day 30; secondary endpoints included components of the primary endpoint, as well as the need for mechanical ventilation by Day 30. Participants reported by telephone the occurrence of any study endpoints at 15 and 30 days after randomization; in some cases, clinical data were confirmed or obtained by medical chart reviews.

Results

- The study enrolled 4,488 participants.
- The primary endpoint occurred in 104 (4.7%) of 2,235 participants in the colchicine arm and 131 (5.8%) of 2,253 participants in the placebo arm (OR 0.79; 95% CI, 0.61–1.03; P = 0.08).
- There were no statistically significant differences between the arms for the secondary outcomes.
- In a prespecified analysis of 4,159 participants (93% of those enrolled) with SARS-CoV-2 infection confirmed by PCR testing of an nasopharyngeal specimen:
 - Participants in the colchicine arm were less likely than those in the placebo arm to reach the primary endpoint (4.6% vs. 6.0%; OR 0.75; 95% CI, 0.57–0.99; *P* = 0.04).
 - Participants in the colchicine arm had fewer hospitalizations than those in the placebo arm (4.5% vs. 5.9%; OR 0.75; 95% CI, 0.57–0.99).
- More participants in the colchicine arm than the placebo arm experienced gastrointestinal adverse events, including diarrhea (13.7% vs. 7.3%; P < 0.0001).
- More pulmonary emboli were reported in the colchicine arm than the placebo arm (11 events [0.5% of participants] vs. 2 events [0.1% of participants]).

Limitations

- The trial stopped at approximately 75% of the target enrollment, which may have limited the study's power to detect differences for the primary outcome.
- Some patient-reported clinical outcomes potentially were misclassified.

PRINCIPLE Trial: Nonhospitalized Patients

PRINCIPLE was a randomized, open-label, platform trial that evaluated colchicine in symptomatic, nonhospitalized patients with COVID-19.⁵ Included participants had symptoms for \leq 14 days and were aged \geq 65 years or aged \geq 18 years with comorbidities or shortness of breath. Participants were randomized to receive colchicine 0.5 mg daily for 14 days or usual care. The coprimary endpoints, which included time to first self-reported recovery or hospitalization or death due to COVID-19 by Day 28, were analyzed using a Bayesian model. Participants were followed through symptom diaries. Futility was defined as not reaching a clinically meaningful benefit (i.e., a hazard ratio \geq 1.2, corresponding to about 1.5 days of faster recovery in the colchicine arm) for the endpoint of time to first self-reported recovery.

Results

- The study enrolled 4,997 participants: 212 participants were randomized to receive colchicine; 2,081 to receive usual care alone; and 2,704 to receive other treatments.
- The prespecified primary analysis included participants with a positive test for SARS-CoV-2 (156 participants in the colchicine arm; 1,145 in the usual care arm; and 1,454 in the other treatments arm).

- The trial stopped early because of futility; the median time to self-reported recovery was similar in the colchicine arm and the usual care arm (HR 0.92; 95% CrI, 0.72–1.16).
- Analyses showed no significant differences between the colchicine and usual care arms for selfreported time to recovery and for hospitalizations or death due to COVID-19.
- There were no statistically significant differences between the colchicine and usual care arms for the secondary outcomes in both the primary analysis population and in the subgroups, including the subgroups based on symptom duration, baseline disease severity, age, and comorbidities.
- The occurrence of adverse events was similar in the colchicine and usual care arms.

Limitations

- The study had an open-label design.
- The sample size of the colchicine arm was small.

RECOVERY Trial: Hospitalized Patients

In the RECOVERY trial, hospitalized patients with COVID-19 were randomized 1:1 to receive colchicine (1 mg followed by 0.5 mg 12 hours later, then 0.5 mg twice daily for 10 days or until discharge) or usual care.⁶

Results

- The study enrolled 11,340 participants.
- At randomization, 94% of participants were receiving corticosteroids.
- In both arms, the primary endpoint of all-cause mortality at Day 28 occurred in 21% of participants (rate ratio 1.01; 95% CI, 0.93–1.10; P = 0.77).
- There were no statistically significant differences between the arms for the endpoints of median time to discharge alive, discharge from the hospital within 28 days, and receipt of mechanical ventilation or death.
- The incidence of new cardiac arrhythmias, bleeding events, and thrombotic events was similar in the 2 arms. Two serious adverse events were attributed to colchicine: 1 case of severe acute kidney injury and 1 case of rhabdomyolysis.

Limitation

• The study had an open-label design.

COLCOVID Trial: Hospitalized Patients

COLCOVID was a multicenter, open-label, randomized trial in hospitalized adults with confirmed or suspected SARS-CoV-2.⁷ Patients were assigned 1:1 to receive either colchicine (1.5 mg followed by 0.5 mg orally within 2 hours of initial dose, then twice daily for 14 days or until hospital discharge) plus usual care or usual care alone.

Results

- The study enrolled 1,279 participants.
- There were no statistically significant differences between the colchicine and usual care arms for either of the coprimary outcomes, which were mortality by Day 28 (HR 0.88; 95% CI, 0.70–1.12) and mechanical ventilation or mortality by Day 28 (HR 0.83; 95% CI, 0.67–1.02).
- More individuals in the colchicine arm than in the usual care arm experienced diarrhea (11.3% vs. 4.5%).

Limitation

• The study had an open-label design.

GRECCO-19 Trial: Hospitalized Patients

GRECCO-19 was a prospective, open-label, randomized clinical trial that included patients with COVID-19 from 16 hospitals in Greece.⁸ Participants were assigned 1:1 to receive colchicine (1.5 mg followed by 0.5 mg after 60 minutes, then 0.5 mg twice daily for up to 3 weeks or until hospital discharge, whichever comes first) plus the standard of care or the standard of care alone.

Results

- The study enrolled 105 participants.
- Fewer participants in the colchicine arm (1 of 55 participants) than in the standard of care arm (7 of 50 participants) reached the primary clinical endpoint of clinical status deterioration from baseline by 2 points on a 7-point clinical status scale (OR 0.11; 95% CI, 0.01–0.96).
- Participants in the colchicine arm were significantly more likely to experience diarrhea than those in the standard of care arm (45.5% vs. 18.0%; P = 0.003).

Limitations

- The study had an open-label design.
- The sample size and number of clinical events were small.

The results of several small, randomized trials and retrospective cohort studies that evaluated various doses and durations of colchicine in hospitalized patients with COVID-19 have been published in peer-reviewed journals or been made available as preliminary, non-peer-reviewed reports.⁹⁻¹² Some of those studies showed benefits of colchicine use, including less need for supplemental oxygen, improvements in clinical status on an ordinal clinical scale, and reductions in certain inflammatory markers. In addition, some studies reported higher discharge rates or fewer deaths among patients who received colchicine than among those who received comparator drugs or placebos. However, the findings from these studies are difficult to interpret due to significant design or methodological limitations, including small sample sizes, open-label designs, differences in the clinical and demographic characteristics of participants, and differences in the cotreatments (e.g., remdesivir, corticosteroids) permitted in the treatment arms.

Adverse Effects, Monitoring, and Drug-Drug Interactions

Common adverse effects of colchicine include diarrhea, nausea, vomiting, abdominal cramping and pain, bloating, and loss of appetite. In rare cases, colchicine is associated with serious adverse events, such as neuromyotoxicity and blood dyscrasias. Colchicine clearance is decreased in patients with impaired renal function and may require dose reduction along with increased monitoring for adverse effects. Significant increases in colchicine plasma levels may occur when colchicine is coadministered with drugs that inhibit cytochrome P450 (CYP) 3A4 or P-glycoprotein (P-gp), increasing the risk of colchicine-induced adverse effects. The risk of myopathy may be increased with concomitant use of certain HMG-CoA reductase inhibitors (e.g., atorvastatin, lovastatin, simvastatin) due to potential competitive interactions mediated by CYP3A4 and P-gp pathways.^{13,14} Fatal colchicine toxicity has been reported in individuals with renal or hepatic impairment who received colchicine in conjunction with P-gp inhibitors or strong CYP3A4 inhibitors.

Considerations in Pregnancy

There are limited data on the use of colchicine in pregnancy. Fetal risk cannot be ruled out based on

data from animal studies and the drug's mechanism of action. Colchicine crosses the placenta and has antimitotic properties, which raises a theoretical concern for teratogenicity. However, a recent metaanalysis did not find that colchicine exposure during pregnancy increased the rates of miscarriage or major fetal malformations. There are no data for colchicine use in pregnant women with acute COVID-19. Risks of use should be balanced against potential benefits.^{13,15}

Considerations in Children

Colchicine is most commonly used in children to treat periodic fever syndromes and autoinflammatory conditions. Although colchicine is generally considered safe and well-tolerated in children, there are no data on the use of the drug to treat pediatric acute COVID-19 or multisystem inflammatory syndrome in children (MIS-C).

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Granulocyte-Macrophage Colony-Stimulating Factor Inhibitors

Last Updated: March 24, 2022

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a myelopoietic growth factor and proinflammatory cytokine that plays a central role in a broad range of immune-mediated diseases. GM-CSF, which is secreted by macrophages, T cells, mast cells, natural killer cells, endothelial cells, and fibroblasts, regulates macrophage number and function. It acts as a pro-inflammatory signal, prompting macrophages to launch an immune cascade that ultimately results in tissue damage.^{1,2} GM-CSF is believed to be a key driver of lung inflammation in severe and critical COVID-19 pneumonia, operating upstream of other pro-inflammatory cytokines and chemokines.¹⁻⁶ Anti-GM-CSF monoclonal antibodies (mAbs) may mitigate inflammation by inhibiting this signaling axis upstream and thus minimizing downstream production of numerous pro-inflammatory mediators involved in the pathogenesis of COVID-19.⁷ Gimsilumab, lenzilumab, namilumab, and otilimab target GM-CSF directly, neutralizing the biological function of GM-CSF by blocking the interaction of GM-CSF with its cell surface receptor.^{1,8,9} Mavrilimumab targets the alpha subunit of the GM-CSF receptor, blocking intracellular signaling of GM-CSF.^{8,10} None of these agents are currently FDA approved for any indication.

Recommendation

• There is insufficient evidence for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of GM-CSF inhibitors for the treatment of hospitalized patients with COVID-19.

Rationale

Clinical data are lacking to definitively establish the potential benefits and risks associated with the use of GM-CSF inhibitors in patients with COVID-19. Data from a double-blind randomized controlled trial of lenzilumab did show a significant improvement in the primary endpoint of ventilator-free survival through Day 28 among those who received the GM-CSF inhibitor.¹¹ However, preliminary data from a large, double-blind randomized trial of otilimab (primary endpoint: alive and free of respiratory failure at Day 28) and published results of a small, double-blind, randomized trial of mavrilimumab (primary endpoint: proportion alive and off supplemental oxygen at Day 14) did not show a survival benefit for the GM-CSF inhibitors compared to placebo.¹²⁻¹⁴ The study populations differed; the lenzilumab and mavrilimumab studies primarily included patients on room air or low-flow oxygen and excluded patients receiving mechanical ventilation, whereas the otilimab study included only patients receiving high-flow oxygen, noninvasive ventilation, or mechanical ventilation. Lenzilumab and mavrilimumab continue to be investigated, whereas clinical development of otilimab for the treatment of COVID-19 has ceased.

Clinical Data for COVID-19

Lenzilumab, mavrilimumab, namilumab, and otilimab have been evaluated in clinical trials in hospitalized adults with SARS-CoV-2 pneumonia.¹²⁻¹⁵ Clinical data are not yet published for gimsilumab. The Panel's recommendations are based on the results of the available clinical studies.

Clinical Trials

See <u>*ClinicalTrials.gov*</u> for a list of ongoing clinical trials that are evaluating the use of GM-CSF inhibitors for the treatment of COVID-19.

Adverse Effects

The primary risks associated with GM-CSF inhibitors being reported and evaluated are related to bacterial infection. Other adverse events that have been reported with these agents include acute kidney injury and elevated liver transaminases.¹⁰ Autoimmune pulmonary alveolar proteinosis has been associated with a high-titer of anti-GM-CSF auto-antibodies.¹⁶

Considerations in Pregnancy

Pregnant patients have been excluded from clinical trials evaluating GM-CSF inhibitors for the treatment of COVID-19. There is insufficient evidence to recommend for or against their use in pregnant individuals with COVID-19.

Considerations in Children

There are no data on the use of GM-CSF inhibitors in children.

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Granulocyte-Macrophage Colony-Stimulating Factor Inhibitors: Selected Clinical Data

Last Updated: March 24, 2022

The clinical trials described in this table do not represent all the trials that the Panel reviewed while developing the recommendations for GM-CSF inhibitors. The studies summarized below are those that have had the greatest impact on the Panel's recommendations.

The information in this table may include data from preprints or articles that have not been peer reviewed. This section will be updated as new information becomes available. Please see <u>*ClinicalTrials.gov*</u> for more information on clinical trials that are evaluating GM-CSF inhibitors.

Methods	Results	Limitations and Interpretation
LIVE-AIR: Double-Blind RCT of Lenzilumab in Hospitalized	tates and Brazil ^{1,2}	
Key Inclusion Criteria:	Participant Characteristics:	Key Limitations:
 Hospitalized with SARS-CoV-2 pneumonia 	Mean age 61 years; 65% men; 72% White	Not powered to detect a survival
• $\text{SpO}_2 \leq 94\%$ on room air or required low-flow	• 55% BMI ≥30	benefit
supplemental oxygen, HFNC oxygen, or NIV	 At baseline: 41% received HFNC oxygen or NIV 	Access to supportive care differed across study sites
Key Exclusion Criteria:	• 94% received corticosteroids; 72% received RDV; 69%	
• MV or ECMO	received corticosteroids and RDV	Interpretation:
 Bacterial pneumonia, fungal or viral infection 	• Median CRP 79 mg/L	Lenzilumab improved ventilator-free aunvival in participants with hyperversion
 48-hour survival not expected 	Primary Outcome:	who were not receiving MV with the
• Use of IL-1 inhibitors, IL-6 inhibitors, kinase inhibitors, or mAbs within prior 8 weeks	 Survival without MV through Day 28: 84% in lenzilumab arm vs. 78% in placebo arm (HR 1.54; 95% CI, 1.02– 	greatest benefit among those with lower CRP levels.
Interventions:	2.32; $P = 0.040$)	
• 3 doses of lenzilumab 600 mg IV 8 hours apart (n = 236)	Key Secondary Outcomes:	
• Placebo (n = 243)	 Mortality: 10% in lenzilumab arm vs. 14% in placebo arm (HB 0 72: 95% CL 0 42–1 23: P = 0 24) 	
Primary Endpoint:	 Incidence of death or requiring MV or ECMO: 15% in 	
Survival without MV through Day 28	lenzilumab arm vs. 21% in placebo arm (HR 0.67; 95%	
Key Secondary Endpoints:	CI, 0.41–1.10; <i>P</i> = 0.11)	
Mortality	Exploratory Outcome:	
 Incidence of death or requiring MV or ECMO 	• Survival without MV for baseline CRP <150 mg/L: 90% in	
Exploratory Endpoint:	lenzilumab arm vs. 79% in placebo arm (HR 2.54; 95% CL 1 46–4 41' $P = 0.0009$)	
 Survival without MV, stratified by baseline CRP 		

Methods	Results	Limitations and Interpretation	
MASH-COVID: Double-Blind RCT of Mavrilimumab in Hospitalized Patients With Severe COVID-19 Pneumonia and Systemic Hyperinflammation in the United States ³			
Key Inclusion Criteria:	Participant Characteristics:	Key Limitations:	
Hospitalization with SARS-CoV-2 pneumonia	• Median age 57 years; 65% men; 40% African American	Very small sample size	
• SpO ₂ <92% on room air or required supplemental oxygen	• At baseline:	• Ended early due to slow enrollment	
• CRP >5 mg/dL	 50% required HFNC oxygen or NIV 	Interpretation:	
Key Exclusion Criteria:	 65% received corticosteroids 	Among participants with systemic	
• MV	• 75% received RDV	hyperinflammation and severe	
• ANC <1,500/mm ³	Primary Outcome:	evidence that use of mayrilimumab	
Uncontrolled bacterial infection	• Alive and off supplemental oxygen at Day 14: 57% in	improved supplemental oxygen-free	
Interventions:	mavrilimumab arm vs. 47% in placebo arm (OR 1.48;	survival by Day 14.	
• Mavrilimumab 6 mg/kg as single IV infusion (n = 21)	95% CI, 0.43–5.16, $P = 0.76$)		
• Placebo (n = 19)	Key Secondary Outcomes:		
Primary Endpoint:	• Mortality at Day 28: 1 (5%) in mavrilimumab arm vs. 3 (16%) in placebo arm (HB 3 72: 95% CL 0 39–35 79: P-		
Alive and off supplemental oxygen at Day 14			
Key Secondary Endpoints:	• Alive without respiratory failure at Day 28: 95% in		
Mortality at Day 28	mavrilimumab arm vs. 79% in placebo arm (OR 5.33; 95% CL 0.54–52.7: $P = 0.43$)		
Alive without respiratory failure at Day 28	337001, 0.37 - 32.7, 7 - 0.73)		

Methods	Results	Limitations and Interpretation	
OSCAR: Double-Blind RCT of Otilimab in Patients With Severe COVID-19 Pneumonia in 17 Countries4			
Key Inclusion Criteria:	Participant Characteristics:	Key Limitations:	
Hospitalized with SARS-CoV-2 pneumonia	• Mean age 59 years; 72% men; 66% White	Changes in SOC during study may	
 Required HFNC oxygen, NIV, or MV ≤48 hours before 	• At baseline:	have affected outcomes.	
dosing	 77% received HFNC oxygen or NIV; 22% received MV 	Interpretation:	
• CRP or territin >ULN	 83% received corticosteroids; 34% received RDV 	• For participants with severe COVID-19	
Key Exclusion Criteria:	Primary Outcome:	significantly reduce the probability of	
• Death likely <48 hours	• Alive and free of respiratory failure at Day 28: 71% in	respiratory failure or death.	
Multiple organ failure	difference 5 3%: 95% CL =0.8 to 11 4: P = 0.00)		
• SOFA score >10 if in ICU	$\mathbf{U}_{\text{reference}}^{\text{reference}} = \mathbf{U}_{\text{reference}}^{\text{reference}} = \mathbf{U}_{r$		
• EUMU	All cause mortality at Day 60: 22% in atilimab arm ve		
• Dialysis	24% in placebo arm (model-adjusted difference -2.4%)		
• High-dose horadrenaline (>0.15 ug/kg/mm) or equivalent	95% CI, -8.0 to 3.3; P = 0.41)		
Interventions:			
• Otilimab 90 mg IV as single infusion (n = 395)			
• Placebo (n = 398)			
Primary Endpoint:			
• Alive and free of respiratory failure at Day 28			
Key Secondary Endpoint:			
All-cause mortality at Day 60			

Key: ANC = absolute neutrophil count; BMI = body mass index; CRP = C-reactive protein; ECMO = extracorporeal membrane oxygenation; GM-CSF = granulocytemacrophage colony-stimulating factor; HFNC = high-flow nasal cannula; ICU = intensive care unit; IL = interleukin; IV = intravenous; mAb = monoclonal antibody; MV = mechanical ventilation; NIV = noninvasive ventilation; RCT = randomized controlled trial; RDV = remdesivir; SOC = standard of care; SOFA = sequential organ failure assessment; SpO₂ = oxygen saturation; ULN = upper limit of normal

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- 4. Patel J, Beishuizen A, Ruiz X, et al. A randomized trial of otilimab in severe COVID-19 pneumonia (OSCAR). *medRxiv*. 2021;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.04.14.21255475v1.

Lopinavir/Ritonavir and Other HIV Protease Inhibitors

Last Updated: February 11, 2021

The replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) depends on the cleavage of polyproteins into an RNA-dependent RNA polymerase and a helicase.¹ Two proteases are responsible for this cleavage: 3-chymotrypsin-like protease (3CLpro) and papain-like protease (PLpro).

Lopinavir/ritonavir and darunavir/cobicistat have been studied in patients with COVID-19. The clinical trials discussed below have not demonstrated a clinical benefit for protease inhibitors in patients with COVID-19.

Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends against the use of lopinavir/ritonavir and other HIV protease inhibitors for the treatment of COVID-19 in hospitalized patients (AI).
- The Panel **recommends against** the use of **lopinavir/ritonavir** and **other HIV protease inhibitors** for the treatment of COVID-19 in nonhospitalized patients (AIII).

Rationale

The pharmacodynamics of lopinavir/ritonavir raise concerns about whether it is possible to achieve drug concentrations that can inhibit the SARS-CoV-2 proteases.^{2,3} In addition, lopinavir/ritonavir did not show efficacy in two large randomized controlled trials in hospitalized patients with COVID-19.^{4,5}

There is currently a lack of data on the use of lopinavir/ritonavir in nonhospitalized patients with COVID-19. However, the pharmacodynamic concerns and the lack of evidence for a clinical benefit among hospitalized patients with COVID-19 undermine confidence that lopinavir/ritonavir has a clinical benefit at any stage of SARS-CoV-2 infection.

Adverse Events

The adverse events for lopinavir/ritonavir include:

- Nausea, vomiting, diarrhea (common)
- QTc prolongation
- Hepatotoxicity

Drug-Drug Interactions

Lopinavir/ritonavir is a potent inhibitor of cytochrome P450 3A. Coadministering lopinavir/ritonavir with medications that are metabolized by this enzyme may increase the concentrations of those medications, resulting in concentration-related toxicities. Please refer to the *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV* for a list of potential drug interactions.

Considerations in Pregnancy

- There is extensive experience with the use of lopinavir/ritonavir in pregnant women with HIV, and the drug has a good safety profile.
- There is no evidence of human teratogenicity (a 1.5-fold increase in the risk of overall birth defects can be ruled out).

- Lopinavir has low placental transfer to the fetus. Please refer to the <u>Recommendations for the</u> <u>Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce</u> <u>Perinatal HIV Transmission in the United States</u> for more information.
- Lopinavir/ritonavir oral solution contains 42.4% (volume/volume) alcohol and 15.3% (weight/ volume) propylene glycol and **is not recommended** for use during pregnancy. Please refer to the *Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States* for more information.
- The use of once-daily dosing for lopinavir/ritonavir is not recommended during pregnancy.

Considerations in Children

- Lopinavir/ritonavir is approved for the treatment of HIV in infants, children, and adolescents.
- There are no data on the efficacy of using lopinavir/ritonavir to treat COVID-19 in pediatric patients.

Summary of Clinical Data for COVID-19

- The plasma drug concentrations achieved using typical doses of lopinavir/ritonavir are far below the levels that may be needed to inhibit SARS-CoV-2 replication.³
- Lopinavir/ritonavir did not demonstrate a clinical benefit in hospitalized patients with COVID-19 during a large randomized trial in the United Kingdom.⁴
- In a large international randomized trial, lopinavir/ritonavir did not reduce the mortality rate among hospitalized patients with COVID-19.⁵
- A moderately sized randomized trial (n = 199) failed to find a virologic or clinical benefit of lopinavir/ritonavir over standard of care.⁶
- Results from a small randomized controlled trial showed that darunavir/cobicistat was not effective for the treatment of COVID-19.⁷
- There are no data from clinical trials that support using other HIV protease inhibitors to treat COVID-19.
- Please see Clinical Data for COVID-19 below for more information.

Clinical Data for COVID-19

The information presented in this section may include data from preprints or articles that have not been peer reviewed. This section will be updated as new information becomes available. Please see <u>*ClinicalTrials.gov*</u> for more information on clinical trials that are evaluating lopinavir/ritonavir.

Lopinavir/Ritonavir in Hospitalized Patients With COVID-19: The RECOVERY Trial

The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial is an ongoing, open-label, randomized controlled trial with multiple arms, including a control arm; in one arm, participants received lopinavir/ritonavir. The trial was conducted across 176 hospitals in the United Kingdom and enrolled hospitalized patients with clinically suspected or laboratory-confirmed SARS-CoV-2 infection.⁴

Patients were randomized into several parallel treatment arms; this included randomization in a 2:1 ratio to receive either the usual standard of care only or the usual standard of care plus lopinavir 400 mg/ ritonavir 100 mg orally every 12 hours for 10 days or until hospital discharge. Patients who had severe hepatic insufficiency or who were receiving medications that had potentially serious or lifethreatening interactions with lopinavir/ritonavir were excluded from randomization into either of these arms.

Mechanically ventilated patients were also underrepresented in this study because it was difficult to administer the oral tablet formulation of lopinavir/ritonavir to patients who were on mechanical ventilation. The primary outcome was all-cause mortality at Day 28 after randomization.

The lopinavir/ritonavir arm was discontinued on June 29, 2020, after the independent data monitoring committee concluded that the data showed no clinical benefit for lopinavir/ritonavir.

Patient Characteristics

- Of the 7,825 participants who were eligible to receive lopinavir/ritonavir, 1,616 were randomized to receive lopinavir/ritonavir and 3,424 were randomized to receive standard of care only. The remaining participants were randomized to other treatment arms in the study.
- In both the lopinavir/ritonavir arm and the standard of care arm, the mean age was 66 years; 44% of patients were aged ≥70 years.
- Test results for SARS-CoV-2 infection were positive for 88% of patients. The remaining 12% had a negative test result.
- Comorbidities were common; 57% of patients had at least one major comorbidity. Of those patients, 28% had diabetes mellitus, 26% had heart disease, and 24% had chronic lung disease.
 At randomization, 4% of patients were receiving invasive mechanical ventilation, 70% were receiving oxygen only (with or without noninvasive ventilation), and 26% were receiving neither.
- The percentages of patients who received azithromycin or another macrolide during the follow-up period were similar in both arms (23% in the lopinavir/ritonavir arm vs. 25% in the standard of care arm). In addition, 10% of patients in both arms received dexamethasone.

Results

- There was no significant difference in the primary outcome of 28-day mortality between the two arms; 374 patients (23%) in the lopinavir/ritonavir arm and 767 patients (22%) in the standard of care arm had died by Day 28 (rate ratio 1.03; 95% CI, 0.91–1.17; P = 0.60).
- A similar 28-day mortality was reported for patients who received lopinavir/ritonavir in an analysis that was restricted to the 4,423 participants who had positive SARS-CoV-2 test results (rate ratio 1.05; 95% CI, 0.92–1.19; P = 0.49).
- Patients in the lopinavir/ritonavir arm and patients in the standard of care arm had similar median times to discharge (11 days in both arms) and similar probabilities of being discharged alive within 28 days (69% vs. 70%).
- Among participants who were not on invasive mechanical ventilation at baseline, patients who received lopinavir/ritonavir and those who received standard of care only had similar risks of progression to intubation or death.
- Results were consistent across subgroups defined by age, sex, ethnicity, or respiratory support at baseline.

Limitations

- The study was not blinded.
- No laboratory or virologic data were collected.

Interpretation

Lopinavir/ritonavir did not decrease 28-day all-cause mortality when compared to the usual standard of care in hospitalized persons with clinically suspected or laboratory-confirmed SARS-CoV-2 infection. Participants who received lopinavir/ritonavir and those who received standard of care only had similar

median lengths of hospital stay. Among the patients who were not on invasive mechanical ventilation at the time of randomization, those who received lopinavir/ritonavir were as likely to require intubation or die during hospitalization as those who received standard of care.

Lopinavir/Ritonavir in Hospitalized Patients with COVID-19: The Solidarity Trial

The Solidarity trial was an open-label, randomized controlled trial that enrolled hospitalized patients with COVID-19 in 405 hospitals across 30 countries. The study included multiple arms; in one arm, participants received lopinavir/ritonavir. The control group for this arm included people who were randomized at the same site and time who could have received lopinavir/ritonavir but received standard of care instead. Lopinavir 400 mg/ritonavir 100 mg was administered orally twice daily for 14 days or until hospital discharge. Only the oral tablet formulation of lopinavir/ritonavir was available, which precluded administration to those on mechanical ventilation. The primary outcome was in-hospital mortality.⁵

After the results of the RECOVERY trial prompted a review of the Solidarity data, the lopinavir/ ritonavir arm ended enrollment on July 4, 2020. At that time, 1,411 patients had been randomized to receive lopinavir/ritonavir, and 1,380 patients received standard of care.

Patient Characteristics

- In both the lopinavir/ritonavir arm and the standard of care arm, 20% of the participants were aged ≥70 years and 37% were aged <50 years.
- Comorbidities were common. Diabetes mellitus was present in 24% of patients, heart disease in 21%, and chronic lung disease in 7%.
- At randomization, 8% of patients were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation, 53% were receiving oxygen only (with or without noninvasive ventilation), and 39% were receiving neither.
- Similar percentages of patients received corticosteroids in the lopinavir/ritonavir arm and the standard of care arm (23% vs. 24%). Other nonstudy treatments were administered less often, and the use of these treatments was balanced between arms.

Results

- There was no significant difference in in-hospital mortality between the two arms; 148 patients (9.7%) in the lopinavir/ritonavir arm and 146 patients (10.3%) in the standard of care arm had died by Day 28 (rate ratio 1.00; 95% CI, 0.79–1.25; P = 0.97).
- Progression to mechanical ventilation among those who were not ventilated at randomization occurred in 126 patients in the lopinavir/ritonavir arm and 121 patients in the standard of care arm
- In-hospital mortality results appeared to be consistent across subgroups.

Limitations

- The study was not blinded.
- Those who were on mechanical ventilation were unable to receive lopinavir/ritonavir.
- The study includes no data on time to recovery.

Interpretation

Among hospitalized patients, lopinavir/ritonavir did not decrease in-hospital mortality or the number of patients who progressed to mechanical ventilation compared to standard of care.

Lopinavir/Ritonavir Pharmacokinetics in Patients With COVID-19

In a case series, eight patients with COVID-19 were treated with lopinavir 400 mg/ritonavir 100 mg orally twice daily and had plasma trough levels of lopinavir drawn and assayed by liquid chromatography-tandem mass spectrometry.³

Results

- The median plasma lopinavir concentration was $13.6 \ \mu g/mL$.
- After correcting for protein binding, trough levels would need to be approximately 60-fold to 120-fold higher to achieve the in vitro half-maximal effective concentration (EC_{50}) for SARS-CoV-2.

Limitations

- Only the trough levels of lopinavir were quantified.
- The concentration of lopinavir required to effectively inhibit SARS-CoV-2 replication in vivo is currently unknown.

Interpretation

The plasma drug concentrations that were achieved using typical doses of lopinavir/ritonavir are far below the levels that may be needed to inhibit SARS-CoV-2 replication.

Other Reviewed Studies

The Panel has reviewed other clinical studies that evaluated the use of protease inhibitors for the treatment of COVID-19.^{6,8,9} These studies have limitations that make them less definitive and informative than larger randomized clinical trials. The Panel's summaries and interpretations of some of these studies are available in the <u>archived versions of the Guidelines</u>.

- 1. Zumla A, Chan JF, Azhar EI, Hui DS, Yuen KY. Coronaviruses drug discovery and therapeutic options. *Nat Rev Drug Discov*. 2016;15(5):327-347. Available at: <u>https://www.ncbi.nlm.nih.gov/pubmed/26868298</u>.
- Marzolini C, Stader F, Stoeckle M, et al. Effect of systemic inflammatory response to SARS-CoV-2 on lopinavir and hydroxychloroquine plasma concentrations. *Antimicrob Agents Chemother*. 2020;64(9). Available at: <u>https://www.ncbi.nlm.nih.gov/pubmed/32641296</u>.
- 3. Schoergenhofer C, Jilma B, Stimpfl T, Karolyi M, Zoufaly A. Pharmacokinetics of lopinavir and ritonavir in patients hospitalized with coronavirus disease 2019 (COVID-19). *Ann Intern Med.* 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32422065.
- Group RC. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2020. Available at: <u>https://www.ncbi.nlm.nih.gov/pubmed/33031764</u>.
- 5. WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed antiviral drugs for COVID-19—interim WHO Solidarity Trial results. *N Engl J Med*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33264556.
- 6. Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19. *N Engl J Med.* 2020;382(19):1787-1799. Available at: <u>https://www.ncbi.nlm.nih.gov/pubmed/32187464</u>.
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- 8. Hung IF, Lung KC, Tso EY, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, Phase 2 trial.

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 Li Y, Xie Z, Lin W, et al. Efficacy and safety of lopinavir/ritonavir or arbidol in adult patients with mild/ moderate COVID-19: an exploratory randomized controlled trial. *Med.* 2020:[In Press]. Available at: <u>https://www.sciencedirect.com/science/article/pii/S2666634020300015</u>.

Nitazoxanide

Last Updated: July 8, 2021

Nitazoxanide is a broad-spectrum thiazolide antiparasitic agent that is approved by the Food and Drug Administration (FDA) for the treatment of *Cryptosporidium parvum* and *Giardia duodenalis* infections in children aged ≥ 1 year and adults. Nitazoxanide is rapidly metabolized to its active metabolite, tizoxanide, and has in vitro antiviral activity against a range of viruses, including influenza viruses, hepatitis B and C viruses, norovirus, rotavirus, Ebola virus, Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2.¹⁻³ The mechanism of antiviral activity is not fully characterized. Nitazoxanide inhibits host enzymes, which impairs the posttranslational processing of viral proteins. It also has inhibitory effects on proinflammatory cytokines. With the exception of a Phase 2b/3 trial for uncomplicated influenza, the evidence for clinical activity of nitazoxanide against other viruses is limited or of low quality.⁴

Recommendation

• The COVID-19 Treatment Guidelines Panel (the Panel) recommends against the use of nitazoxanide for the treatment of COVID-19, except in a clinical trial (BIIa).

Rationale

Two randomized controlled trials that were conducted in Brazil and the United States did not find a significant clinical benefit for nitazoxanide treatment in nonhospitalized adults with COVID-19 when treatment was initiated within 2 to 5 days after illness onset.^{5,6} One of these trials, which has not yet been published, reported that fewer patients in the nitazoxanide arm progressed to severe COVID-19 than in the placebo arm. However, the study was underpowered to detect a difference, and this finding was not statistically significant.⁶ Additional small, unpublished studies were reviewed; however, due to their limitations, they did not provide support for the use of nitazoxanide.^{7,8} Nitazoxanide was well tolerated in these trials. The Panel concluded that results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of nitazoxanide in the treatment of COVID-19.

Monitoring, Adverse Effects, and Drug-Drug Interactions

- Nitazoxanide is generally well tolerated. The most commonly reported side effects include abdominal pain, diarrhea, headache, nausea, vomiting, urine discoloration, and, rarely, ocular discoloration.
- Nitazoxanide is a highly plasma protein-bound drug (>99.9%). Drug-drug interactions may occur when nitazoxanide is administered concurrently with other highly plasma protein-bound drugs due to competition for binding sites. If nitazoxanide is coadministered with other highly protein-bound drugs with narrow therapeutic indices, monitor the patient for adverse drug reactions.

Considerations in Pregnancy

According to the animal study data included in the product label, nitazoxanide does not appear to affect fertility, nor does it cause fetal toxicity.⁹ There are no data on using nitazoxanide to treat COVID-19 in pregnant women.

Considerations in Children

Nitazoxanide is approved by the FDA for use in children aged ≥ 1 year old to treat *Cryptosporidium*

parvum and *Giardia duodenalis* infections. Dosing for the nitazoxanide suspension or tablets is available for children that provides exposure that is similar to the approved adult dose of oral nitazoxanide 500 mg twice daily. There are no data on using nitazoxanide to treat COVID-19 in children.

Clinical Trials

Several clinical trials that are evaluating the use of nitazoxanide for the treatment of COVID-19 are currently underway or in development. Please see <u>*ClinicalTrials.gov*</u> for the latest information.

- 1. Jasenosky LD, Cadena C, Mire CE, et al. The FDA-approved oral drug nitazoxanide amplifies host antiviral responses and inhibits ebola virus. *iScience*. 2019;19:1279-1290. Available at: <u>https://www.ncbi.nlm.nih.gov/pubmed/31402258</u>.
- 2. Rossignol JF. Nitazoxanide: a first-in-class broad-spectrum antiviral agent. *Antiviral Res.* 2014;110:94-103. Available at: <u>https://www.ncbi.nlm.nih.gov/pubmed/25108173</u>.
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- 5. Rocco PRM, Silvia PL, Cruz FF, et al. Early use of nitazoxanide in mild COVID-19 disease: randomised, placebo-controlled trial. *Eur Respir J*. 2021;Published online ahead of print. Available at: <u>https://www.ncbi.nlm.nih.gov/pubmed/33361100</u>.
- Rossignol J, Bardin MC, Oaks JB,et al. Early treatment with nitazoxanide prevents worsening of mild and moderate COVID-19 and subsequent hospitalization. *medRxiv*. 2021;Preprint. Available at: <u>https://www.medrxiv.org/content/10.1101/2021.04.19.21255441v1</u>.
- Blum VF, Cimerman S, Hunter JR, et al. Nitazoxanide in vitro efficacy against SARS CoV-2 and in vivo superiority to placebo to treat moderate COVID-19—a Phase 2 randomized double-blind clinical trial. *Preprints with the Lancet*. 2021. Available at: <u>https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3763773</u>.
- 8. Silva M, Espejo A, Pereyra ML, et al. Efficacy of nitazoxanide in reducing the viral load in COVID-19 patients: randomized, placebo-controlled, single-blinded, parallel-group, pilot study. *MedRxiv*. 2021;Preprint. Available at: <u>https://www.medrxiv.org/content/10.1101/2021.03.03.21252509v1.full.pdf</u>.
- 9. Nitazoxanide (Alinia) [package insert]. Lupin Pharma. 2021. Available at: <u>https://www.accessdata.fda.gov/</u> <u>drugsatfda_docs/label/2016/021497s001,021498s004lbl.pdf</u>.

Nitazoxanide: Selected Clinical Data

Last Updated: July 8, 2021

The information in this table may include data from preprints or articles that have not been peer reviewed. This section will be updated as new information becomes available. Please see <u>*ClinicalTrials.gov*</u> for more information on clinical trials that are evaluating NTZ for the treatment of COVID-19. The clinical trials described in this table do not represent all the trials that the Panel reviewed while developing recommendations for NTZ.^{1,2}

Study Design	Methods	Results	Limitations and Interpretation				
Early Treatment of Mild COVID-19 with Nitazoxanide ³							
Randomized, double-blind, placebo- controlled trial in nonhospitalized adults with mild COVID-19 in Brazil (n = 475)	 Key Inclusion Criteria: Clinical signs and symptoms of COVID-19 for ≤3 days (fever, dry cough, and/or fatigue) Key Exclusion Criteria: Negative SARS-CoV-2 RT-PCR result from an NP swab 	 Number of Participants: NTZ (n = 194) and placebo (n = 198) Participant Characteristics: Median age of patients was 37 years. Percentage of patients aged 18–39 years: 58% Percentage of patients aged 40–59 years: 36% 	 Key Limitations: In general, the patients in this study were young and relatively healthy. At baseline, the median VL was 0.43 log₁₀ c/mL lower in the NTZ arm than in the placebo arm; however, this difference was not statistically 				
(11 = 473)	 Renal, heart, respiratory, liver, or autoimmune diseases Participant had a history of cancer in the past 5 years Interventions: NTZ 500 mg 3 times daily for 5 days using the oral liquid formulation Color-matched placebo 3 times daily for 5 days 	 Percentage of patients aged 60–77 years: 6% 53% of patients were women. 69% of patients were White. 31% of patients had a BMI ≥30. 85% of patients had no reported comorbidities. Median time from symptom onset to first dose of study drug was 5 days (IQR 4–5 days). Baseline median SARS-CoV-2 VL was 7.06 log₁₀ c/mL (IQR 5.77–8.13) in NTZ arm and 7.49 log₁₀ c/mL (IQR 6.15–8.32) in placebo arm (P = 0.065). 	 significant (trend toward a significant difference; P = 0.065). Although the difference in absolute VLs between the arms at Day 5 was reported as statistically significant, without the information on the change in VL in each arm, it is difficult to interpret the significance of the findings. Some participants who received the study drug were excluded from the analysis population due to discontinued intervention (21 in NTZ arm vs. 18 in placebo arm); AEs (6 in NTZ arm vs. 1 in placebo arm); hospitalization (5 in NTZ arm vs. 5 in placebo arm); and protocol deviations (7 in NTZ arm vs. 7 in placebo arm). This complicates the interpretation of the study results, because an ITT analysis was not included. 				
	 Primary Endpoint: Complete resolution of dry cough, fever, and/or fatigue after receiving treatment for 5 days Key Secondary Endpoints: Reduction in SARS-CoV-2 VL Incidence of hospital admission after completing therapy 	 Primary Outcome: There was no difference in time to complete resolution of symptoms between NTZ and placebo arms (P = 0.277) Secondary Outcomes: After 5 days, median SARS-CoV-2 VL was lower in NTZ arm (3.63 log₁₀ c/mL [IQR 0–5.03]) than in placebo arm (4.13 log₁₀ c/mL [IQR 2.88–5.31]; P = 0.006). 					

Study Design	Methods	Results	Limitations and Interpretation			
Early Treatment of Mild COVID-19 with Nitazoxanide ³ , continued						
		 29.9% of patients in NTZ arm and 18.2% of patients in placebo arm had a negative SARS-CoV-2 RT-PCR result at the fifth treatment visit (<i>P</i> = 0.009). In the ITT study population, 5 patients on NTZ and 5 on placebo were hospitalized due to clinical deterioration; 2 who received NTZ required ICU admission vs. 0 who received placebo. These individuals were excluded from the analysis population because they did not complete the 5-day treatment course before clinical progression occurred. Other Outcomes: Mild to moderate AEs occurred in about 30% of participants in each arm who completed 5 days of therapy. 	 Interpretation: NTZ did not improve time to resolution of symptoms compared to placebo. Median VL was lower at Day 5 in the NTZ arm than in the placebo arm, but this may reflect differences in baseline VLs. NTZ was well tolerated. 			
Early Treatment of Mild to Moderate COVID-19 with an Investigational Formulation of Nitazoxanide ⁴						
Randomized, double-blind, placebo- controlled trial in nonhospitalized patients with COVID-19 in the United States and Puerto Rico (n = 1,092) This is a preliminary, unpublished report that has not been peer reviewed.	 Key Inclusion Criteria: Aged ≥12 years Enrollment ≤72 hours of symptom onset Mild to moderate COVID-19 ≥2 respiratory symptom domains with a score ≥2 on FLU-PRO questionnaire at screening, and no improvement in overall symptom severity compared to previous day Key Exclusion Criteria: Signs or symptoms of severe COVID-19 Previous COVID-19 or any symptom suggestive of COVID-19 Recent acute upper respiratory tract infection Severe immunodeficiency Severe heart, lung, neurological, or 	 Number of Participants: mITT analysis: NTZ (n = 184) and placebo (n = 195) Participant Characteristics: Median age of patients was 40 years. 43.5% of patients were men. 87.6% of patients were White. Median BMI was 28.9. Median time from symptom onset to randomization was 45.9 hours. 64.8% of patients had mild disease. 35.2% of patients were at risk for severe illness. Primary Outcome: NTZ was not associated with a reduction in median time to sustained response compared to placebo (13.3 days in NTZ arm vs. 12.4 days in placebo arm; P = 0.88) Secondary Outcomes: Progression to severe disease occurred in 1 of 184 patients (0.5%) in NTZ arm and 7 of 195 natients (3.6%) in placebo arm (P 	 Key Limitations: Information is limited in this preliminary report. Because the number of high-risk participants who progressed to severe COVID-19 in this study was small, the results for this subgroup are fragile. Larger studies are needed. Interpretation: NTZ did not demonstrate significant clinical or virologic benefits when compared to placebo. NTZ was well tolerated. 			

Study Design	Methods	Results	Limitations and Interpretation			
Early Treatment of Mild to Moderate COVID-19 with an Investigational Formulation of Nitazoxanide4, continued						
	 Interventions: 2 investigational NTZ 300 mg extended-release tablets (for a total dose of 600 mg) PO with food twice daily for 5 days Matching placebo for 5 days All subjects received a vitamin B complex supplement twice daily to mask potential NTZ-associated chromaturia. 	 Among a subgroup of patients who had a high risk for severe illness according to CDC criteria, 1 of 112 patients (0.9%) in NTZ arm and 7 of 126 patients (5.6%) in placebo arm progressed to severe disease (<i>P</i> = 0.07). 1 of 184 patients (0.5%) in NTZ arm and 5 of 195 (2.6%) in placebo arm were hospitalized (<i>P</i> = 0.18). There was no significant difference in viral endpoints between arms at Days 4 and 10. Other Outcomes: The safety analysis included 935 participants (472 in NTZ arm 				
Primary Endpoint:	Primary Endpoint:	and 463 in placebo arm).				
	 Time from first dose to sustained response 	 2 patients in NTZ arm and 3 patients in placebo arm stopped the study drug due to AEs. 				
	Secondary Endpoint:					
	 Rate of progression to severe COVID-19 					

Key: AE = adverse event; BMI = body mass index; CDC = Centers for Disease Control and Prevention; FLU-PRO = Influenza Patient Reported Outcomes; ICU = intensive care unit; ITT = intention-to-treat; mITT = modified intention-to-treat; NP = nasopharyngeal; NTZ = nitazoxanide; the Panel = the COVID-19 Treatment Guidelines Panel; PO = orally; RT-PCR = reverse transcription polymerase chain reaction; VL = viral load

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